Table B: EURAS Study: Confirmed Thromboembolic AEs – Number of Events, Incidence, 95% CI

Event Category	Yasmin (19,530 WY)			LNG-containing OCs (18,476 WY)			Other OCs (26,097 WY			Total
	N	Per 104 WY	95% CI	N	Per 104 WY	95% CI	N	Per 104 WY	95% CI	N
All VTE & ATE	13	6.7	3.5 - 11.4	14	7.6	4.1 – 12.7	23	8.8	5.6 – 13.2	50
All VTE	12	6.1	3.2 - 10.7	11	6.0	3.0 – 10.7	19	7.3	4.4 – 11.4	42
PE	3	1.5	0.3 – 4.5	2	1.1	0.1 – 3.9	2	0.8	0.1 – 2.8	7
All ATE	1	0.5	0.0 – 2.9	3	1.6	0.3 – 4.8	4	1.5	0.4 – 3.9	8
AMI	0	0.0	0.0 – 1.9	1	0.5	0.0 – 3.0	2	0.8	0.1 – 2.8	3
CVA	1	0.5	0.0 – 2.9	2	1.1	0.1 – 3.9	2	0.8	0.1 – 2.8	5
All Fatal VTE/ATE	0	0.0	0.0 – 1.9	2	1.1	0.1 – 3.9	0	0.0	0.0 – 1.4	2

VTE = venous thromboembolic event, ATE = arterial thromboembolic event, AMI = acute myocardial infarction, CVA = cerebrovascular accident, WY = women-years
Source: Applicant's 17 Aug 2004 submission, page 10 of 37

The US postmarketing surveillance study (Ingenix Study of United Health Care Patients) was initially designed to monitor adverse events related to hyperkalemia. There has been no signal to suggest that hyperkalemia has been a clinical problem with Yasmin since its approval. The Ingenix Study was later modified to monitor thrombotic and thromboembolic adverse events. The most recent interim analysis of the Ingenix Study (see Table C) does not show a higher risk for Yasmin, compared to other oral contraceptives, for thrombotic and thromboembolic adverse events.

Table C: Ingenix Study Results (Confirmed Cases of Thrombotic and Thromboembolic Events)

Outcome (a)	Yasmin Initiators (n=14,295)			Other OC Initiators (n=28,590)		
	Claims-Based	Chart Confirmed	Chart Not Found	Claims-Based	Chart Confirmed	Chart Not Found
Number of Charts Requested	20			58		
Pulmonary embolism	4	1	0	11	9	1
Venous thrombosis	12	8	1	27	20	3
Arterial embolism	1	1	0	8	0	1
Stroke	2	0	0	7	3	1
TIA	0	0	0	0	0	0

(a) A woman can have multiple events in multiple categories
(b) Women with claims for procedures or anticoagulant therapy only
Source: Applicant submission 7 Oct 2004

2.4 DOSING

The daily dosing of both the 24-day and 21-day regimens incorporates 0.02 mg of ethinyl estradiol compared to 0.03 mg ethinyl estradiol in the approved product Yasmin. Most combination oral contraceptives utilize 21 days of active drug that are followed by 7 placebo tablets. Seasonale is an oral contraceptive that is taken for 84 days and followed by 7 placebo tablets. Mircette utilizes 21 active combination tablets followed by 2 placebo tablets and then 5 tablets containing 0.01 mg of ethinyl estradiol.

If the applicant receives marketing approval for the 24-day regimen, it will be the first 24-day regimen available. Although the medical literature (provided by the applicant) suggests that expanding the active phase of oral contraceptives may have potential benefits, adequate and

controlled clinical trials have not performed comparing the 24-day to the 21-day regimen. It has been suggested that follicular development appears to be suppressed more with longer duration of active tablets by sonogram analysis. This could translate into some contraceptive benefit for low dose pills where missing just a few pills leads to unintended pregnancies. Proving this potential benefit however would require an extremely large clinical study.

The applicant also is developing the 24-day regimen for the added indications of prevention of PMDD and treatment of acne in women desiring contraception and who elect to use oral contraception.

Table D provides the annual hormonal exposure of the presently marketed drospirenone product (Yasmin) and the two Yasmin 20 products described in this review:

Table D: Annual Exposure to Ethinyl estradiol and DRSP with Yasmin and the Yasmin 20 Products

Product	Ethinyl Estradiol	DRSP
Yasmin	8.19 mg	819 mg
Yasmin 20, 24-day regimen	6.24 mg	936 mg
Yasmin 20, 21-day regimen	5.46 mg	819 mg

Although both of the Yasmin 20 regimens are deemed safe and effective based on the data presented in this NDA, this reviewer prefers the 21-day regimen since it provides the same contraceptive efficacy with less hormonal exposure. It is acknowledged that the applicant has ongoing programs for the 24-day regimen that seek the additional secondary indications of PMDD and acne. Approval of either of these supplemental indications would impact this reviewer's assessment of the risk/benefit ratio for the 24-day regimen and would further support approval of the 24-day dosing regimen.

2.5 SPECIAL POPULATIONS

Gender. Combination oral contraceptives are intended for the population of women at risk for pregnancy.

Race. A small pharmacokinetic study was performed by the applicant comparing Japanese and Caucasian women. This study showed no differences in these two ethnic populations.

The racial distribution for the 24 and 21-day regimens in the pivotal trials for the 21-day and 24-day regimens are listed in Table E.

Table E: Racial Distribution in the Pivotal 24 and 21-Day Studies

Dosing Regimen	Caucasian (%)	Hispanic (%)	Black (%)	Asian (%)	Other (%)
24-day (303740)	87.8	4.6	4.3	1.2	2.1
21-day (303860)	98.1	0.5	0.2	0.5	0.5

Although there are very few non-Caucasians in these studies, there is no evidence from previous combination oral contraceptive NDAs or from the literature to suspect that the safety or efficacy of estrogen/progestin combination orals differ based on the race of the user.

Renal and Hepatic Impairment. No studies with Yasmin 20 (both regimens) were conducted in subjects with renal or hepatic impairment. Because of anti-mineralocorticoid activity and

potential risk for producing hyperkalemia, Yasmin 20 (both regimens), are contraindicated in women with renal insufficiency, hepatic dysfunction, or insufficiency.

Pediatric Studies. No additional pediatric studies are required. It is generally accepted that the safety and efficacy profiles of combination oral contraceptives are similar in all post-menarchal, reproductively competent adolescents and women.

Clinical Review

1. INTRODUCTION AND BACKGROUND

1.1 DRUG ESTABLISHED AND PROPOSED TRADE NAME, DRUG CLASS, APPLICANT'S PROPOSED INDICATION(S), DOSE, REGIMENS, AGE GROUPS

Established Name:
YAZ: drospirenone 3 mg/ethinyl estradiol betadex 0.02 mg (tablets)

Proposed Trade Name:
YAZ: 24-day active dosing regimen

Drug Class: Combination oral contraceptive

Proposed Indication: Prevention of pregnancy in women who elect to use an oral contraceptive.

Dose/Regimen:
YAZ: One active tablet (drospirenone 3 mg/ethinyl estradiol betadex 0.020 mg) daily for 24 consecutive days followed by one placebo tablets for 4 consecutive days)

One active tablet (drospirenone 3 mg/ethinyl estradiol betadex 0.020 mg) daily for 21 consecutive days followed by tablet free interval for 7 consecutive days)

Age Group: Reproductive age women

1.2 STATE OF ARMAMENTARIUM FOR INDICATION(S)

Contraceptive methods currently used include the following:

Barriers
- Diaphragms
- Cervical caps
- Male Condoms
- Female Condoms

Combination Oral Contraceptives (Estrogen/Progestin)
- Ethinyl estradiol/Desogestrel
- Ethinyl estradiol/Drospirenone
- Ethinyl estradiol/Ethynodiol diacetate
- Ethinyl estradiol/Norethindrone
- Ethinyl estradiol/Norethindrone acetate
- Ethinyl estradiol/Norgestimate
- Ethinyl estradiol/Norgestrel
- Mestranol/Norethindrone

Hormonal Skin Injections
- medroxyprogesterone acetate
- medroxyprogesterone acetate/estradiol cypionate

Hormonal Skin Implant (levonorgestrel)

Hormonal Skin Patch (Ethinyl estradiol/Norelgestromin)

Hormonal Vaginal Ring (Ethinyl estradiol/Etonogestrel)

Intrauterine Devices
- Copper containing
- Hormone containing (levonorgestrel)

Periodic Abstinence
- Calendar
- Ovulation method
- Sympto-thermal
- Post-ovulation

Post Coital Hormonal Contraception
- Use of combination oral contraceptives
- Use of levonorgestrel

Progestin Only Oral Contraceptives
- Levonorgestrel
- Norethindrone

Spermicides (nonoxynol-9)
- Aerosol foams
- Gels and creams
- Soluble films
- Sponge
- Suppositories

Sterilization
- Female
- Male

Withdrawal

Most of the combination oral contraceptives (COCs) are similar in regard to safety and efficacy. There are a large number of originator and generic marketed COC products (approximately 60)

In regard to the present submission, there is only one other combination oral contraceptive that contains ethinyl estradiol/drospirenone (Yasmin)

1.3 IMPORTANT MILESTONES IN PRODUCT DEVELOPMENT

The significant dates in the development of this product prior to NDA filing are the following:

- 14 July 2000 (Pre-IND guidance meeting)
- 22 August 2000 (Submission of IND 60,738)
- 20 February 2003 (Pre-NDA meeting)

14 July 2000 (Pre-IND Guidance Meeting)

The applicant's questions in this meeting were primarily focused on Pharm/Tox and Clinical Pharmacology issues in relationship to the applicant's existing studies with Yasmin. The applicant provided a rationale for the 24-day dosing regimen. They reported a trend toward better symptom control (less bloating, improved mood). The division recommended that lab chemistry (including electrolytes, liver function tests, renal function tests and good quality serum potassium data) be obtained at baseline, after drug has reached steady state (approx. day 21), 6 months and 12 months.

22 August 2000 (Submission of IND 60,738)

After review of the IND submission of the pivotal trial (Protocol 303740) the division had the following comments and questions for the applicant:

1. You have indicated that a single pivotal Phase III study (Protocol No. ME303740) will be conducted to assess the efficacy and safety of Yasmin 20 for support of the US NDA and registration. Please ensure that the study will include at least 10,000 treatment cycles on Yasmin 20 as this is the minimal acceptable number.
2. Please clarify the following for Protocol No. ME303740.
   a. Pg. 15. Please clarify Exclusion Criteria 22 that states: "All women who are predisposed to hyperkalemia." Does this mean that subjects who are taking any potassium sparing drugs (e.g., ACE inhibitors) or drugs that may increase serum potassium (e.g., NSAIDS) will be excluded? If so, the value of the clinical trial in terms of assessing the potential risk of hyperkalemia in the general population may be reduced.
   b. Pg. 14 and 15 (Exclusion Criteria 10 and 16). Why are women with "any venous thromboembolic event that occurred in a close relative at a younger age" or endometriosis excluded from the clinical trial?
   c. Pg. 20 and 21. Please clarify if a subject will be required to use back up contraception if she is more than 12 hrs but less than 24 hrs late in taking a Yasmin 20 tablet. If she is required to use backup contraception in this situation, instructions for the patient in the drug label and patient packet insert will need to be similar.
   d. Pg. 25. What is the earliest day on which withdrawal bleeding can commence and still be classified as a normal withdrawal bleed as "4 days before the hormonal withdrawal" is not day 22?

e. Pg. 21 and Pg. 28. Will a pregnancy test be required in (a) all instances in which a subject does not have a withdrawal bleed by Day 7 of the subsequent cycle or (b) only in those instances in which a subject has missed one or more tablets of Yasmin in the preceding treatment cycle? Will a pregnancy test be required if a subject does not have a withdrawal bleed within 7 days of her final tablet of Yasmin (i.e., by her study termination visit)? Page 21 implies that a pregnancy test is required only if one or more tablets are not taken in the prior cycle. Please ensure (by protocol amendment, if necessary) that a pregnancy test is obtained whenever a withdrawal bleed does not occur.

f. Pg. 34. Does the protocol require a urinalysis? On page 34, it is stated that a urine specimen will be collected but a urinalysis is not listed in the Study Flow Chart (Pg. 12).

3. Please correct the following typographic errors on Pg. 10 under "Visits 3-7" for gynecologic examination, cervical smear and safety laboratory blood samples. These procedures will be performed during (cycle 6/visit 5) and not (cycle 6/visit 4).

Medical Officer's Comments:

The applicant responded to the preceding comments on June 28, 2002 in submission no. 45 to IND 60,738. Many of the applicant's corrections to the comments were part of amendment #3 to the protocol, which was sent to the FDA on 6-26-01. Key points from the applicant's response are the following:

- ***Based on a lower drop out rate than originally expected the applicant stated that they expected to fulfill the minimal acceptable number of 10,000 treatment cycles.***
- ***The applicant deleted the exclusion "All women who are predisposed to hyperkalemia" in amendment #3.***
- ***The applicant maintained the exclusion "any venous thromboembolic event that occurred in a close relative at a younger age". This exclusion was also included in the Yasmin studies. Consideration should be given to mention this exclusion in the label.***
- ***The exclusion criteria "endometriosis" was deleted from the protocol in amendment #3.***
- ***The applicant increased interval allowed for missing tablets to 24 hours rather than 12 hours in amendment #3.***
- ***The reference to day 22 on page 25 of the protocol was deleted in amendment #3.***
- ***The applicant stated that a pregnancy test is required in all instances in which a subject does not have a withdrawal bleed by Day 7 of the subsequent cycle.***
- ***In amendment #3, the applicant corrected a typing error concerning urinalysis and stated it should be performed at all visits where blood samples are taken.***
- ***In amendment #3, the applicant corrected the typographic errors related to gynecologic examination, cervical smear and safety labs (visit 5 rather than 4).***

20 February 2003 (Pre-NDA Meeting)

In regard to clinical issues, the applicant stated that they would be providing data from at least 200 women completing 13 cycles of treatment on YAZ and approximately 11,000 cycles.

The division also requested the applicant to provide the following

- CRFs for all pregnancies
- Outcome information for the pregnancies for the NDA
- Data sets for ISS, as well as data sets for the individual studies
- Further follow-up on the two deaths in the pivotal clinical trials
- Pregnancy rates for other phase III trials with YAZ

1.4 OTHER RELEVANT INFORMATION

The pertinent clinical review information is covered in the other sections of the review. There is no additional information required for this section.

1.5 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED AGENTS

There is a long history of clinical studies and approvals of oral combination contraceptives.

The important issues with combination oral contraceptives are the following:

- Contraceptive efficacy in the pivotal trials (Pearl Index and life table analysis)
- Whether the safety profile differs from other approved OC products
- Cycle control (especially in regard to the level of unanticipated bleeding and drug induced amenorrhea)

Important issues related specifically to a combination oral contraceptive containing drospirenone and ethinyl estradiol include the following:

- Potential risk of hyperkalemia in certain high-risk patients with predisposing conditions
- Assessment of VTE risk of this product compared to other oral contraceptives

All five of these issues are addressed in this review.

2. CLINICALLY RELEVANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, MICROBIOLOGY, BIOPHARMACEUTICS, STATISTICS AND/OR OTHER CONSULTANT REVIEWS

2.1 PHARMACOLOGY/TOXICOLOGY

- **Recommendation on Approvability**: Pharmacology/toxicology recommends approval of NDA 21-676 based on previous finding of safety and prior approval of Yasmin (Berlex NDA 21-098), a contraceptive, which contains 3 mg DRSP and 0.03 mg EE. The present proposed formulation, Yaz has the same indication i.e., contraception and is administered by the same route of administration but contains only 0.02 mg of EE compared to 0.03 mg in Yasmin.
- **Recommendation for Nonclinical Studies**: Preclinical safety is supported by reference to studies that were submitted to support approval of NDA 21-098 for Yasmin. In addition this NDA (NDA 21-676) contains eight pharmacology reports (AW63, B273, B283, A04834, AQ61, AF46 and AF45), six ADME reports (B206), AV64, B589, B824, A618 and B320) and eight toxicology reports (AG69, B178, B839, AS78, A09791, A09897, A11703 and A11637), which were not previously submitted in NDA 21-098. These are reviewed and summarized under the appropriate headings in this review.

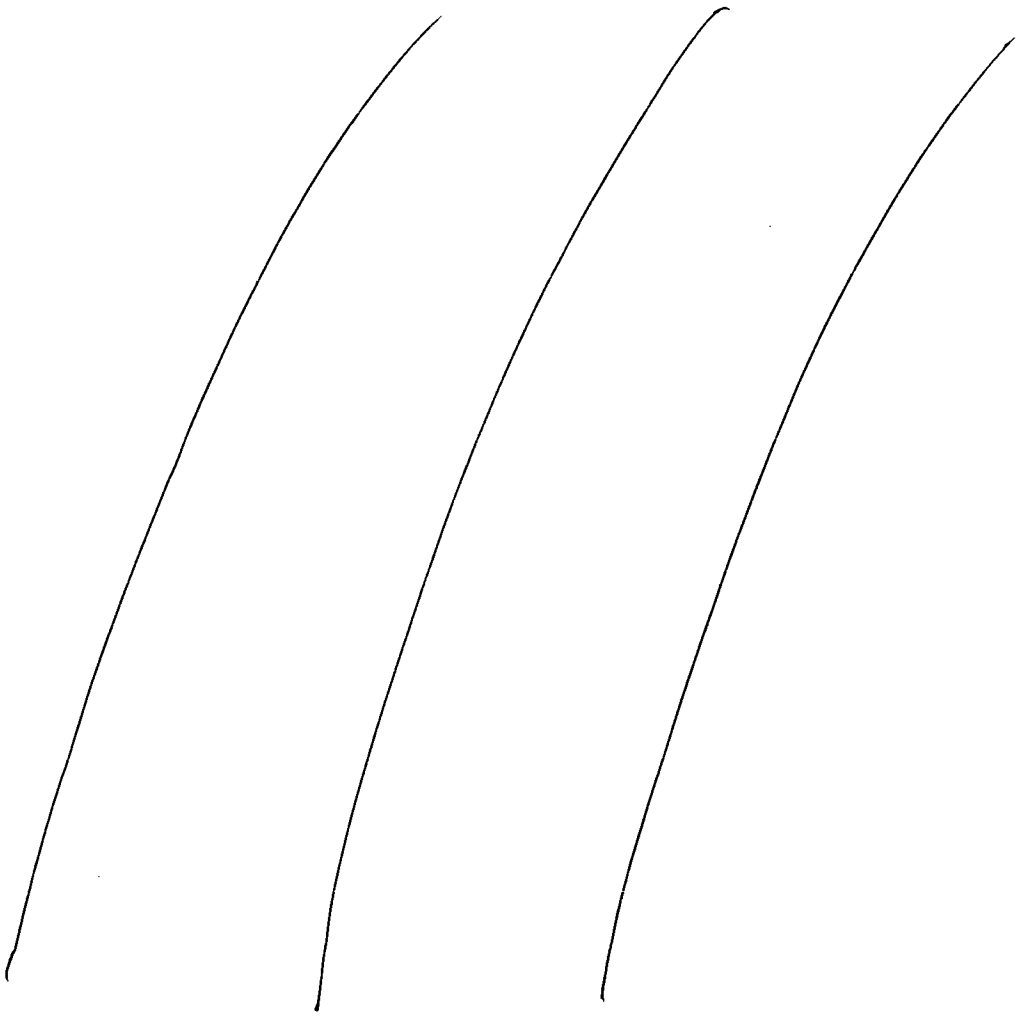
- **Recommendations on Labeling**: Labeling will be similar to that for approved NDA 21-098 for Yasmin.

2.2 CHEMISTRY

Chemistry is recommending approval of Yasmin 20, 24-day regimen contingent on appropriate labeling. A tightening of the dissolution specification (Q= ⁻ at 30 minutes) was agreed to by the applicant. Additionally the applicant submitted data allowing for a 36-month expiry. If the applicant elects to market the 21-day regimen of Yasmin 20, some minor review of the cartons may be required.

2.3 DIVISION OF DRUG MARKETING, ADVERTISING, AND COMMUNICATIONS

Corrinne Kulick from DDMAC provided the following clinical recommendations for the label:



2.4 DIVISION OF BIOMETRICS

The summary statement from biometrics is the following:

"Based on the data provided by the applicant, from the statistical standpoint, Drospirenone 3 mg/Ethinyl Estradiol 0.02 mg (YAZ) tablets seem adequate for demonstrating the effectiveness of this drug in the prevention of pregnancy for both the 24-day and 21-day regimen. However, the 21-day study, with a total of 3 pregnancies and Pear Index of 0.35 (95% CI from 0.06 to 1.02) showed superior results than that of the 24-day regimen study with total of 12 pregnancies and Pearl Index of 1.41 (95% CI from 0.73 to 2.42)."

These results are very similar to the applicant's recalculated results.

2.5 DIVISION OF DRUG RISK EVALUATION

The consultations and interactions with the DDRE are reported in section 6 of the appendix.

2.6 DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT

DMETS has reviewed and evaluated the [redacted] Study for the proposed proprietary name, YAZ and continues to be concerned that the proposed name could be misinterpreted as an abbreviation for the medication Yasmin. The proposed name looks like a three-letter abbreviation for something rather than a name itself. Therefore healthcare professionals and patients may attempt to associate the name as an abbreviation for another medication. The [redacted] market research study has shown that without prior knowledge of the product information (unaided research) 19 physicians and/or pharmacists (9.5%) associated the name YAZ with the proprietary name Yasmin. No information has been presented in the [redacted] Study to alleviate DMETS concern that the introduction of the proprietary name YAZ into the marketplace would increase the risk of confusion and medication errors between the medications YAZ and Yasmin. Thus, the information provided has failed to provide persuasive evidence for DMETS to reverse its initial decision on the acceptability of the proprietary name "YAZ".

Medical Officer's Comments:

- ***I support the applicant's position and reasons for retaining the YAZ trade name (applicant's submission, May 21, 2004, EDR). I feel that it is unlikely that there will be confusion between these names. There are no significant safety concerns if a rare accidental switch was to occur.***

2.7 DIVISION OF SCIENTIFIC INVESTIGATIONS

Dr. Bachmann's site was the only US site. DSI reviewed this site between April 14-19, 2004. The DSI assessment is as follows

Site #1
Gloria Bachmann, M.D.
Women's Health Institute 125
Paterson Street
New Brunswick, New Jersey 08901-1977

87 subjects were screened for the study. Ten (10) subjects were screen failures and 24 dropped out. All consent forms were reviewed. Subject 1274's pregnancy was reported in the efficacy data listings but subject 1224's pregnancy was not. Both subjects were reported as prematurely discontinuing the study.

A Form 483 was issued noting the single observation that study records for subjects 1243 and 1270 were inadvertently shredded but were reconstructed from other existing documentation. Original consent forms and the nurse's notes for study visits for these two subjects could not be replaced.

OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The data submitted by Dr. Bachmann appear satisfactory in support of the relevant submission.

Medical Officer's Comments:

- ***The DSI consult was signed 24 Jun 2004. Subject 1224 listed above corresponds to PID #39. I concur with the applicant that this pregnancy's conception date occurred before use of study drug. Subject 1274 corresponds to PID # 92 who was included in the "during treatment" pregnancies. Review of the datasets did not indicate that subjects 1243 and 1270 had potential problems that would require original source documents for full analysis.***

2.8 DIVISION OF SURVEILLANCE, RESEARCH AND COMMUNICATION SUPPORT

The following recommendations were made:

- Revise the Patient Package Insert (PPI) to a
- Simplify the vocabulary and sentence structure for lower literacy readers.
- Do not provide
- Avoid the use of UPPER CASE lettering (except trade name)
- Avoid presenting data in tables.
- Explain percentages and other rate information

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

The clinical pharmacology studies submitted with this NDA include:

- Bioavailability study (protocol 301780)
- Single-dose pharmacokinetic studies (protocols 300080, 304326)
- Multiple-dose pharmacokinetic study (protocol 305103)
- Drug interaction with simvastatin (protocol 303741)
- Ovulation inhibition studies (protocols 305466, 14588)

See the Biopharmaceutics review of these studies for findings.

Leslie Kenna from the division of Biopharmaceutics (OCPB) made the following recommendation regarding approval:

"This NDA is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics given that labeling comments are accepted by the applicant."

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1 OVERALL DATA

The data utilized in this review is specified in Section 5.1 and Section 5.2..

4.2 TABLE LISTING THE MAJOR CLINICAL TRIALS

The major clinical trials supporting NDA 21-676 are listed in Table 1.

Table 1: Overview of Major Clinical Trials

Protocol (Study) No. **(Report No.)** **{Objective}**	**Design** **(Country of Sites)** **{No. Subjects Tx}**	**Treatment** **Max. Duration of Treatment**	**No. of Treatment Cycles** **Women–Yrs Treatment** No. of Completers
24-day Dosing Regimen			
Protocol 303740 (A12007) {Efficacy and safety for 24-day dosing regimen}	Phase 3, Non comparative (Argentina, Austria, Brazil, Poland, USA) {1027 subjects}	Yasmin 20 * • 13 Cycles	11,410 cycles for efficacy 11,480 cycles for safety 883 women-years for safety 746 women completed 13 cycles
Protocol 301888 (A09151) {Lipid, hemostatic and carbohydrate study}	Phase 3, Open label, randomized, active comparator Single Center 29 subjects (Yasmin 20)	Yasmin 20 • 7 cycles 0.15 mg DSG + 20 µg EE,	Yasmin 20 group • Approximately 182 cycles • Approx. 14 women-yrs • 26 completed 7 cycles
21-day Dosing Regimen			
303860 (A15129) {Efficacy and safety for 21-day dosing regimen}	Phase 3, non-comparative (Germany & Switzerland) 516 subjects	Yasmin 20 • 26 cycles	11,166 cycles for efficacy 11,510 cycles for safety 885 women-years for safety 438 women complete 13 cycles 375 women complete 26 cycles
14523 (A09653) {Cycle control study}	Phase 3 Open-label, randomized, active comparator (Belgium, Czech Republic, Italy, United Kingdom) 220 subjects (Yasmin 20)	Yasmin 20 • 7 cycles 0.15 mg DSG + 20 µg EE,	Yasmin 20 group • 1435 cycles for safety • 110 women-years for safety • 193 women completed 7 cycles

* Yasmin 20 = 3 mg DRSP/0.02 mg EE

DSG = desogestrel

Source: 16 Oct 2003 submission (Table of All Studies) and 18 Mar 2004 submission

4.3 POSTMARKETING EXPERIENCE

The applicant provided the following information:

> "Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.020 mg Tablets have not been approved for marketing in any country to date.

The combination of 3 mg DRSP and 0.030 mg EE (Yasmin tablets, NDA 21-098) has been approved by health authorities worldwide beginning in March 2000 and is now available in over 40 countries."

Medical Officer's Comments:

A discussion of the postmarketing experience with Yasmin is found in the Safety section.

4.4 LITERATURE REVIEW

Applicant's Literature submission

The applicant's literature review contains a summary of the published literature from 1991 to 31 Mar 2003. As a result of the on-line searches, approximately 73 publications (full articles, abstracts, and letters to the editor) were compiled. NDA-21-355 (submitted in 2001) provided a comprehensive summary of the literature on DRSP/EE tablets from 1966 to 01 Jun 2001.

Medical Officer's Comments:

Most of published literature submitted by the applicant refers to Yasmin. Only one published article and information from two poster presentations relates specifically to YAZ. The reference for the published article is the following:

Oelkers W, Foidart JM, Dombrovicz N, Welter A, Heithecker R. Effects of a new oral contraceptive containing an antimineralocorticoid progestogen, drospirenone, on the renin-aldosterone system, body weight, blood pressure, glucose tolerance, and lipid metabolism. J Clin Endocrinol Metab 1995; 80(6): 1816-21.

This study included a treatment arm where women taking the 3 mg DRSP/ 20 mcg EE product for 6 cycles were evaluated in regard to weight loss, blood pressure, renin-aldosterone system, glucose tolerance and lipid metabolism. The findings for the 3 mg DRSP/ 20 mcg EE group include:

- ***Mean body weight fell by 0.68 kg***
- ***Mean systolic blood pressure decreased by 0.9 mmHg***
- ***Mean diastolic blood pressure decreased by 2.3mmHg***
- ***Plasma renin substrate, plasma aldosterone and plasma renin activity increased***
- ***HDL-cholesterol and triglyceride levels increased***

An additional 24 journal articles on drospirenone published since March 2003 were reviewed in PUBMED. None of these articles are specific to the YAZ formulation.

5. CLINICAL REVIEW METHODS

5.1 HOW THE REVIEW WAS CONDUCTED

The review was conducted utilizing the following:

- Review of the electronic submission
- Independent data analysis utilizing JMP software
- Independent review of the literature
- Consultation for safety utilizing the AERS database and ODS consultations
- Consultative meetings regarding the data findings and clinical issues
- Interactions with applicant for clarification and additional data

5.2 OVERVIEW OF MATERIALS CONSULTED IN REVIEW

Materials consulted in review include:

- All electronic submissions for NDA 21-676
- Pertinent submissions to IND 60,738 and other related INDs
- Postmarketing safety reviews for Yasmin
- Consultation reports from the other disciplines
- Pubmed searches and journal review

5.3 OVERVIEW OF METHODS USED TO EVALUATE DATA QUALITY AND INTEGRITY

Methods used to evaluate data quality and integrity include:

- Review of possible bias based on financial ties
- Consultation with DSI regarding clinical site review
- Checking the electronic database with JMP analysis

5.4 WERE TRIALS CONDUCTED IN ACCORDANCE WITH ACCEPTED ETHICAL STANDARDS

The applicant provided the following statement in the clinical study report of the pivotal trial 303740 (source page 19 of study report A12007A)

> "The planning and conduct of this clinical study was subject to national laws. Only when all of the requirements of the appropriate regulatory authority had been fulfilled was the study to start. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP)."

Medical Officer's Comments:

- ***Similar statements of accordance with accepted ethical standards were stated in the other protocols listed under evaluation of financial disclosure (protocols 14523, 301888, 305466 and 14588)***

5.5 EVALUATION OF FINANCIAL DISCLOSURE

The applicant provided the following statement in a PDF file entitled "financial information":

> "This application relies on 5 Phase 2 and 3 clinical studies that establish and support the efficacy of DRSP 3 mg/EE 0.020 mg tablets in a 24-day regimen for oral contraception. Pursuant to 21 CFR 54, FINANCIAL DISCLOSURE BY CLINICAL INVESTIGATORS, Berlex Laboratories, Inc. is providing certification for the investigators who participated in these covered studies, which all began after the final rule became effective on February 2, 1999."

Medical Officer's Comments:

- ***The applicant submitted the appropriate Form 3454 and listed the investigators for the pivotal study 303740, two ovulation inhibition studies (305466 & 14588), cycle control study 14523, and the lipid, hemostatic and carbohydrate metabolism study 301888. The applicant certified that there were no additional disclosures necessary in regard to their clinical investigators related to compensation, proprietary interest, equity interest or receipt of other payments [21 CFR 54.2 (a),(b), and (f)].***
- ***Financial disclosure information for the pivotal 21-day clinical trial was not included and will need to be obtained from the Applicant presumably because this study was not part of the original submission.***

6. INTEGRATED REVIEW OF EFFICACY

6.1 BRIEF STATEMENT OF CONCLUSIONS

The primary efficacy endpoint (acceptable Pearl Index) has been met by the applicant for both the 24-day (303740) and 21-day (303860) regimen (see Table 2).

Table 2: Applicant's and FDA's Estimates of Pearl Indices

Dosing Regimen:	24-day (Protocol 303740)	21-day (Protocol 303860)
Applicant's estimate of Pearl Index: (Based on 11 and 2 pregnancies in Studies 303740 and 303860, respectively)	1.29 (2.30 = upper 97.5%)	0.23 (0.84 = upper 97.5%)
FDA's estimate of Pearl Index (Based on 12 and 3 pregnancies in Studies 303740 and 303860, respectively)	1.42 (0.73-2.47, 2-sided 95% CI)	0.35 (0.07-1.04, 2-sided 95% CI)

Source: 16 Oct 2003 submission, 18 Mar 2004 submission, 4 Nov 2004 submission

Since the highest Pearl Index for an approved combination oral contraceptive is 2.39 both the 24-day and 21-day regimen efficacy results are acceptable. The 21-day regimen results appear better than the 24-day regimen but this could be due to the fact that 21-day study was performed in European countries with high drug compliance rates and this study was carried on for 26 cycles rather than 13 cycles.

6.2 GENERAL APPROACH TO REVIEW OF THE EFFICACY OF THE DRUG

The general approach to reviewing the efficacy of a combination oral contraceptive includes the following:

- Verifying the number of "during treatment" pregnancies (excluding cycles where back-up contraception is being used) to allow for calculation of the Pearl Index
- Compare the calculated Pearl Index to historical FDA data of similar contraceptives.

6.3 PROTOCOL 303740 (REPORT A12007) PIVOTAL CLINICAL TRIAL FOR 24-DAY ACTIVE DOSING REGIMEN

The pivotal phase III trial for contraceptive effectiveness and safety for the 24-day active dosing regimen is protocol number 303740 filed under clinical study report A12007 entitled:

"Multi-Center, Open, Uncontrolled Study to Investigate the Efficacy and Safety of the Oral Contraceptive SH T 186 D Containing 0.02 mg Ethinyl Estradiol Beta-Cyclodextrin Clathrate and 3 mg Drospirenone in a 24-day Regimen for 13 Cycles in 1010 Healthy Female Volunteers"

Medical Officer's Comments:

- ***In the following detailed review of protocol 303740, plain text equates to sections copied directly from the applicant's study report (A12007). Page sources will be listed at the end of the sections. Reviewer's narrative is presented in italics. Reviewer's comments are presented in bolded italics.***

6.3.1 CLINICAL PROTOCOL (DESIGN OF CLINICAL TRIAL)

6.3.1.1 Background

Virtually all synthetic progestogens currently used in oral contraceptives (OCs) do not demonstrate the antimineralocorticoid activity characteristic of endogenous progesterone. As a consequence, even low-dose OCs may lead to sodium retention, which in turn leads to an increase in plasma volume. In conventional OC use this can cause symptoms such as breast tension, edema, weight gain, and occasional increases in blood pressure in susceptible women.

Therefore, research was aimed at the development of an OC containing a low dose of ethinyl estradiol (EE) that could be combined with a progestogen with a pharmacodynamic profile similar to that of progesterone.

During the search for new substances drospirenone (DRSP) was synthesized. The characterization of DRSP's biological effects showed that it combined both antimineralocorticoid and progestogenic properties, thus demonstrating a 'physiological profile' similar to progesterone. In addition, DRSP exhibited an antiandrogenic effect. These antimineralocorticoid and antiandrogenic effects are seen at dose levels, which are applicable for fertility control. As pre-clinical and human pharmacological studies showed, DRSP, in contrast to most currently used progestogens, has no other agonistic activities and, in particular, no estrogenic, no androgenic, and no glucocorticoid effects.

In contraceptive use, DRSP is combined with EE to achieve cycle control. Based on clinical results obtained in phase II studies, the combination of 3 mg DRSP and 0.03 mg EE was selected for the further development of a 0.03 mg EE oral contraceptive. In several multinational phase III studies, the study medication proved to be well tolerated in comparison to reference preparations. This preparation was granted regulatory approval by health authorities and is now available on the market. Experience from marketed OCs demonstrate that the bleeding control properties are still acceptable for most of the users if the daily EE dose is reduced from 0.03 mg to 0.02 mg. Therefore, development of a 0.02 mg preparation was pursued. However, the long-term stability of pharmaceutical formulations containing 0.02 mg EE as a free-steroid was assessed as potentially critical. To ensure the stability of the new formulation, EE was not used as free steroid, but was protected against degradation by the formulation of EE / betadex clathrate. For ease of readability, the content of the active moiety will be referred to as EE in this report, rather than EE betadex.

Source: Clinical Study Report No. A12007, page 26 of 3206

Medical Officer's Comments:

- ***Although the applicant mentions other possible benefits related to the antimineralocorticoid effects of drospirenone, the applicant's present submission is directed solely for approval of YAZ as a contraceptive with no other labeling indications. The applicant has separate ongoing studies that are analyzing other indications such as premenstrual dysphoric disorder and acne.***

6.3.1.2 Study Objectives

The study was to investigate the contraceptive efficacy of ST T 186 D. The Pearl Index (PI) was to serve as primary criterion for the assessment of the contraceptive reliability. In addition, a life table analysis was to be performed.

Cycle control parameters as well as tolerability and safety measurements such as adverse events (AEs), general physical and gynecological examination including cervical smear, safety laboratory, body weight, vital signs, and compliance were to be assessed. In a subgroup of 30 volunteers, endometrial biopsies were to be taken at baseline (visit 2) and at cycle 13 (visit 7) to confirm endometrial safety.

Source: Clinical Study Report No. A12007, pages 26-27 of 3206

6.3.1.3 Entry Criteria (Study Population)

Women aged between 18 and 35 years, requesting contraception, without contraindications for COC use and who were in good general health, were to be screened for participation in the study according to the inclusion and exclusion criteria. Smokers were to be recruited only up to the maximum age of 30 years (inclusive).

Source: Clinical Study Report No. A12007, page 27 of 3206

Inclusion Criteria

1. Healthy volunteer requesting contraception
2. Age between 18 and 35 years (inclusive), smokers maximum age of 30 years at inclusion
3. Pap smear taken or Non-suspicious Pap smear with respect to the last 6 months before study entry
4. For endometrial biopsy subgroup only: biopsy to be taken at visit 2
5. At least 3 cycles had to follow delivery, abortion, or lactation before start of treatment
6. Signed informed consent

Source: Clinical Study Report No. A12007, page 28 of 3206

Medical Officer's Comments:

- ***The age range limits safety the safety data analysis for women > 35 years of age and for smokers age 30-35. These limitations should be included in the label.***

Exclusion Criteria

1. Pregnancy, lactation
2. Known hypersensitivity to any of the study drug ingredients
3. Any disease or condition that might have compromised the function of body systems and which could have resulted in altered absorption, excessive accumulation, impaired metabolism, or altered excretion of the study medication
4. Severe systemic disease that might have interfered with the conduct of the study or the interpretation of the results
5. Uncontrolled thyroid disorders
6. Current or history of clinically significant depression in the last year
7. Abnormal, clinically significant findings which, according to the assessment of the investigator, could have worsened under hormonal treatment
8. Intake of an experimental drug within 30 days prior to inclusion in the study
9. Liver diseases: previous, acute and chronic progressive liver diseases, e.g. disturbances of the bilirubin excretion in the bile (Dubin-Johnson and Rotor syndromes), disturbances of the bile secretion, disturbances in the bile flow (a history of or current cholestasis), idiopathic icterus or pruritus during a former pregnancy or estrogen-progestogen treatment. There was to be an interval of at least 6 months between the subsidence of a viral hepatitis (normalization of the liver parameters) and the start of study medication intake
10. Vascular diseases: existing or previous venous thromboembolic diseases (deep vein thrombosis, pulmonary embolism), existing or previous arterial thromboembolic diseases (myocardial infarction, stroke), and any condition which could have increased the risk to suffer any of the above mentioned disorders, e.g. coagulation disorders, hereditary AT-III, protein-C and / or protein-S deficiency, any venous thromboembolic event that occurred in a

close relative at a younger age, specific heart diseases, cardiac or renal dysfunction, varicose veins, previous phlebitis

11. Uncontrolled arterial hypertension (confirmed systolic blood pressure >140 mmHg or confirmed diastolic blood pressure >90 mmHg)
12. Known diabetes mellitus, impaired glucose tolerance
13. Sickle-cell anemia
14. Known disturbances of lipid metabolism
15. Tumors: malignant tumors or premalignant tumors
16. Other diseases: pemphigoid gestationis during a previous pregnancy, middle-ear deafness (otosclerosis), endometrial hyperplasia, migraine with neurologic symptoms (complicated migraine), genital bleeding of unknown origin, uterus myomatosus confirmed by ultrasonography, manifest kidney disease with impaired renal function (see section 9.8.3, amendment no. 3)
17. Alcohol, drug, or medicine abuse (e.g. laxatives)
18. Prohibited concomitant medication: use of additional sex steroids, hydantoins, barbiturates, phenytoin, primidone, carbamazepin, rifampicin, continuous use of antibiotics over a period of more than 10 days, oxcarbazepine, topiramate, felbamate, ritonavir, griseofluvin, and the herbal remedy St. John's Wort (hypericum perforatum)
19. Other contraceptive methods such as sterilization or intrauterine device
20. Substantial overweight (Body mass index > 35) [1] (see section 9.8.3, amendment no. 3)
21. Clinically relevant pathological safety laboratory results according to a lab instruction sheet which was to be provided by the central laboratory

Source: Clinical Study Report No. A12007, pages 28-30 of 3206

Medical Officer's Comments:

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6.3.1.4 Removal of Subjects from Treatment or Assessment

Every volunteer had the right to refuse further participation in the study at any time and without providing reasons for this decision. A volunteer's participation was to terminate immediately upon her request. The investigator was to seek to obtain the reason and record this on the CRF.

If, at the time of withdrawal of consent, a dose of the investigational product had already been administered, the volunteer was to be advised to agree to follow-up safety investigations. A final examination was to be done even in case of premature discontinuation. In case a volunteer discontinued due to wish for pregnancy, the time to return to fertility was to be documented for up to 1 year, if information was available. All drop-outs were to be observed for 3 months after end of study to collect data on pregnancies after end of study.

The volunteer may have been withdrawn from the study at any time at the discretion of the investigator; the reason was to be fully documented on the CRF. Should the volunteer, during the

course of the study, have developed conditions which would have prevented her entry into the study according to the safety and efficacy related medical exclusion criteria (e.g. absolute contraindications, co-medication), she was to be withdrawn immediately. The reasons were to be fully documented on the CRF.

The termination of an individual's participation was to be considered in case of a serious adverse event (SAE) or considerably worsening of the volunteer's clinical symptoms.

Particularly, the following factors were reasons for immediate termination of the medication for the individual volunteer:

- First signs of venous inflammation or blood clots (thrombosis, embolism), e.g. marked pain or swelling in the legs, stabbing pain on breathing or cough of unknown origin, pain and a feeling of constriction in the chest
- Before scheduled major operations (6 weeks prior), and/or in case of prolonged immobility (e.g. after accidents)
- Migraine headache (hemicranial headache with sudden onset, accompanied by dizziness and vomiting), occurring for the first time or more frequently with unusual severity
- Sudden sensory disturbances (visual, auditory, etc.)
- Motor disturbances (particularly paralysis)
- Pregnancy
- Repeated, excessive, persistent intracyclic bleeding
- Immoderate increase in blood pressure (> 140/90 mmHg)
- 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

The study medication was also to be withdrawn if unusual upper abdominal complaints, which did not rapidly and spontaneously disappear, occurred. In rare cases, benign, and even less frequently, malignant changes of liver tissue have been reported after administration of hormone-based active ingredients such as those contained in study medication. Because individual cases led to life-threatening hemorrhage in the abdominal cavity, imaging procedures to rule out tumors were to be employed early on.

Source: Clinical Study Report No. A12007, pages 30-31 of 3206

6.3.1.5 Treatment (Dosing Schedule)

The overall treatment duration was 13 cycles of 28 days each, i.e. 12 calendar months, without a break between cycles. In each treatment cycle, 24 hormone-containing tablets were to be taken in sequence, followed by a 4-day placebo-tablet period. Each blister pack contained 1 tablet per cycle day, making a total of 28 tablets.

The treatment administered was:

Cycle days 1-24: 3.0 mg DRSP/0.02 mg EE tablets
Cycle days 25-28: Placebo tablets

For both COC switchers and new starters, the first tablet was to be taken on the first day of the withdrawal bleeding, which was then counted as day 1 of the first medication cycle. Thereafter, tablet intake was to follow a predetermined intake plan and was not to be triggered by any bleeding events. Tablets were to be taken orally, once daily.

If the menstrual period started in the evening, women who found it easier to remember to take their study medication in the morning were to take their first tablet in the morning of the following day. Women who found it easier to remember the evening intake were to take their first tablet that evening (i.e. on the same day).

The tablets were to be taken in the morning or evening, but the interval between 2 tablets was to be as close as possible to 24 hours. This interval was not to be exceeded by more than 24 hours, otherwise contraceptive protection might have been compromised. If the volunteer generally took the tablet in the evening before going to bed, the intake was to be documented for the same day, even if she went to bed shortly after midnight.

In case of missed tablets, the volunteer was to take the missed tablet as soon as she remembered, at the latest with the next tablet. If she was less than 24 hours late in taking 1 of the hormone tablets, contraceptive protection was not reduced. If she was more than 24 hours late in taking any of the hormone tablets, contraceptive protection could have been reduced. Missed tablets management was to be based on the following 2 basic rules

Intake of hormones-containing tablets was never to be discontinued for longer than 7 days
Seven days of uninterrupted tablet intake were necessary to attain adequate suppression of the hypothalamic-pituitary-ovarian axis

General recommendations if the volunteer was 24 hours or more late in taking the pill:

Take last missed tablet as soon as remembered even if this means taking 2 tablets at the same time. Continue tablet intake as usual. In addition if within Days 1-24 use back-up contraception for the next seven days. If during days 25-28 no back-up contraception is necessary.

If the woman missed tablets and subsequently had no withdrawal bleeding from day 24 by day 7 of the next cycle (inclusive), the possibility of a pregnancy was to be considered. Pregnancy was to be ruled out immediately at home by a HCG urine test.

Not more than 2 tablets were to be taken on a given day.

If the volunteer vomited within 4 hours after tablet intake, absorption may not have been complete. In such an event, another hormone tablet had to be taken from the reserve blister. The same procedure applied for diarrhea.

Source: Clinical Study Report No. A12007, pages 32-36 of 3206

6.3.1.6 Treatment Compliance

In order to monitor compliance, the volunteers were to record tablet intake daily on their diary cards. At each visit, the completed diary cards were to be collected, reviewed, and signed by the investigator. The original diary card was to become part of the CRF. The volunteer was to note every tablet intake in her diary card. On days without tablet intake, '0' was to be ticked (checked), otherwise the number of tablets swallowed during the day was to be ticked (a maximum of 2 tablets was to be taken on any given day).

Additionally, the volunteer was to return all used, partly used, or unused blisters to the investigator. The returned blisters were to be labeled with volunteer number, study number, and cycle. The return was to be documented on the CRF by the investigator. The blisters were to be balanced and returned to the clinical research associate (CRA). A written explanation was to be submitted for any uneven balance between dispensation, use, and return.

Source: Clinical Study Report No. A12007, page 37 of 3206

6.3.1.7 Study Procedures

The Schedule of Study Procedures is summarized in Table 3.

Table 3: Schedule of Study Procedures (Protocol 303740)

Assessment	S	A	Treatment Days 12-19 of the respective cycle					Final Exam Follow-up Days 10-17
Visit	1	2	3	4	5	6	7	8
Cycle			1	3	6	9	13	After cycle 13
Volunteer information Informed consent	X							
Demographics, Medical history, Entry criteria, Smoking and alcohol history	X	X						
Heart rate, BP, Body weight	X	X	X	X		X		X
General physical	X							X
Gynecological examination	X					Cycle 6		X
Cervical smear	X	R				Cycle 6		X
Blood and urine sample	X	R	X			Cycles 6,13		X
Endometrial Biopsy (subgroup only)		X	R			Cycle 13		R
AE/concomitant medications			X	X		X		X
Back-up contraception			X	X		X (except visit 7)		X
Medication dispensed		X		X		4 cycles of medication given at cycle 9		
Diary cards dispensed		X				Daily entries by volunteer		
Blisters and diary cards returned				X		X (except visit 7)		X
HCG-urine test dispensed		X				As required (a)		
Subjective assessment of well being								X

Abbreviations in the table: S = Screening, A = Admission, R = Result
(a) In absence of monthly bleeding (in Austria, pregnancy test had to be performed in every cycle; for US in case of pregnancy, the pregnancy report form had to be filled in.
Source: Clinical Study Report No. A12007, page 40 of 3206

6.3.1.8 Discontinuation

Every volunteer had the right to refuse further participation in the study at any time and without providing reasons for this decision. A volunteer's participation was to terminate immediately upon her request. The investigator was to seek to obtain the reason and record this on the CRF.

If, at the time of withdrawal of consent, a dose of the investigational product had already been administered, the volunteer was to be advised to agree to follow-up safety investigations. A final examination was to be done even in case of premature discontinuation. In case a volunteer discontinued due to wish for pregnancy, the time to return to fertility was to be documented for up to 1 year, if information was available. All drop-outs were to be observed for 3 months after end of study to collect data on pregnancies after end of study.

The volunteer may have been withdrawn from the study at any time at the discretion of the investigator; the reason was to be fully documented on the CRF. Should the volunteer, during the course of the study, have developed conditions which would have prevented her entry into the study according to the safety and efficacy related medical exclusion criteria (e.g. absolute contraindications, co-medication), she was to be withdrawn immediately. The reasons were to be fully documented on the CRF.

The termination of an individual's participation was to be considered in case of a serious adverse event (SAE) or considerably worsening of the volunteer's clinical symptoms.

At the discretion of the study manager, the entire study may have been canceled for medical reasons. In addition, Schering / Berlex Laboratories retained the right to end the study at any time if the study could not have been carried out as agreed upon in the protocol.

Particularly, the following factors were reasons for immediate termination of the medication for the individual volunteer:

- First signs of venous inflammation or blood clots (thrombosis, embolism), e.g. marked pain or swelling in the legs, stabbing pain on breathing or cough of unknown origin, pain and a feeling of constriction in the chest
- Before scheduled major operations (6 weeks prior), and/or in case of prolonged immobility (e.g. after accidents)*
- Migraine headache (hemicranial headache with sudden onset, accompanied by dizziness and vomiting), occurring for the first time or more frequently with unusual severity
- Sudden sensory disturbances (visual, auditory, etc.)
- Motor disturbances (particularly paralysis)
- Pregnancy
- Repeated, excessive, persistent intracyclic bleeding
- Immoderate increase in blood pressure (> 140/90 mmHg)
- 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

The study medication was also to be withdrawn if unusual upper abdominal complaints, which did not rapidly and spontaneously disappear, occurred. In rare cases, benign, and even less frequently, malignant changes of liver tissue have been reported after administration of hormone-based active ingredients such as those contained in study medication. Because individual cases led to life-threatening hemorrhage in the abdominal cavity, imaging procedures to rule out tumors were to be employed early on.

In case of premature termination or suspension of the study, the study manager was to promptly inform the investigator / institutions, regulatory authorities, and IEC / IRBs of the termination or suspension and the reason for the measure.

In case women were not admitted to the study after the screening phase (i.e. were not assigned a volunteer number), the screening process was to continue to achieve the number of volunteers agreed on for the center. Data generated from screening failures were to be listed according to main reason for not being admitted into the treatment phase."

Source: Clinical Study Report No. A12007, page 30-31 of 3206

6.3.1.9 Pregnancy Testing

A HCG urine test (pregnancy home test) was to be performed at home by the volunteer before the first tablet intake. In the US, the first HCG urine test was to be performed in the investigator's office within 1 week prior to the first dose of study medication. If the volunteer did not get her menses within 2 weeks of the negative pregnancy test, she then was to return to the investigator's office for an additional pregnancy test before start of study medication. At the investigator's discretion, the volunteer was to take a home pregnancy test the day her menses started. A negative result was prerequisite for (further) medication. If throughout the study no bleeding occurred until day 7 of the subsequent cycle, the volunteer had to perform a pregnancy test at home*. The test was to be provided by Schering AG. If the test result was positive, the medication was immediately to be stopped. The volunteer was to be asked to agree to further follow-up examinations. In the case of a (suspected) pregnancy, immediate reporting to the applicant was to follow.

* In Austria, a pregnancy test had to be performed in every cycle. In the US, the pregnancy test had to be performed at the site of the investigator instead of the volunteer's home

The investigator was to submit a complete report for any pregnancy detected during the study (i.e. after recruitment) or which might have been exposed to the treatment (i.e. detected after the study) to the study manager immediately. This report was to be sent on the Pregnancy Report Form provided by Schering AG. The investigator was required to document, as far as possible, the calculated time of conception, the diagnostic measures used, and the course of pregnancy, including the pregnancy outcome.

The investigator was also to ascertain if the volunteer had taken any other substance or had a concomitant illness which might have affected absorption, or if there were any tablet-taking errors, vomiting, or diarrhea.

All pregnancies occurring in the course of the study were to be followed up for the final outcome of both mother and child. To document the pregnancy outcome, the respective pregnancy outcome form was to be filled in by the investigator.

Source: Clinical Study Report No. A12007, page 46-47 of 3206

6.3.1.10 Primary Efficacy Endpoint and Analysis Plan (Pregnancy Rate Based on Pearl Index)

The primary efficacy variable was the number of observed unintended pregnancies and was to be used to calculate the Pearl Index (PI).

The date of conception was to be determined applying the diagnostic measures ultrasonography, gynecological examination, last menstrual period and bleeding information from the volunteer, determination of gestational age at delivery, and quantitative HCG determination (pregnancy test). In the case of any inconsistencies between the different diagnostic measures, the most accurate one (i.e. higher in hierarchy) was to be used.

The PI was the primary criterion to assess contraceptive reliability. It was to be assessed assuming that all volunteers were at risk for pregnancy in all medication cycles unless back-up contraception, medication with contraceptive side effect, or any other reason which reduced the chance of conception were documented.

At each visit, the investigator was to collect information on back-up contraceptive measures (e.g. condoms, postcoital pill as emergency contraceptive) and note them on the CRF."

All volunteers who belong to the FAS, i.e. all volunteers who took at least 1 unit of study medication and where at least 1 observation after study medication intake was available, were included into the calculation of the PI until they dropped out. The length of the drug-free interval, i.e. 4 days was added to the exposure time for each volunteer. Hence treatment exposure was defined as the last day of pill intake plus 1 minus first day of pill intake plus 4. It should be noted that this time period was calculated irrespectively of treatment interruptions.

There were 2 exceptions to this rule

- Treatment exposure after conception was not counted
- Treatment exposure during which additional contraceptive measures (back-up contraception) were taken was not counted

If a volunteer used back-up contraception or if no information was available whether back-up contraception was used, the respective cycle was not included into treatment exposure.

The first day of pill intake was derived from the diaries. The last day of pill intake was derived from CRF panel 'End of Study Medication' (EOSM).

The number of pregnancies was derived as follows: a pregnancy for which the estimated day of conception was during treatment or not later than 4 days after the last day of pill intake was regarded as 'during treatment'.

Source: Clinical Study Report No. A12007, pages 41,53,64,65 of 3206

Medical Officer's Comments:

- ***A window of 14 days should be used rather than 4 days.***

6.3.1.11 Secondary Analysis of Efficacy (Life Table Analysis)

The cumulative failure rate, i.e. the probability of getting pregnant, was to be calculated using the Kaplan Meier estimator on the basis of unintended pregnancies which became known within the framework of the study, including the follow-up.

Source: Clinical Study Report No. A12007, page 41 of 3206

6.3.1.12 Diary Cards

The diary card recorded the following:

- *Date*
- *Day when new package was started*
- *Number of tablets taken (0,1,2)*
- *Bleeding (none, spotting, light, normal, heavy)*

Source: Clinical Study Report No. A12007, page 42 of 3206

6.3.1.13 Secondary Outcomes

The bleeding pattern indices and the cycle control parameters were analyzed as secondary efficacy parameters.

Based on the day-to-day data obtained from the diary cards, the bleeding pattern was to be descriptively reported using reference periods of 90 days. For each woman and for each reference period, the number of bleeding days and bleeding episodes was to be calculated. A bleeding/spotting episode was defined as a number of days with bleeding / spotting preceded and followed by at least 2 bleed-free days; correspondingly, a spotting-only episode was defined as a number of days with spotting preceded and followed by at least 2 bleed-free days. A bleeding-free interval consists of at least 2 days without bleeding/spotting preceded and followed by at least 1 bleeding/spotting day.

Additionally, regular bleeding and intracyclic bleeding episodes were to be identified and analyzed. A regular bleeding episode during treatment was defined as the first bleeding episode from day 25 on. In case a bleeding episode was ongoing on the last day of the EE / DRSP combination period and also on the following day, this episode was to be regarded as the withdrawal bleeding episode, provided it did not start more than 4 days before the hormone withdrawal. Both the onset and the duration of the episodes were to be assessed. All other (unexpected) bleeding episodes were to be considered intracyclic bleeding. If no bleeding occurred until the next hormonal withdrawal, this was to be assessed as absence of regular bleeding in the preceded treatment cycle.

Source: Clinical Study Report No. A12007, pages 43, 66, of 3206

6.3.1.14 Study Amendments

Amendment No. 1 (July 19, 2000)

The changes noted in this amendment were the following:

- *Safety labs were instituted at all sites at baseline, cycle 1, cycle 6, cycle 13 and the follow-up visit*
- *Precautions were provided regarding samples for analysis of potassium (avoiding tourniquets if possible, releasing tourniquet immediately after venipuncture, avoiding high negative pressure on the syringe, avoiding potassium containing specimen tubes, discarding hemolyzed samples)*
- *Laboratory samples will be processed according to the same standard in all countries under the supervision of one laboratory*
- *"Clinically relevant pathological safety laboratory results" added as exclusion criteria*
- *"All women that are predisposed to hyperkalemia" added as exclusion criteria*
- *Clarified that for the USA pregnancy tests will be performed at the study site rather than at home as stated in the protocol*

Source: Clinical Study Report No. A12007, pages 66-70 of 3206

Amendment No. 2 (August 14, 2000)

The changes noted in this amendment were the following:

- Revised the wording of the first urine pregnancy test to read:

  "The first test: a urine pregnancy test will be done in the investigators office within 1 week prior to the first dose of study medication. If the subject does not get her menses within 2 weeks of the negative pregnancy test then she must return to the office for another pregnancy test before starting study medication. At the investigators discretion the subject will take a home pregnancy test the day her menses starts"

- Revised the wording of the laboratory safety exclusion criterion no. 21 to read:
  "Clinically relevant pathological safety laboratory results according to a lab instruction sheet which will be provided by the central laboratory"

Source: Clinical Study Report No. A12007, pages 70-71 of 3206

Amendment No. 3 (January 24, 2001)

The changes noted in this amendment were the following:

- *Removing endometriosis as an exclusion criterion for the study*
- *Adding new prohibited concomitant medications (oxcarbazepine, topiramate, felbamate, ritonavir, griseofulvin and St. John's Wort)*
- *Elevation of the upper BMI limit to 35 kg/m2*
- *Deletion of the exclusion criteria "All women that are predisposed to hyperkalemia"*
- *Increased the allowed interval for missing tablets from 12 hours to 24 hours*
- *Removed a typographical error in relationship to defining the withdrawal bleeding episode*

- *Corrected a typing error that resulted in a missing urinalysis procedure*
- *Corrected a typing error with regard to the numbering of visits under treatment*

Source: Clinical Study Report No. A12007, pages 71-75 of 3206

6.3.2 PROTOCOL 303740 (REPORT A12007): DEMOGRAPHICS, SUBJECT DISPOSITION, AND EFFICACY OUTCOMES

6.3.2.1 Study Period / Study sites

The study ran from 2 Nov 2000 to 14 Jan 2003. There were 35 study sites: Austria (15), Argentina (7), Brazil (8), Poland (4), United States of America (1) See Appendix section 3 for the number of subjects studied at each site.

6.3.2.2 Disposition of Volunteers

Of 1202 women initially screened there were 153 screening failures. Of the 1,049 women eligible for treatment:

- *746 completed medication and the study*
- *273 discontinued prematurely (70 were for adverse events, see Safety section)*
- *20 were never administered medication*
- *10 were listed as unknown*

Medical Officer's Comments:

- ***Of the 1049 women eligible, the applicant considered 1027 as the number in the full analysis set for efficacy and safety (taken at least 1 tablet of study medication or had at least 1 visit after study medication intake.) 22 were included as listing only.***
- ***The applicant stated that 678 qualified for the per-protocol-set.***

Source: Clinical Study Report No. A12007, pages 82-85 of 3206

6.3.2.3 Premature Discontinuation

The reasons for premature discontinuation from study medication (273) include:

Adverse events: 70
Lost to follow-up: 50
Withdrawal of consent: 34
Protocol deviation: 28
Pregnancy: 11
Other: 80

6.3.2.4 Protocol Deviations

Medical Officer's Comments:

- ***This reviewer did not find protocol violations that impacted the efficacy analysis of the product***

Source: Clinical Study Report No. A12007, page 84 of 3206

6.3.2.5 Demographics and Medical Histories

The mean age in the ITT population (referred to as the FAS or full analysis set by the Applicant) was 24.7 years. The mean BMI was 22.4 kg/m2. Evaluation of ethnicity showed 87.8% Caucasian, 4.6% Hispanic, 4.3% Black, 1.2% Asian and 2.1% classified as "other". In terms of educational level 47.9% had some secondary education. Seven (7) subjects listed themselves as sexually inactive (and were excluded in the medical officer's calculation of the Pearl Index). Of the ITT population, 25.6% were smokers. Of these smokers, 54 subjects were listed as smoking more than 10 cigarettes per day. The majority of the subjects had never given birth before (69.9%). A previous history of intracyclic bleeding was noted in 6.4% of subjects.

Source: Clinical Study Report No. A12007, pages 84-87 of 3206

6.3.2.6 Contraceptive Method Used at Screening

The contraceptive methods used and the percentage of subjects using them just prior to study start were:

- *None (11.0%)*
- *OCs (59.7%)*
- *Condoms (27.1%)*
- *IUDs (0.3%)*
- *Other (1.9%, this includes three using depot contraceptive – PIDs 441, 540, 1046)*

Source: Clinical Study Report No. A12007, pages 88–89 of 3206

6.3.2.7 Pregnancies Reported for Study 303740 (Case Listings)

Pretreatment Pregnancies (Conceptions)

There were 18 pregnancies reported as identified either during primary screening or in randomized subjects but prior to starting study drug. The countries and PID numbers for these subjects are as follows:

- *Argentina (n = 5, PIDs 564, 579, 552, 595, 753)*
- *Austria (n = 5, PIDs 468, 966, 1065, 1335, 1017)*
- *Brazil (n = 7,PIDs 1252, 1169, 1113, 1212, 1185, 1194, 885)*
- *Poland (n = 1, PID 932)*

Source: A12007 Study Report Table 261 (page 3118 of 3206)

Medical Officer's Comments

- ***There were 2 additional pregnancies where conception occurred prior to the onset of short-term use of study drug (Table 4). In both cases, the subjects took study drug for 6 days. Early sonogram gestational dating established that the conception date for each occurred before the date of first use of study drug.. For PID 39, the applicant provided an estimated date of conception as 15 Feb 01. However, this reviewer's calculation of the date***

of conception, based on the sonogram, was about a week earlier (i.e., 7 Feb 01 as listed in Table 4).

Table 4: Pregnancies (Conceptions) Classified as Occurring Before the Onset of Treatment in Subjects Who Were Exposed to Study Drug for <7 days (Protocol 303740)

PID	DFT	DLT	ExD	LMP	EDconcep	Treatment period	Comment
589	23 Jan 02	28 Jan 02	6		Nov-Dec 01	Before	Sono on 16 Jan 02 indicates 7-8 week pregnancy
39	21 Feb 01	26 Feb 01	6	4 Jan 01	7 Feb 01	Before	Sono on 22 Mar 01 indicates 8 wk pregnancy

PID = Patient Identification number; DFT = Date of first treatment dose; DLT = Date of last treatment dose; ExD = Exposure duration; Edconc = Estimated day of conception; LMP = Last menstrual period start date; EDconcep = Estimated date of conception
Source: A12007 Study Report Table 261 (page 3118-19 of 3206)

During Treatment Pregnancies (Conceptions)

Pregnancies identified by the Applicant and/or Medical Reviewer for which conception occurred "during treatment" or within 14 days after the final dose of study drug are listed in Table 5.

Table 5: Pregnancies (Conceptions) That Occurred "During Treatment" or Within 14 days of Last Dose of Study Drug (Protocol 303740)

PID	DFT	DLT	ExD	LMP	EDconcep	Treatment period	Comment
92	4 Sep 01	14 Mar 02	191	8 Feb 02	25 Feb 02	During	Although the applicant lists this as a method failure the subject reported not being very compliant with pill taking. This was a 22 year subject at the US site. The pregnancy outcome was induced abortion
168	12 Feb 01	24 Jun 01	132	10 May 01	24 May 01 (sono)	During	Subject missed "extra" three pills for the 24 active dosing. The pregnancy outcome for this 36 year old from Austria is not known.
721	1 Aug 01	5 Dec 01	126	29 Oct 01	7 Nov 01 (sono)	During	Considered method failure by applicant. This 21 year old from Argentina had a full term healthy male infant on —
871	29 Sept 01	4 Jan 02	97	22 Dec 01	6 Jan 02 (sono)	After by 2 days	This case counts as a subject failure, conception occurred during a non-compliant cycle. This 23 year old from Brazil had a healthy full term female infant on —
1110	13 Aug 01	21 Jul 02	342	13 Jun 02	2 Jul 02 (sono)	During	Considered method failure by applicant. This 26 year old from Brazil had a healthy full term infant on —
1171	30 Jul 01	28 Oct 01	90	4 Oct 01	19 Sep 01	During	Subject took medication incorrectly at time of conception. This 26 year old from Brazil had a full term healthy female on —
1253	6 Aug 01	17 Feb 02	195	21 Jan 02	28 Jan 02	During	Considered a subject failure but the missed pills appear to have occurred after the conception date. This 27 year old from Brazil delivered a full term healthy female on — would consider this as a method failure.
1256	13 Jul 01	14 Feb 02	216	11 Jan 02	25 Jan 02 (sono)	During	Subject missed 6 tablets around the time of conception. The pregnancy outcome for this 30 year old from Brazil is not known
1273	4 Sep 01	19 Mar 02	196	18 Mar 02	20 Mar 02 (sono)	After by 1 day	Considered method failure by applicant. The pregnancy outcome for this 21 year old from Brazil is not known
1289	18 Aug 01	18 Jan 02	153	3 Dec 01	16 Dec 01 (sono)	During	Considered method failure by applicant, although the subject missed many pills. This 21 year old from Brazil is reported to have delivered a healthy 2600 gram female — about a month before her due date
1317	22 May 01	23 Mar 02	305	24 Feb 02	10 Mar 02 (sono)	During	Subject missed "early" pills in conception cycle. This 30 year old from Austria delivered a full term male on —
1338	14 Dec 00	23 Dec 01	374	22 Dec 01	5 Jan 02	After by 12 days	There was no comment about non-compliance for this subject around the time of conception, so I would consider her to be a method failure. This 20 year old from Austria underwent an induced abortion.

PID = Patient Identification number; DFT = Date of first treatment dose; DLT = Date of last treatment dose; ExD = Exposure duration; Edconc = Estimated day of conception; LMP = Last menstrual period start date, Edconcep = Estimated date of conception
Source: Clinical Study Report No. A12007, pages 97, 163-167 of 3206

Medical Officer's Comments:

- ***The applicant included 11 of the above 12 pregnancies in their pearl index calculation. This reviewer believes that Subject 1338 should also be classified as a "during treatment"***

conception because the estimated date of conception falls within 14 days of the date of the last tablet intake.

- ***None of the subjects with "during treatment" pregnancies weighed more than 75 kg.***

The number of conceptions that occurred during treatment or within 14 days of treatment (both method and subject failures) by countries are as follows:

- *US (n = 1, 1 method failure)*
- *Austria (n =3, 1 method failure, 2 subject failures)*
- *Argentina (n = 1, 1 method failure)*
- *Brazil n = 7, (3 method failures, 4 subject failures)*

Medical Officer's Comments:

- ***Brazil had a disproportionately high number of pregnancies compared to the number reported from the study sites in other countries. In the full analysis set (FAS) of 1027 subjects, Brazil contributed 190 subjects. Based on the percentage of subjects who became pregnant during the treatment period in the overall clinical trial, 2-3 pregnancies, rather than 7, should have been reported from sites in Brazil.***

Posttreatment Pregnancies (Conceptions)

There were 3 pregnancies (conceptions) reported by the Applicant that occurred more than 14 days after the last dose of study drug. They are listed in Table 6.

Table 6: Pregnancies (Conceptions) That Occurred > 14 days After Last Dose of Study Drug

PID	DFT	DLT	ExD	LMP	EDconcep	Treatment period	Comment
602	23 Nov 01	14 Mar 02	111	Unknown	May 02 (sono)	After by 49 days	This 25 year old from Argentina had an induced abortion.
604	18 Nov 01	15 Dec 01	27	13 Dec 01	22 Jan 02	After by 38 days	This 18 year old from Argentina had a spontaneous abortion on 22 Mar 02
1238	10 Aug 01	12 Aug 02	367	6 Sep 02	8 Oct 02 (sono)	After by 57 days	This 25 year old from Brazil delivered a premature healthy male (1450 grams) on

PID = Patient Identification number; DFT = Date of first treatment dose; DLT = Date of last treatment dose; ExD = Exposure duration; Edconcep = Estimated day of conception; LMP = Last menstrual period start date; EDconcep = Estimated date of conception

Source: Clinical Study Report No. A12007, pages 97 and 163, Table 261 TT25

6.3.2.8 Primary Efficacy Analysis (Pearl Index Estimates of Pregnancy Rates)

The number of cycles (excluding those in which back up contraception was used) utilized by the applicant in their original calculation of the Pearl Index was 11,140 cycles. The applicant's original Pearl Index of 1.29 pregnancies per 100 women-years of use was based on 11 "during treatment" pregnancies.

Utilizing 12 "during treatment' pregnancies (i.e., adding PID 1338) results in the following PI calculation:

Pearl Index = 12 x 1300 / 11140 = 1.40 (calculation by Medical Reviewer)

As mentioned earlier in the demographics section, 7 subjects were listed as not being sexually active. The number of cycles from these 7 subjects included in the "at risk" for pregnancy dataset is 81 cycles. Subtracting 81 cycles from 11140 = 11059. Recalculation of the pearl index gives:

Pearl Index = 12 x 1300/ 11059 = 1.41 (calculation by Medical Reviewer)

Either Pearl Index (1.29 or 1.41) is acceptable. The highest Pearl Indices for clinical trials supporting approval of combination oral contraceptives has been in the 2.39 range.

On 4 Nov 2004, the applicant recalculated, at the request of the Division, the Pearl Indices for the 24-day regimen. These recalculations were based on 12 "during treatment" pregnancies with the proper exclusions (i.e., no cycles during which backup contraception was used, no women >35 years at entry, and no sexually inactive women). The recalculated PI and the 2-sided 95% confidence intervals (95% CIs) are provided in Table 7 *numbers are similar to my calculation.*

Table 7: Final Pearl Index Values for 24-day Active Dosing Regimen (Protocol 303740)

Total time of exposure		Days with backup contraception	Adjusted exposure		Pearl Index	2-sided 95% confidence interval
Days	Cycles		Days	Cycles		
317,228	11,330	7842	309386	11,050	**1.42**	**0.73-2.47**

Medical Officer's Comments

- ***The applicant in the original submission proposed a method failure Pearl Index ("perfect use" Pearl Index) of 0.72, based on their assessment that (1) 5 pregnancies were method failures and (2) there were 252,281 at risk days during which study drug was properly (i.e., the number of compliant days used in the denominator of the calculation).***
- ***I would add 2 subjects (Nos. 1253 and 1338) to the list of method failures. Therefore, based on 252, 281 compliant days/ 28 days per cycle = 9010 compliant cycles, my calculation of the method failure Pearl Index is:***

  Method Failure Pearl Index = 7 x 1300 / 9010 = 1.0 pregnancies/100 women-yrs

- ***Recalculation by subtraction of the cycles of the sexually inactive subjects does not alter this result. Method failure Pearl indices are not included in the clinical section of the label. The usefulness of this index can be debated. Different applicants have different definitions for compliant cycles.***

6.3.2.9 Life Table Analysis (Secondary Analysis for Primary Efficacy Endpoint)

Applicant's Original Estimation. *Based on 11 "during treatment' pregnancies, the applicant's estimation of the 1 year pregnancy rate according to Kaplan Meier life table analysis, in their original submission was* ***1.26% with a 95% confidence interval of [0.52%; 2.01%].***

Applicant's Revised Estimation. *Based on 12 "during treatment" pregnancies, the life table recalculation resulted in a higher estimated cumulative failure rate with a wide 95% confidence interval* ***(2.2% [95% CI: 21%; 4.2%]).***

Medical Officer's Comment:

- ***The wide CI resulted because the added 12th pregnancy occurred at end of the study (day 388) with relatively few remaining subjects.***

6.3.2.10 Secondary Efficacy Endpoints

Medical Officer's Comments:

- ***Cycle control issues regarding bleeding patterns will be discussed in the safety section.***
- ***The applicant's quality of life analysis included physical and emotional well being questions.***

Source: Clinical Study Report No. A12007, page 169 of 3206

6.3.2.11 Statistical Analysis Plan

All subjects in the full analysis set who took at least one dose of study medication and had at least one postbaseline observation were included in the calculation of the Pearl Index until they dropped out. The length of the drug free interval (4 days) was added for each subject. The Pearl Index was defined as the number of pregnancies divided by the exposure in women years multiplied by 100.

Source: ISE, Study Report A12007, page 13 of 47.

6.4 PROTOCOL 303860 (REPORT A15129) PIVOTAL CLINICAL TRIAL FOR 21-DAY ACTIVE DOSING REGIMEN

The pivotal phase III trial for contraceptive effectiveness and safety for the 21-day active dosing regimen was Protocol Number 303860 filed under clinical Study Report A15129 entitled:

"Multi-center, open, uncontrolled study to investigate the efficacy and safety of the oral contraceptive SH T 186 D containing 0.02 mg ethinyl estradiol and 3 mg drospirenone in a 21-day regimen for 26 cycles in 504 healthy female volunteers"

Medical Officer's Comment:

- ***In the following review of protocol 303860, plain text generally represents narrative/data copied directly from the applicant's Study Report (A15129). Source page references, for the most part, are listed at the end of each section. This Reviewer's descriptions of study findings are generally presented as non-bolded, italicized text while this reviewer's comments are presented as bolded and italicized text.***

6.4.1 CLINICAL PROTOCOL (DESIGN OF CLINICAL TRIAL)

6.4.1.1 Study Objectives

The primary efficacy objective of this study was to determine the contraceptive efficacy of Yasmin 20 (21-day) based on the number of pregnancies that occurred "during treatment." The Pearl Index (PI) served as primary method of analysis for the assessment of the contraceptive effectiveness. In addition, Contraceptive effectiveness was also presented in terms of a life table analysis of the cumulative risk of pregnancy.

Tolerability and safety measurements such as adverse events, physical and gynecological examinations including cervical smear, body weight, vital signs, and cycle control parameters (e.g., intermenstrual bleeding and failure to have withdrawal bleeding) also were assessed.

Source: Clinical Study Report No. A15129, pages 23 of 908

Medical Officer's Comment:

- ***As mentioned in other sections of the review this 21-day active dosing regimen, according to the Applicant, is not being proposed for marketing in the U.S.***

6.4.1.2 Entry Criteria (Study Population)

Women between the age of 18 and 35 years, requesting contraception, without contraindications for COC use who were in good general health, were to be screened for participation in this study according to the inclusion and exclusion criteria. Smokers were to be recruited only up to the maximum age of 30 years.

Source: Clinical Study Report No. A15129, pages 27 of 908

Medical Officer's Comment:

- ***The inclusion and exclusion criteria are essentially the same as found in protocol 303740 with minor wording changes.***

6.4.1.3 Removal of Subjects from Treatment or Assessment

This section was identical to that of Protocol 303740.

Source: Clinical Study Report No. A15129, pages 31 of 908

6.4.1.4 Treatment (Dosing Schedule)

After assignment of volunteer numbers (= randomization numbers), each individual was to receive medication for 26 treatment cycles. In each treatment cycle, 21 hormone-containing tablets were to be taken in sequence (one blister pack), followed by a tablet-free interval of 7 days. Each cycle lasted a total of twenty-eight days. The overall treatment duration was planned to consist of 26 cycles of 28 days each, i.e., 24 calendar months. Each subsequent cycle was to start immediately after the previously completed cycle without a break between cycles.

- ***Cycle days 1 – 21: hormone-containing tablets (0.02 mg EE+ 3 mg DRSP)***
- ***Cycle days 22 – 28: tablet-free interval of 7 days***

Each volunteer was to receive medication for 26 treatment cycles. Each blister pack SH T 186 D had 21 hormone containing tablets. For both COC switchers and new starters, the first tablet was to be taken on the first day of the withdrawal bleeding, which was then counted as Day 1 of the first medication cycle. On the last seven cycle days, no tablet was to be taken. Thereafter, tablet intake was to follow a predetermined intake plan and was not to be triggered by bleeding events. Tablets were to be taken orally, once daily.

6.4.1.5 Treatment Compliance

In order to monitor compliance, the volunteers were to record tablet intake daily on their diary cards. At each visit, the completed diary cards were to be collected, reviewed, and signed by the investigator. The original diary card became part of the CRF.

6.4.1.6 Study Procedures

The Schedule of Study Procedures is summarized in Table 8.

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Table 8: Schedule of Study Procedures for Protocol 303860

Assessment	S	A	Treatment Days 12-19 of the respective cycle									Final Exam Follow-up Days 10-17 after last tablet
Visit	1	2	3	4	5	6	7	8	9	10	11	12
Cycle			3	6	9	12	15	18	21	24	26	> cycle 26
Volunteer information, Informed consent	X											
Demographics Entry criteria Medical history Medication history	X	X										
Smoking and Alcohol evaluation	X											
Heart rate, BP, Body weight	X	X	X	X								X
Physical examination	X			Visit 4 (Cycle 12)								X
Gynecological examination	X			Visits 4,6 and 8 (cycles 6,12 and 18)								X
Cervical smear	X	R		Visits 4,6 and 8 (Cycles 6,12 and 18)								X
HCG urine test dispensed		X	As required in absence of menstrual bleeding									
HCG urine test results		X	X									X
AE/concomitant medications			X	X								X
Back-up contraception			X	X								X
Medication dispensed		X	X	X (except visit 11)								
Diary cards dispensed		X	Daily entries by volunteer									
Blisters and diary cards returned			X	X								X
Subjective assessment of well being												X

Abbreviations in the table: S = Screening, A = Admission, R = Result

Source: Clinical Study Report No. A15129, pages 26 of 908

6.4.1.7 Pregnancy Testing

Urine pregnancy testing was performed by the subject at home before the first tablet was taken (on the first day of the period). Urine pregnancy tests were dispensed in the absence of monthly bleeding. If a pregnancy was diagnosed the pregnancy report form was completed.

6.4.1.8 Primary Efficacy Endpoint and Analysis Plan (Pregnancy Rate based on Pearl Index)

The primary efficacy variable was the number of observed unintended pregnancies and was to be used to calculate the Pearl Index.

All pregnancies, which became known within the framework of this study (i.e., number of pregnancies; primary efficacy variable), including the post-study follow-up, were to be reported in detail on the respective forms.

The total number of pregnancies under treatment was to be considered the numerator of the PI. The PI and the corresponding 95% confidence interval were calculated according to the Committee for Proprietary Medical Products (CPMP) Guidance on clinical investigation of steroid contraceptives in women. The date of conception was determined applying the following

diagnostic measures: ultrasonography, gynecological examination, last menstrual period and bleeding information from the volunteer, determination of gestational age at delivery, and quantitative HCG determination (pregnancy test). In the case of any inconsistency between the different diagnostic measures, the most accurate one (i.e., higher in hierarchy) was to be used.

The Pearl Index was the primary criterion to assess contraceptive reliability. It was assessed assuming that all volunteers were at risk for pregnancy in all medication cycles unless back-up contraception, medication with contraceptive side effect or any other reason which reduced the chance of conception were documented.

At each visit, the investigator was to collect information on back-up contraceptive measures (e.g., condoms, post-coital pill as emergency contraceptive) and note them on the CRF.

Source: Clinical Study Report No. A15129, pages 36 of 908

6.4.1.9 Secondary Analysis of Efficacy (Life Table Analysis)

The cumulative failure rate, i.e., the probability of getting pregnant, was calculated using the Kaplan Meier estimator on the basis of unintended pregnancies, which became known within the framework of the study, including the follow-up.

Source: Clinical Study Report No. A15129, pages 36 of 908

6.4.1.10 Diary Cards

The diary card recorded the following:

- *Date*
- *Day when new package was started*
- *Number of tablets taken (0,1,2)*
- *Bleeding (none, spotting, light, normal, heavy)*

Source: Clinical Study Report No. A15129, pages 37 of 908

6.4.1.11 Secondary Outcomes

Based on the day-to-day data obtained from the diary cards, the bleeding pattern was to be descriptively reported using reference periods of originally planned 90 days. Since seven treatment cycles comprise the required 180 days, this time period was chosen although it was slightly enlarged compared to the originally stated time period. For each woman and for each reference period, the number of bleeding days and bleeding episodes were to be calculated.

6.4.1.12 Statistical Analysis Plans

All volunteers who have taken at least one unit of study medication and for whom at least one observation after dosing was available were included in the full analysis set (FAS). The other volunteers were classified as 'listing only'. This means their data were presented in the individual volunteer data listings but were not included in any statistical analysis.

The primary target variable (occurrence of a pregnancy) was evaluated on the FAS only. For the secondary target variables (bleeding patterns and cycle control parameters), both a PPS analysis and an analysis based on the FAS have been performed. For the safety variables only an analysis based on the FAS was done. Additionally the subjective assessment of the volunteer was also analyzed for the PPS.

Source: Clinical Study Report No. A15129, pages 52-53 of 908

6.4.2 PROTOCOL 303860 (REPORT A15129): DEMOGRAPHICS, SUBJECT DISPOSITION, AND EFFICACY OUTCOMES

6.4.2.1 Study Period / Investigators

The study ran from August 29, 2000 to April 11, 2003. There were 34 investigators at 33 study centers. There were 27 study centers in Germany and 6 in Switzerland.

6.4.2.2 Disposition of Volunteers

The disposition of the volunteers was as follows:

545 Screened

- *18 Screening failures (13 related to exclusion criteria, 2 withdrew consent, 3 unknown)*
- *527* ***Admitted for treatment*** *(0.02 mg/d EE + 3 mg/d DRSP)*
  - *6 Admitted but never started medication (4 withdrew consent, 2 found to be pregnant)*
  - *5 Lost to follow-up (medication intake unknown)*
  - *140 discontinued medication [AEs (38); withdrew consent (32); protocol deviation (3); lost to follow-up (20); pregnancy (3); other (43); unknown (1)]*
  - ***376 Completed 2 yrs of treatment***

Medical Officer's Comment:

Of the 527 subjects admitted to treatment, the applicant considered that 516 (140 plus 376) belonged to the FAS (ITT) and 401 qualified to be in the per-protocol set.

6.4.2.3 Premature Discontinuation from Study

Study medication was completed by 376 volunteers (71.3%). Study medication was never started by 6 volunteers (1.1%) and the reasons given were withdrawal of consent for 4 (0.8%) volunteers, and pregnancy for 2 (0.4%) volunteers.

For a total of 140 volunteers (26.6%) premature discontinuation of the study medication was documented. Reasons were further specified as AEs for 38 volunteers (7.4%), lost to follow-up for 20 volunteers (3.8%), withdrawal of consent for 32 volunteers (6.1%), protocol deviations for 3 volunteers (0.6%), pregnancy for 3 volunteers (0.6%) and unknown for 1 volunteer (0.1%). Other reasons were given for 43 volunteers (8.2%) and were in most cases specified as wish for pregnancy or unavailability due to moving.

Source: Clinical Study Report No. A15129, page 61 of 908

6.4.2.4 Protocol Deviations

The protocol deviations included these major categories:

- *Time schedule deviations*
- *Treatment deviations*
- *Excluded concomitant medication*
- *Entry criteria errors at study entry*
- *Missing observations (vitals, weight)*
- *Missing source data (diary cards in 5 cases)*

Medical Officer's Comment:

- ***None of the protocol violations are believed to have an impact on the efficacy analysis.***

6.4.2.5 Demographics and Medical History

The mean age at screening in the FAS was 24.6 years. The mean BMI at screening in the FAS was 22.4 kg/m2. In the FAS 29.8% were smokers. Of the smokers 44 reported smoking more than 10 cigarettes per day. At screening 84.1% of the volunteers had never given birth. A history of intracyclic bleeding was reported by 6.4% of volunteers. A history of amenorrhea was reported by 4.3% of volunteers.

The ethnic make up of the FAS was as follows:

- *Caucasian = 506 (98.1%)*
- *Asian = 3 (0.6%)*
- *Hispanic = 3 (0.6%)*
- *Black = 2 (0.4%)*
- *Other = 2 (0.4%)*

Medical Officer's Comments:

- ***Although this study was conducted in Germany and Switzerland and there are very few African Americans, there is no reason to suspect that this oral contraceptive would have altered efficacy in this ethnic group.***
- ***Six (6) subjects in the FAS were listed as having no sexual relations (were sexually inactive). Review of the August 23, 2004 dataset submission, indicated that these subjects contributed the following numbers of "at risk" treatment cycles:***

  PID Cycles
  189 = 26
  193= 26
  363= 12
  371= 5
  650 = 5
  664 = 27

- ***Thus, an additional 101 cycles should be subtracted from the 11,165 at risk cycles used by the Applicant for the original efficacy analysis. This was done in the Applicant's revised analyses of efficacy submitted on 4 November 2004.***

Source: Clinical Study Report No. A15129, pages 63-67 of 908

6.4.2.6 Contraceptive Methods Used at Screening

The contraceptive methods used by the volunteers before study start are:

- *Oral contraceptives (77.9%)*
- *Condoms (11.6%)*
- *IUDs (0.8%)*
- *Other (0.8%, three of these were Depo-Clinovir, recalculating the Pearl Index with these three subjects excluded did not change the Pearl Index)*
- *None (8.9%)*

6.4.2.7 Pregnancies Reported for Study 303860 (Case Listings)

Pretreatment Pregnancies (Conceptions)

Table 9 provides case listings for the 2 pregnancies that were classified as occurring before start of treatment.

Table 9: Pregnancies Occurring Before Start of Treatment in Protocol 303860

PID	V#	EDConcep
123	77	2 Oct 00
114	344	22 Jan 01

PID = Patient identification number, V# = Volunteer number
EDConcep = Estimated date of conception
Source: Clinical Study Report No. A15129, pages 108 of 908

During Treatment Pregnancies (Conceptions)

Table 10 provides case listings for the 2 pregnancies (conceptions) classified by the Applicant as occurring "during treatment."

Table 10: Pregnancies Occurring During Treatment in Protocol 303860

PID	V#	Med start	Med end	EDConc	Comment
135	81	18 Sept 00	15 Jul 01	4 Jul 01	The applicant considers this to be a volunteer failure. This subject was 21 years (BMI=30)
201	142	18 Oct 00	29 Jul 01	9 Jul 01	The applicant considers this to be a method failure. This subject was 20 years (BMI=30)

PID = Patient identification number, V# = Volunteer number, Med start = Start date of medication
Med end = Ending date of medication, EDConcep = Estimated date of conception
Source: Clinical Study Report No. A15129, pages 108 of 908

Posttreatment Pregnancies (Conceptions)

Listings for pregnancies classified as occurring after treatment by the Applicant are listed in Table 11.

Table 11: Pregnancies Occurring After Treatment in Protocol 303860

PID	V#	Med start	Med end	EDConc	Comment
35	37	16 Sept 00	29 Dec 00	11 Jan 01	The applicant considered this after use of study drug. However it is within a 14-day window. The sonogram dating the pregnancy was performed on 6 Feb 2001. Subject delivered on [redacted]
249	202	30 Oct 00	1 July 01	20 Aug 01	This pregnancy occurred significantly after the end of study drug. Subject delivered on [redacted]
246	190	19 Nov 00	18 Aug 01	7 Jan 02	This pregnancy occurred significantly after the end of study drug. Subject delivered on [redacted]

V# = Volunteer number
Source: Clinical Study Report No. A15129, pages 108 of 908

Medical Officer's Comment:

- ***Since the estimated date of conception for subject 35/37 is within 14 days of the last dose of study drug, I would classify this pregnancy as having an onset "during treatment."***

After Study Pregnancies (Conceptions)

The applicant classified 10 pregnancies as "after study" pregnancies in addition to the "after treatment" pregnancies. The "after study" pregnancies are listed in Table 12.

Table 12: After Study Pregnancies Occurring in Protocol 303860

PID	V#	Med start	Med End	EDConc	Outcome
25	26	9 Sep 00	26 Oct 01	15 Mar 02	Spontaneous abortion 17 Apr o2
138	93	11 Oct 00	1 Oct 02	13 Jan 03	Delivery on [redacted]
169	116	24 Nov 00	6 Mar 02	17 Jun 02	Delivery on [redacted]
204	145	18 Nov 00	16 Aug 02	25 Oct 02	Delivery on [redacted]
179	148	9 Oct 00	16 Feb 02	20 Sep 02	Missed abortion detected on 1 Nov 02
257	212	1 Nov 00	9 Feb 02	7 Apr 02	Spontaneous abortion 4 Jun 02
325	223	N/A	N/A	14 Jun 01	Delivery on [redacted]
368	469	27 Oct 00	18 Oct 01	2 Apr 02	Delivery on [redacted]
354	487	11 Dec 00	25 Feb 01	27 May 01	Delivery on [redacted]
510	598	14 Jan 01	22 Jun 02	12 Jul 02	Delivery on [redacted]

V# = Volunteer number
Source: Clinical Study Report No. A15129, pages 108 of 908

Medical Officer's Comment:

- ***Subject 325/223 withdrew consent and never took study medication. All of the pregnancies that the applicant lists as "after study" show estimated dates of conception that are significantly past the last dose of study medication. All of the full term deliveries occurred close to the estimated date of delivery.***

6.4.2.8 Primary Efficacy Analysis (Pearl Index Estimates of Pregnancy Rates)

Based on three rather than 'during treatment' pregnancies the Pearl Index for the 21-day product is

3 X 1300/ 11165 cycles = 0.35

On 4 Nov 2004 the applicant recalculated their Pearl Indices for the 21-day regimen. This is based on 3 pregnancies with the proper exclusions (no backup contraception, no women >35 years and no sexually inactive women) These numbers are similar to my calculation.

Table 13: FDA's Estimate of Pearl Index for the 21-day Regimen

21-day regimen (protocol 303860)						
Total time of exposure		Days with backup contraception	Adjusted exposure		**Pearl Index**	**2-sided 95% confidence interval**
Days	Cycles		Days	Cycles		
317,302	11,332	8166	309136	11,040	**0.35**	**0.07-1.04**

6.4.2.9 Life table analysis (Secondary Analysis for Primary Efficacy Endpoint)

Based on 3 rather than "during treatment" pregnancies, the life table calculation resulted in an estimated cumulative failure at 297 days of 0.0065 [95% CI: 0.0000; 0.0139]

6.4.2.10 Secondary Efficacy Variables

Cycle control parameters and bleeding pattern were assessed as secondary efficacy variables and are described in the safety section.

6.4.3 REVIEWER'S OVERALL ASSESSMENT OF EFFICACY FOR YASMIN 20

- The primary efficacy endpoint (an acceptable Pearl Index) has been met by the applicant in Protocol 303740 for the 24-day regimen (Pearl Index is 1.42 [95% CI: 0.73;2.47])
- The primary efficacy endpoint (an acceptable Pearl Index) has been met by the applicant in Protocol 303860 for the 21-day regimen (Pearl Index is 0.35 [95% CI: 0.07;1.04])
- Since the highest Pearl Index, to date, for an approved combination oral contraceptive is 2.39, both the 24-day and 21-day regimen efficacy results are acceptable. The 21-day regimen results appear better than the 24-day regimen but this could be due to the fact that (1) the 21-day study was performed in European countries with high drug compliance rates and (2) this study was carried on for 26 cycles rather than 13 cycles.
- Study Protocol 14523, a smaller comparative clinical trial) also provided additional efficacy support for the 21-day regimen (Pearl Index of 0.95).

7. INTEGRATED REVIEW OF SAFETY

7.1 BRIEF STATEMENT OF CONCLUSIONS

There are no safety findings in the clinical trials of the 24-day and 21-day regimens that would preclude approval. There is no evidence from the clinical trials of Yasmin 20 or from the postmarketing surveillance trials of Yasmin that hyperkalemia poses a concern. There is no evidence of increased thromboembolic events (above expected rates) in the clinical trials of Yasmin 20. There is strong supportive safety data from two prospective safety surveillance studies that the approved drospirenone containing combination oral contraceptive (Yasmin) does not have higher thrombotic or thromboembolic adverse events than other commonly used oral contraceptives.

Although there is no safety signal that precludes approval of the 24-day regimen, the 21-day regimen is preferable since there is less hormone exposure and no additional confirmed clinical benefits demonstrated to date.

7.2 DESCRIPTION OF PATIENT EXPOSURE TO STUDY DRUGS

*The extent of exposure (number of subjects with 21 and 24-day dosing) is described in the following table (*Table 14*). This table is derived from the 16 Oct 2003 original submission, ISS and the additional 21-day regimen study (303860) submitted 18 Mar 2004*

Table 14: Number of Subjects Exposed in Studies with 21 or 24 Day Dosing Regimen

Study Phase	Yasmin 20 (24 day regimen)	Yasmin 20 (21 day regimen)	Yasmin 20 (21 + 24 day regimen)	Yasmin 30
1	0	48	48	0
2	0	53	53	0
3	1056	736(a)	1803	566
Totals	**1056**	**848**	**1904**	**566**

(a) Of 736 using Yasmin 20 (21 days) in Phase 3, 220 were from 16 Oct 2033 submission and 516 were from study 303860
Source: Text Table 2, ISS, 16 Oct 2003 submission and clinical study report A15129, page 3 of 908

There were 114 additional subjects in Phase 1 single dose studies who took varying doses of either drospirenone alone (1, 3 and 6 mg) or in conjunction with ethinyl estradiol (DRSP= 3 mg and 6 mg, EE = 0.02 mg and 0.04 mg). Exposure data for these subjects are listed in Table 15.

Table 15: Subjects exposed by Study Phase in Single Dose and DRSP Only Studies

	Single Dose				DRSP only		
Study Phase	3 mg DRSP + 0.02 mg EE	6 mg DRSP + 0.04 mg EE	6 mg DRSP + 0.04 mg EE (free steroid)	6 mg DRSP + 0.04 mg EE (suspension)	1 mg DRSP	3 mg DRSP	6 mg DRSP
1	36	18 (a)	18 (a)	18 (a)	12	36	12
2	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0
Totals	36	18 (a)	18 (a)	18 (a)	12	36	12

(a) For subjects participating in a crossover study, each subject is counted only once in the "Totals"
Source: Page 23 of 109 in ISS (16 Oct 2003) submission

Treatment information, based on 28-day cycle exposure from the 16 Oct 2003 submission, are listed in Table 16. These data do not include treatment cycles from the pivotal efficacy and safety study for the 21-day dosing regimen.

Table 16: Number of Subjects Exposed to any Dose of DRSP by Study Phase and Cycles of Exposure (16 Oct 2003 submission)

Study Phase	Total Exposure in 28-Day Cycles							Any exposure to DRSP
	NCO	PE	≤1	>1-4	>4-8	>8-12	>12-16 (a)	
Phase I	114	0	48	0	0	0	0	162
Phase 2/3	0	31	41	160	825	89	749	1895
Total	114	31	89	160	825	89	749	2057

DRSP = drospirenone, NCO= not cycle oriented intake (single dose), PE= possible exposure, drug dispensed but use unknown
(a) 746 completed 13 cycles

Not represented in Table 16 are the 516 subjects in the full analysis set of Study 303860 (principal study for the 21-day regimen). Of these subjects, 438 completed through cycle 13 and 375 completed through cycle 26.

Treatment information, based on 28-day cycle exposure and subject age, from the 16 Oct 2003 submission, are listed in

Table 17. These data do not include treatment cycles from the pivotal efficacy and safety study for the 21-day dosing regimen. Not represented in the Table are the 516 subjects in the full analysis set of Study 303860 (principal study for the 21-day regimen).

Table 17: Number of Subjects Expose to Any Dose of DRSP by Age and Total Cycles of Exposure

Age Group (years)	Total Exposure in Cycles (28 day)							Total
	NCO	PE	≤1	>1-4	>4-8	>8-12	>12-16	
15-22	14	17	20	53	371	28	281	784
23-26	15	3	24	59	201	33	227	562
27-30	19	5	21	29	117	21	144	356
31-34	21	4	22	15	86	7	86	241
35-44	3	2	2	4	50	0	11	72
45-54	8	0	0	0	0	0	0	8
55+	34	0	0	0	0	0	0	34
Total	114	31	89	160	825	89	749	2057

DRSP = drospirenone, NCO= not cycle oriented intake (single dose), PE= possible exposure, drug dispensed but use unknown.

Medical Officer's Comments:

- ***As noted in the preceding table there is very little exposure data on women older than 35 years of age.***
- ***An additional 516 subjects were exposed to Yasmin 20 (21 day cycle regimen) in Study 303860 submitted as Study Report A15129 in the four month safety update. Of the 516 subjects who started in study 303860, 438 went on to complete cycle 13 and 375 went on to complete cycle 26 (source: Table 95, Study report A15129 page 576 of 1143)***

The exposure to Yasmin 20 in the three large phase III studies (protocols 303740, 303860 and 14523) based on 28-day cycles and women-years of exposure are listed in Table 18.

Table 18 Exposure to Yasmin 20 in Protocols 303740, 303860 and 14523

Protocol	Number of subjects	Cycles without BU	Cycles with BU	Total 28-day cycles	Total exposure in women-yrs
303740 (24-day regimen)	1027	11,140	340	11,480	883
303860 (21-day regimen)	516	11,165	345	11,510	885
14523 (21-day regimen; cycle control study)	220	NL	NL	1,435	110
Total	1,763	22,305	685	24,425	1878

BU = Back up contraception; NL = not listed

Sources: Derived from Study Report A12007 (303740), Study Report A15129 (303860) and Study Report; Study Report A9653 (14523)

7.3 OVERVIEW OF THE METHODS AND ORGANIZATION OF THE SAFETY REVIEW

This section contains the safety data from the 24-day regimen (protocol 303740), the 21-day regimen (protocol 303860), integrated safety data from other studies submitted to the 16-Oct-2003 original submission, and 4-month safety update information. Additional safety information in the Appendix consists of case listing of thrombotic and thromboembolic adverse events (section 6) and consultative information for the Office of Drug Safety (section 8).

7.4 PROTOCOL 303740: PIVOTAL CLINICAL TRIAL FOR 24-DAY REGIMEN

7.4.1 SAFETY METHODS ASSESSMENTS AND COLLECTION OF SAFETY DATA

7.4.1.1 Study Visits

The Schedule of Study Procedures, including scheduled safety assessments, is summarized in Table 19

Table 19 Schedule of Study Procedures (Protocol 303740)

Assessment	S	A	Treatment Days 12-19 of the respective cycle					Final Exam Follow-up Days 10-17
Visit	1	2	3	4	5	6	7	8
Cycle			1	3	6	9	13	After cycle 13
Volunteer information, Informed consent	X							
Demographics, Medical history, Entry criteria, Smoking and alcohol history	X	X						
Heart rate, BP, Body weight	X	X	X	X		X		X
General physical	X							X
Gynecological examination	X					Cycle 6		X
Cervical smear	X	R				Cycle 6		X
Blood and urine sample	X	R	X			Cycles 6,13		X
Endometrial Biopsy (subgroup only)		X	R			Cycle 13		R
AE/concomitant medications			X	X		X		X
Back-up contraception			X	X		X (except visit 7)		X
Medication dispensed		X		X		4 cycles of medication given at cycle 9		
Diary cards dispensed		X	Daily entries by volunteer					
Blisters and diary cards returned				X		X (except visit 7)		X
HCG-urine test dispensed		X				As required (a)		
Subjective assessment of well being								X

Abbreviations in the table: S = Screening, A = Admission, R = Result
(a) In absence of monthly bleeding (in Austria, pregnancy test had to be performed in every cycle; for US in case of pregnancy, the pregnancy report form had to be filled in.
Source: Clinical Study Report No. A12007, page 40 of 3206

Information concerning adverse events was to be obtained at each clinical visit (i.e. ,at cycles 1, 3, 6, 9, 13 and the final examination)

7.4.1.2 Endometrial safety

To demonstrate the endometrial safety of the 24-day regimen, endometrial biopsies were to be conducted for a subgroup of 30 volunteers at baseline (visit 2) and at cycle 13 (visit 7).

7.4.1.3 Clinical Lab Safety Monitoring

The safety labs consisted of the following:

- *Sodium, potassium, chloride*
- *Fasting blood glucose*
- *Blood urea nitrogen / creatinine*
  Calcium, phosphorus
- *Uric acid*
- *Total bilirubin*
- *Total protein, albumin*
- *Cholesterol total, HDL-cholesterol, LDL-cholesterol, triglycerides*
- *SGOT (AST), SGPT (ALT), alkaline phosphatase, gamma-glutamyltransferase*
- *T3 uptake, T4, FT4 I (free thyroxin index) at baseline visit*
- *Urinalysis*

Source: Clinical Study Report No. A12007, page 67 of 3206

Precautions for Proper Handling of Blood Samples for Potassium Analysis

False increases in potassium concentrations can occur and are usually related to venous stasis resulting from a combination of tourniquet compression and muscular activity before venipuncture (repeated fist clenching). This common practice was to be avoided, if possible, and it was recommended that warm arm or hand packs be used instead.

The following list gave general recommendations for the handling of blood samples:

- If possible, the blood samples for potassium analysis were to be taken without a tourniquet.
- If this procedure was not feasible, the tourniquet was to be released immediately after venipuncture; withdrawal of blood was to start only 2 minutes thereafter.
- A distinct negative pressure when the blood was drawn into the syringe had to be avoided in order to prevent hemolysis (e.g. by rapid withdrawal if a cannula of low diameter was used).
- Blood was not to be ejected vigorously into the collection tube and the collection tubes had to be kept at room temperature.
- Potassium containing (such as potassium oxalate) specimen tubes were to be avoided.
- After centrifugation, the sample was to be assessed visually and photometrically for hemolysis. If hemolyzed, the sample was to be discarded and a further sample was to be taken.

Source: Clinical Study Report No. A12007, page 52 of 3206

Medical Officer's Comment:

- ***Despite these precautions, there were still episodes of hemolytic specimens and transport problems resulting in apparent pseudohyperkalemia. This is fully described later in this review in the section on serum potassium concentrations.***

7.4.2 SAFETY FINDINGS

7.4.2.1 Deaths

Two deaths were reported for subjects participating in Protocol 303740.

PID #40. Approximately 1 month after discontinuation of the study treatment, the volunteer suddenly died. She had received her first dose of study medication on 22 Feb 2001. She returned to the clinic on 12 Mar 2001 and reported a self-diagnosed upper respiratory infection beginning on 8 Mar 2001, which she treated with Tylenol Cold Capsules from 9 Mar to 10 Mar 2001. The volunteer missed study visit 4 on 3 May 2001. She was contacted by the site on 4 May 2001 and reported experiencing nausea and vaginal spotting and elected not to continue in the study. She informed the site that she had discontinued study medication 2 weeks prior on 20 Apr 2001. In an attempt to reschedule a termination visit, the study site contacted the volunteer's workplace and was notified that the volunteer had expired on while on vacation in Jamaica. The deceased had died almost a sudden death. Based on autopsy findings, observations from toxicological analyses of stomach contents and blood sample (dated 21 Aug 2001) and histopathological examination of tissues from various internal organs, the opinion as to the cause of death is acute hemorrhagic pancreatitis and pulmonary edema, secondary to toxic effects of Endosulfan (an organochlorine pesticide) and caffeine. The vaginal spotting which had started on 1 May 2001 was considered a non-serious adverse event of mild intensity, continuous, and had required no drug treatment. It was classified as being probably related to the study medication by the study investigator. The nausea which had started on 1 May 2001 was also considered a non-serious adverse event of mild intensity, intermittent, and had required no drug treatment; it was classified as being possibly related to the study medication by the study investigator. Both events had reportedly resolved on 22 Apr 2001.

Source: Clinical Study Report No. A12007, page 2207 of 3206

PID # 61. Approximately 3 months after start of the study treatment, the volunteer suddenly died. The cause of death as listed on the certificate of death was carbon monoxide toxicity sustained from inhalation of fumes caused by a fire in her apartment building on

Source: Clinical Study Report No. A12007, page 2208 of 3206

Medical Officer's Comment:

- ***Neither of these deaths is felt to be related to study drug.***

7.4.2.2 Serious Adverse Events

The reported serious adverse events and the Investigators' assessment of their relationship to study drug are listed in Table 20.

Table 20: Serious Adverse Events in Study Protocol 303740

PID	V#	Country	HARTS term	Relation	Discontinue
14	172	Austria	Migraine	Probable	Yes
14	172	Austria	Epistaxis	Possible	Yes
14	172	Austria	Depression	Probable	Yes
40	1226	USA	Death, pesticide poisoning	None	-
61	1236	USA	Death, accidental injury	None	-
193	111	Austria	Surgery (arthroscopy of knee)	None	No
243	181	Austria	Accidental injury (ruptured tendon)	None	No
244	182	Austria	Accidental injury (dog bite)	None	No
277	131	Austria	Ovarian cyst	None	No
277	131	Austria	Surgery (chronic tonsillitis)	None	No
337	219	Austria	Surgery (conization)	None	No
363	108	Austria	Abdominal pain (pelvic inflammatory disease)	None	No
420	313	Austria	Surgery (appendicitis)	None	No
422	318	Austria	Upper respiratory infection (acute tonsillitis)	None	No
424	316	Austria	Surgery (appendicitis)	None	No
512	267	Austria	Hernia	None	No
545	955	Argentina	Vascular disorder (congenital etiology)	Possible	Yes
589	1113	Argentina	Abortion	Unlikely	Yes
604	1021	Argentina	Abortion	Unlikely	Yes
643	1085	Argentina	Accidental injury (burns)	None	No
668	1054	Argentina	Suicide attempt other than overdose	Unlikely	Yes
743	1016	Argentina	Papanicolaou smear suspicious (HSIL)	Possible	No
745	1018	Argentina	Bone fracture (not spontaneous)	None	Yes
844	595	Poland	Eye disorder, Headache,, Myasthenia, Neuropathy	Possible	Yes
973	384	Austria	Surgery (chronic tonsillitis)	None	No
974	385	Austria	Cholelithiasis	None	No
1019	438	Austria	Laboratory test abnormal (creatinine increase)	Unlikely	No
1033	359	Austria	Laboratory test abnormal (creatinine increase)	Unlikely	No
1093	652	Brazil	Psychotic depression	Unlikely	Yes
1133	692	Brazil	Accidental injury	None	Patient lost
1143	701	Brazil	Allergic reaction (bronchitis)	None	No
1160	773	Brazil	Pyelonephritis	None	No
1196	789	Brazil	Pharyngitis	Unlikely	No

Source: Clinical Study Report No. A12007, page 121 of 3206

Medical Officer's Comment:

- ***The relationship of cholelithiasis to study drug is considered possible for PID 974.***
- ***A summary for Subject PID 545 is provided below.***

Approximately 8 months after starting study treatment, PID 545 (vol. no. 955) suffered a severe meningeal syndrome with headache, vomiting, and photophobia from which she recovered following treatment. An MRI performed 2 weeks earlier had diagnosed a probable vascular malformation in the protuberance, and this was confirmed 2 weeks after the meningeal syndrome by a second MRI. The volunteer was treated for meningeal syndrome and recovered. Encephalic

vascular malformation is a congenital condition. It is possible that the meningeal syndrome was a complication of the encephalic malformation, but this was not confirmed by the second MRI, which showed no changes to the previous MRI. The applicant therefore assessed the study drug relationship as being unclassifiable due to insufficient data. The investigator assessed that the symptoms were possibly related to the study treatment.

Source: Clinical Study Report No. A12007, pages 122-123 of 3206

Medical Officer's Comment:

- ***There does not appear to be a thrombotic etiology for the subject 545's symptomatology.***

7.4.2.3 Discontinuations Due to Adverse Events

There were 69 subjects listed in the disposition section of this review that were noted to have premature discontinuation due to adverse events. Table 21 *lists the number of subjects who reported experiencing these adverse events. Many of the subjects had more than one adverse event listed as the reason for their discontinuation.*

Table 21: Adverse Events Leading to Study Drug Discontinuation (Protocol 303740)

Adverse event contributing to discontinuation	Number of incidents
Headache	14
Intermenstrual bleeding	7
Nausea	7
Depression	6
Libido decreased	6
Dysmenorrhea	5
Emotional lability	5
Vomiting	5
Abdominal pain	4
Breast pain	4
Migraine	4
Weight gain	4
Acne	3
Rash	3
Asthenia	2
Back pain	2
Dizziness	2
Edema	2
Lab test abnormality	2
Menorrhagia	2
Somnolence	2
Sweating increased	2
Allergic reaction	1
Amenorrhea	1
Bone fracture	1
Breast enlargement	1
Constipation	1
Dermatitis	1
Diarrhea	1
Dry skin	1
Dyspepsia	1
Epistaxis	1
Erythema nodosum	1
Eye disorder	1
Face edema	1
Flatulence	1
Leukorrhea	1
Menstrual disorder	1
Metrorrhagia	1
Muscle cramps	1
Myasthenia	1
Nervousness	1
Neuropathy	1
Oral moniliasis	1
Pain in extremity	1
Pelvic pain	1
Peripheral edema	1
Pruritus	1
Suicide attempt	1
Vaginal moniliasis	1
Vascular disorder (Meningeal syndrome)	1

Source: Derived by reviewer from AE02 by Medical Reviewer (Adverse Event Dataset 16 Oct 2033 submission)

Medical Officer's Comment:

- ***Headache was the adverse event that contributed most often to premature discontinuation (14/1027 = 1.3%). In the Seasonale principal clinical trial [a] headaches accounted for discontinuation of 0.4% of the Seasonale users and 1.8% of the subjects taking the Nordette comparator. Therefore, Yasmin 20 (24 day))is in the same percentage range as other COCs. When counting headaches plus migraine, the percentage of subjects discontinuing for headaches in the Yasmin pivotal trial [b] was also 1.3% (NDA 21-098). In the Yasmin trial the most common AE leading to discontinuation was intracyclic bleeding (1.6%).***

[A] Source = NDA 21-544, page 49 of medical officer review.
[B] Source = NDA 21-098 page 20 of medical officer review.

7.4.2.4 Adverse Events

A listing of the adverse events by HARTS coding that were reported in >2 % of subjects and the number (%) of the 1027 subjects reporting each of them is found in Table 22.

Table 22: Adverse Events (>2%) in Protocol 303740

HARTS term	N	%
Headache	137	13.3
Upper respiratory infection	137	13.3
Breast pain	71	6.9
Vaginal moniliasis	67	6.5
Leukorrhea	58	5.6
Diarrhea	52	5.1
Nausea/ Vomiting	47	4.6
Vaginitis	45	4.4
Abdominal pain	42	4.1
Flu syndrome	39	3.8
Dysmenorrhea	38	3.7
Allergic reaction	33	3.2
Accidental injury	32	3.1
Urinary tract infection	32	3.1
Cystitis	31	3.0
Tooth disorder	29	2.8
Sore Throat	28	2.7
Infection	26	2.5
Fever	24	2.3
Surgery	23	2.2
Sinusitis	23	2.2
Back pain	21	2.0

Source: Clinical Study Report No. A12007, pages 1470-1476 of 3206

Medical Officer's Comment:

- ***These percentages of adverse events are less than that seen with Yasmin (Headache 19.9%, Breast pain 14.9%, Abdominal pain 12.0%, Vaginal moniliasis 9.7% - from medical officer review of Yasmin NDA 21-098, page 18 of 74)***

7.4.2.5 Cervical Smear Results

At cycle 6 and the final examination, cervical smears were abnormal in 1.8% and 2.2%, respectively. These percentages are not greater than that seen in the general population over that period of time. ASCUS rates run as high as 5-6%.

Source: Clinical Study Report No. A12007, page 160 of 3206

7.4.2.6 Endometrial Biopsy Results

Endometrial biopsies were performed in 2 centers in Austria (center nos. 5 and 14) at baseline (visit 2) and at cycle 13 (visit 7) in a subgroup only. In case of insufficient tissue at baseline, the volunteer was no longer part of the biopsy group but could continue with the study. At baseline, endometrial biopsies were performed in 49 volunteers and were assessed as normal in 37 volunteers. Twelve biopsies were not assessable. At cycle 13, 38 volunteers were still within the endometrial subgroup. Biopsies assessed were normal in 25 volunteers, were not assessable in 8 volunteers, and were not done in 5 volunteers.

Of 27 biopsies assessed as normal at baseline, 21 were assessed as normal at cycle 13, 4 were not assessable, and 2 were not done. Of 11 biopsies not assessable at baseline, 4 were assessed as normal at cycle 13, 4 were still not assessable, and 3 were not done.

Source: Clinical Study Report No. A12007, page 167 of 3206

Medical Officer's Comment:

- ***Review of the dataset HISPAT01 shows that the histologic reporting was divided into normal, abnormal and not assessable. There were no abnormal reports. There was no discussion of the hormonal changes associated with Yasmin 20. The histologic effects of combination oral contraceptives on the endometrium have been well documented since introduction of COCs in the 1960s. Higher strength progestins in the pill result in small scanty inactive glands and decidualized appearing endometrial stroma. Pills with lower strength progestins have less of these effects and may result in a weakly secretory type pattern. The only pills ever to produce hyperplastic changes in the endometrium were sequential pills like Oracon. There is no indication in either the oral contraceptive literature in general or in the postmarketing safety for Yasmin of any reports of rare uterine malignancies (either epithelial or stromal).***

7.4.2.7 Vital Signs and Body Weight

There were no significant mean changes in heart rate or blood pressure. Eleven (11) subjects (0.1%) had elevated systolic (>140 mmHg) or diastolic (>90 mmHg) blood pressure at more than 1 visit.

The mean body weight at screening, cycle 13 and final examination was 61.0, 60.9 and 61.1, respectively.

Source: Clinical Study Report No. A12007, pages 158 and 160 of 3206 and

Medical Officer's Comment:

- ***Increased blood pressure values are a known effect of oral contraceptives. Higher dose COCs have been reported to induce hypertension in up to 5% of users (Reference: Speroff, Clinical Gynecologic Endocrinology and Infertility, 1999, page 895)***

7.4.2.8 Safety Lab Results

Lipid Measurements

The screening and final values for total-, HDL-, and LDL-cholesterol and triglycerides, and the mean changes for these values in women using Yasmin 20 are listed in Table 23). Also listed in the Table are the mean changes for these lipid measurements in women who used Yasmin obtained from the NDA for Yasmin.

Table 23: Mean Lipid Concentrations in Users of Yasmin 20 (Protocol 303740) or Yasmin

Lab Parameter	Yasmin 20 (24 day regimen) (mg/dL)			Yasmin (mg/dL)
	Screening	Final	Mean change	Mean change
Total Cholesterol	183.6	195.5	+11.9	+15.7
HDL-Cholesterol	61.3	66.2	+4.9	+9.5
LDL-Cholesterol	107.0	110.1	+4.1	+2.3
Triglycerides	101.4	116.9	+15.5	+21.3

Source: Medical officer review for Yasmin (NDA 21-098) and YAZ Clinical Study Report No. A12007, pages 130-132 of 3206

Medical Officer's Comment:

- ***Yasmin 20, like Yasmin, shows mean increases in all lipid parameters. These changes overall are similar to those associated with many other oral contraceptives. The long term clinical significance of these small changes is not known.***

General Blood Chemistry Measurements

Mean alkaline phosphatase concentrations decreased slightly (minus 7.3 U/L). Mean total protein and albumin concentrations decreased slightly (minus 1.9 g/L and 1.2 g/L, respectively). Mean glucose levels were essentially unchanged throughout the study.

Hematology

There were no significant mean changes in hematologic parameters.

Electrolytes (see separate section for potassium)
There were no significant mean changes in sodium, calcium, chloride or inorganic phosphate.

Liver and kidney parameters
There were no significant mean changes in GGT, ASAT, ALAT bilirubin, BUN, uric acid or creatinine. There were some individual increased levels of creatinine compared to baseline, but these appeared to be lab errors (repeat testing was normal) or were minor increases associated with urinary tract infections.

Urinalysis
There were no significant changes in urinalysis findings overall. The mean erythrocyte count was increased but this was found to be associated with two outlier subjects (PID 1173 and 1196) The mean leukocyte count was also increased but found to be influences by three outlier subjects (PID 1184, 1227 and 1250).

Source for the above lab information: Clinical Study Report No. A12007, pages 126-148 of 3206

7.4.2.9 Potassium Measurements

Mean potassium levels varied only slightly throughout the study. Potassium values were within the reference range for the majority of volunteers at all time points.

Source: Clinical Study Report No. A12007, page 141 of 3206

The reference range for potassium in the central lab for this study was 3.6-5.0 mmol/L. The mean and median values along with the mean changes from baseline are listed in Table 24

Table 24: Mean Potassium Levels During Protocol 303740

Visit	Mean/median absolute value (mmol/L)				Mean change from baseline (mmol/L)		
	N	Mean	SD	Median	N	Mean	SD
Screening	1020	4.25	0.34	4.20			
Cycle 1	980	4.29	0.37	4.30	978	0.05	0.42
Cycle 6	872	4.20	0.41	4.20	870	-0.05	0.46
Cycle 13	714	4.25	0.43	4.20	713	0.01	0.46
Final	915	4.18	0.58	4.10	913	-0.07	0.63

Source: Clinical Study Report No. A12007, page 141 of 3206

Single potassium values above 5 mmol/L were reported for 65 volunteers. In most of theses cases, values were only slightly increased and did not exceed the alert range (>5.75 mmol/L). For 14 volunteers potassium values above the alert range were recorded after the screening visit. In volunteers (PIDs 949, 320, 854, 325, 943, 945), potassium values reached levels not compatible with life. For none of the volunteers with potassium values above the alert range, were any AEs, likely to be related to hyperkalemia. In all cases, potassium values were normal at the next visit and /or were verified as within the normal range by repeated tests at the same time point. In 1 volunteer, the unphysiologically high

potassium value was caused by a hemolytic blood sample as shown by high serum hemoglobin concentration (PID 1310 / vol. no. 689 at cycle 13). In several other cases, pre-analytical problems are suspected because the occurrences of unphysiologically high potassium values were clustered in 3 centers.

Source: Clinical Study Report No. A12007, pages 151-152 of 3206

Medical Officer's Comments:

- ***The applicant was asked to verify that there were no adverse events at the time of these spuriously elevated potassium values. The data from their response (May 21, 2004) indicated that there were no adverse events recorded at the time of these potassium elevations. Retesting and other potassium determinations during treatment did not indicate any true hyperkalemia. Practically all the cases of increased potassium determinations (levels above 5.5 mEq/L) were reported from 3 study sites, which strongly suggests indicates either a collection or transport problem. These sites were:***

  Study site 9 (Austria) 3 instances
  Study site 71 (Poland) 4 instances
  Study site 72 (Poland) 8 instances

- ***A listing of the subjects with potassium values > 5.5 mEq/L is provided in Table 25.***

Table 25 Subject Listing for Potassium Values >5.5 mEq/L

PID	Site #	Study day Point	Potassium mEq/L	Re-Test mEq/L	Comment	Clinical Adverse event at time of potassium elevation?
74	90	375	5.7			No
242	9	419	7.7	3.8	Latent hemolysis	No
320	72	160	10.8	4.4 in cycle 13 4.1 at final	Latent hemolysis	No
321	72	161	7.9	4.6 in cycle 13 4.1 at final	Increased transport time	No
325	72	429	10.7	4.5	Latent hemolysis	No
333	6	353	5.6			No
447	5	373				No
799	74	12	5.5			No
824	71	310	5.7		Latent hemolysis	No
854	71	361	9.1	4.4 at final	Latent hemolysis	No
866	71	357	6.6	4.0 at final	Latent hemolysis	No
914	71	355	6.3	3.7 at final	Long tourniquet time recorded	No
943	72	399	15.4	3.8	Latent hemolysis	No
944	72	395	6.6		Latent hemolysis	No
944	72	401	6.9	4.0	Latent hemolysis	No
945	72	395	11.5	3.9	Latent hemolysis	No
949	72	13	9.7	4.3	Increased transport time	No
1001	9	25	6.2	4.0	Latent hemolysis	No
1033	11	163	5.6		Increased transport time	No
1050	9	378	5.5		Increased transport time	No
1310	58	319	6.7	4.1 at final	Increased free hemoglobin	No

Although there is a theoretical risk of hyperkalemia with drospirenone based on its mechanism of action, there is no evidence in this pivotal trial of true hyperkalemia with accompanying symptomatology. The outlier potassium elevations in this trial are felt to be spurious levels related to collection and transport issues and not reflective of true hyperkalemia. This assessment is based on normal levels of potassium at retesting and no adverse events recorded at the time of the elevated levels. Additionally, the segregation of most of these events to three study sites further suggests collection and/or transport problems.

In study protocol 14523 which compared Yasmin 20 (21 day dosing regimen) versus Mercilon, spurious elevations of potassium without associated adverse events also occurred. Three of the elevations occurred in the Mercilon treatment arm, which has no theoretical mechanism for elevating potassium. The preponderance of cases also occurred at one study site in Italy.

Two subjects in protocol 303740 took ACE inhibitors (PIDs 844 and 1277) Neither of these subjects had elevated potassiums during the study, nor adverse events related to hyperkalemia. Subject 844 had study medication withdrawn due to an SAE not related to study drug (retrobulbar neuritis).

Only 1 subject taking NSAIDs in the protocol 303740 had a significantly elevated potassium determination. Subject 949 took ibuprofen for endometriosis. Her potassium of 9.7 was repeated and found to be normal. Her study site had 7 other instances of apparent "pseudohyperkalemia". No subject in this study used spironolactone or potassium-sparing diuretics.

The applicant additionally presented interim findings of the European Postmarketing Surveillance Study of Yasmin (EURAS) where subjects with new arrhythmias were analyzed. There was no indication that the heart findings were related to use of the oral contraceptive. Yasmin showed no difference from other contraceptives. (Source: interim EURAS report, 8 Apr 2004 submission to EDR)

Prior to the issuance of approval for Yasmin for marketing in the U.S., Berlex agreed to postmarketing study commitments related to the potential for hyperkalemia. They instituted an educational outreach protocol for healthcare providers and patients. They have monitored physician awareness of the unique labeling contraindications and warnings regarding potassium. As of April 2004, the survey results of physician awareness varies from 64% to 93% depending on question and the type of practitioner (Ob-Gyn versus Primary Care).

The applicant also had a commitment to evaluate inappropriate prescribing practice in regard to prescribing Yasmin to contraindicated patients and to performing first cycle potassium determinations in patients receiving concomitant medications that may increase potassium. This surveillance study was arranged through Ingenix United Healthcare. On the last review for the fourth quarter of 2003, there was Yasmin dispensing to 3 patients in the adrenal watch list, 7 patients in the renal watch list, and 15 patients in the hepatic watch list. The Ingenix study as of the fourth quarter of 2003 indicated that about 1% of patients prescribed Yasmin are also taking medications that may predispose to increasing potassium levels. The level of potassium monitoring in the first cycle, however, appears to be low. The applicant stated that "Prescribing physicians appear to be skeptical of the need to measure potassium in patents taking Yasmin plus a potassium sparing drug despite current labeling".

The Ingenix postmarketing surveillance study in regard to hyperkalemia and associated symptoms is still ongoing. Study table reports from Quarter 3, 2001 through Quarter 1, 2003 have shown two cases of hyperkalemia in the Yasmin cohort (the chart was not found for one of these cases). There is no strong signal of hyperkalemia problems to date.

Source for the above Ingenix data = 3 Sept 2004 submission to IND 51,693 serial # 095

Medical Officer's Comment:

- ***Although there is evidence of Yasmin prescribing to potential at-risk individuals (adrenal, renal and hepatic) and a low number of potassium determinations for individuals taking concomitant potassium altering medications, the postmarking surveillance clinical data do not indicate that hyperkalemia is a significant risk with Yasmin. This reviewer feels that no***

additional labeling contraindications or warnings regarding potassium (over and above which exists for Yasmin) are required in the Yasmin 20 label.

7.4.2.10 Menstrual Bleeding Patterns (Intracyclic and Withdrawal Bleeding)

Intracyclic Bleeding

The number(%) of subjects with intracyclic bleeding during each cycle is shown in Table 26.

Table 26: Intracyclic Bleeding Analysis for Protocol 303740

Cycle	Intracyclic Bleeding			
	No		Yes	
	N	%	N	%
1	704	75	231	25
2	768	86	123	14
3	753	86	121	14
4	757	86	115	14
5	766	90	87	10
6	727	86	116	14
7	748	91	73	9
8	713	89	84	11
9	687	90	76	10
10	678	90	72	10
11	674	92	59	8
12	645	90	68	10
13	442	85	81	15

Source: Clinical Study Report No. A12007, pages 1448 of 3206.

Medical Officer's Comment:

- ***After the first cycle of use, the percentage of days with intracyclic bleeding remains generally in the 10-15% range, which is acceptable. There were only 7 incidents of intermenstrual bleeding leading to discontinuation of study drug.***

Withdrawal Bleeding

A majority (89.6%) of the volunteers in the FAS experienced withdrawal bleeding in treatment cycle 1. The number of volunteers with withdrawal bleeding increased slightly afterwards and ranged between 91.7% and 94.4% at cycles 2 to 13. In the FAS, the mean length of withdrawal bleeding was 5.2 days (SD 3.2) at cycle 1, ranged between 4.6 days (SD 2.1) and 4.9 days (SD 2.2) at cycles 2 to 12, and was 2.6 days (SD 1.7) at cycle 13.

In the FAS, the maximum intensity at cycles 1 to 12 was normal in 51.2% to 59.4% of the volunteers, light in 23.4% to 28.5% of the volunteers, spotting in 6.8% to 11.3% of the volunteers, and heavy in 8.1% to 11.9% of the volunteers. At cycle 13, the maximum intensity was normal in 39.4% of the volunteers, light in 33.4% of the volunteers, spotting in 21.2% of the volunteers, and heavy in 6.0% of the volunteers. In the FAS, the mean onset of withdrawal

bleeding was 3.1 days (SD 4.1) at cycle 1, ranged between 3.2 days (SD 3.5) and 3.6 days (SD 4.4) at cycles 2 to 12, and was 2.2 days (SD 2.7) at cycle 13.

Source: Clinical Study Report No. A12007, pages 100-101 of 3206

Medical Officer's Comment:

- ***Withdrawal bleeding approaches 94%. Therefore, the number of amenorrheic episodes on this product are small. The mean length of withdrawal bleeding is acceptable as well as the percentage of subjects who reported somewhat heavier withdrawal bleeding (8-12%)***

7.5 Protocol 303860 (Report A15129): Pivotal Clinical Trial For 21-Day Regimen

7.5.1 Safety Assessments and Collection of Safety Data

7.5.1.1 Study Visits

The Schedule of Study Procedures, including scheduled safety assessments, is summarized in Table 27.

Table 27: Schedule of Study Procedures for Protocol 303860

Assessment	S	A	Treatment Days 12-19 of the respective cycle									Final Exam Follow-up Days 10-17 after last tablet
Visit	1	2	3	4	5	6	7	8	9	10	11	12
Cycle			3	6	9	12	15	18	21	24	26	> cycle 26
Volunteer information, Informed consent	X											
Demographics Entry criteria Medical history Medication history	X	X										
Smoking and Alcohol evaluation	X											
Heart rate, BP, Body weight	X	X	X	X								X
Physical examination	X			Visit 4 (Cycle 12)								X
Gynecological examination	X			Visits 4,6 and 8 (cycles 6,12 and 18)								X
Cervical smear	X	R		Visits 4,6 and 8 (Cycles 6,12 and 18)								X
HCG urine test dispensed		X	As required in absence of menstrual bleeding									
HCG urine test results		X	X									X
AE/concomitant medications			X	X								X
Back-up contraception			X	X								X
Medication dispensed		X	X	X (except visit 11)								
Diary cards dispensed		X	Daily entries by volunteer									
Blisters and diary cards returned			X	X								X
Subjective assessment of well being												X

Abbreviations in the table: S = Screening, A = Admission, R = Result

7.5.1.2 Endometrial Safety

Endometrial safety was not assessed in this clinical trial.

Medical Officer's Comment:

- ***Endometrial safety data obtained from Yasmin 20 (24 day dosing) and the on market product Yasmin support the endometrial safety of the 21-day active dosing regimen for Yasmin 20***

7.5.1.3 Clinical Lab Safety Monitoring

No clinical laboratory safety monitoring were conducted in this clinical trial.

7.5.2 SAFETY FINDINGS

7.5.2.1 Deaths

There were no reported deaths in this study.

7.5.2.2 Serious Adverse Events

A total of 1399 AEs were reported in 350 out of 516 volunteers (67.8%) of which 34 (2.4%) were SAEs in 30 volunteers (5.8%). Seven SAEs in six volunteers were assessed as probably or possibly related to the study drug by the investigator (fibrocystic breast, pelvic or left leg vein thrombosis and pulmonary embolus (n = 2), pain in extremity, ovarian cyst, migraine / abnormal vision). A total of eight volunteers with SAEs discontinued the study. All volunteers fully recovered from the observed SAEs, except for the volunteer with recurrent fibroadenomas. This patient was diagnosed with fibroadenomas since 1998 (before study start), and also in Apr 2001, Aug 2001, and, after discontinuation of the study drug, in Nov 2002.

Source: Clinical Study Report No. A15129, page 87 of 908

The reported serious adverse events and the Investigators' assessment of their relationship to study drug are listed in Table 28.

Table 28: Listing of SAEs in Protocol 303860

PID	V#	HARTS code/Diagnosis	Relationship	Discontinuation
10	7	Surgery / appendectomy	None	No
6	8	Fibrocystic breast / fibroadenoma left breast	Probable	Yes
6	8	Skin hypertrophy / keloid scar	None	Yes
118	71	Surgery / right knee	None	No
156	94	Surgery / appendectomy	None	No
149	103	Surgery / tonsillectomy	None	No
163	***110***	***Pulmonary embolus / + thrombosis left leg***	***Probable***	***Yes***
215	131	Fibrocystic breast / fibroadenoma right breast	Unlikely	No
194	***160***	***Pain in extremity***	***Possible***	***Yes***
268	176	Gastroenteritis	Unlikely	No
262	211	Surgery / gnathoplasty (deviated maxilla)	None	No
306	229	Constipation	None	No
329	245	Accidental injury / smoke intoxication	None	No
189	251	Surgery / scheduled plastic surgery (nasal septum)	None	No
317	276	Ovarian cyst / pain in back and abdomen	Possible	No
313	282	Surgery / appendectomy	None	Yes (a)
60	310	Bone fracture / left leg	None	No
671	327	Abnormal vision / sudden visual disturbance	Probable	Yes
671	327	Migraine	Probable	Yes
655	336	Tooth disorder / teeth correction	None	No
655	336	Tooth disorder / teeth correction	None	No
96	345	Surgery / appendectomy	None	No
115	352	Cholecystitis	None	No
94	362	Encephalitis	None	No
75	365	Surgery / plastic surgery (nasal septum)	None	No
70	384	Surgery / breast reduction	None	No
371	***472***	***Pulmonary embolus / + pelvic vein thrombosis***	***Possible***	***Yes***
371	472	Surgery / appendectomy	None	Yes
355	483	Surgery / appendectomy	None	No
399	505	Infection / erysipelas	None	No
450	547	Surgery / appendectomy	None	No
462	553	Skin melanoma / superficial spreading melanoma (abdominal skin right, level III, 0.7cm depth)	Unlikely	Yes
486	573	Abdominal pain	None	No
512	597	Cervix carcinoma in situ / (cervix uteri)	None	Yes

(a) the discontinuation was for weight gain, not the surgery

Medical Officer's Comments:

- ***The case of cholecystitis may be related to study medication.***
- ***The pertinent SAE case summaries of the documented or suspected thromboembolic adverse events (2 cases of pulmonary embolus and 1 case of a possible DVT) are as follows:***

"Volunteer No. 110 (PID 163) felt pain in the area poplitea of the left leg about two years after start of treatment. At first the complaints had been interpreted as contusion or possible muscle fiber tear and was treated with diclofenac from 5 Aug to 9 Aug 2002. The 22 year-old patient

had been sent to establish the diagnosis because of additional breathing problems. She discontinued the study medication on 26 Aug 2002 and was hospitalized on — .. No existing or previous thromboembolic diseases or risk factors of herself or mother and grandmother were known, she was a smoker of 6 cigarettes per day. A femoral vein thrombosis and embolization of the right lung were diagnosed. She was treated with diclofenac, Novalgin, heparin, and after hospitalization she started with Marcumar. The relationship to treatment of this SAE was assessed by the investigator as 'probable' and applicant as being 'possible' as a causal relationship cannot be excluded. The patient discontinued the study drug, and fully recovered."

Source: Clinical Study Report No. A15129, page 97 of 908

Medical Officer's Comments:

- ***This reviewer considers this SAE of pulmonary embolus as probably primarily related to study medication.***

"Volunteer No. 472 (PID 371), 24 year-old, non smoker with no history or family history of thrombosis and no factor V Leiden mutation, suffered from abdominal pain about four months after treatment start. The patient felt pain in the abdomen and back for two days like already a week before. The tentative diagnosis was an acute appendicitis. The appendectomy on — — revealed a subacute appendicitis. Postoperatively, the patient developed increasing discomfort in the right leg. Phlebography was performed or — and revealed deep leg and right pelvic vein thrombosis. CT angiography of Vena pulmonalis showed a pulmonary embolism with thromboembolism of the left inferior pulmonary lobe artery of the apical inferior right pulmonary lobe. Pelvic CT showed thrombosis of the right Vena iliaca reaching about 5 cm in the Vena cava inferior. On — venous thrombectomy of leg and pelvic vein was performed. Histologic examination showed parts of 'fresh and not so fresh thrombosis' (3 weeks and ~1 week old) with focal mild signs of parietal organization. Laboratory investigations while taking coagulants on 5 Apr 2001 showed 37% decreased protein C, APC resistance ratio: 0.66 APC ratio, Protein S, phospholipid antibodies (IgG), cardiolipin, and phosphatidylserin were not increased. A ventilation perfusion scintigraphy on — confirmed the pulmonary embolism. She was treated with Marcumar, Ultiva, Succinyl, Novalgin, Tramundin, Fragmin, Ambroxol, Unazid, heparin, Orgaran, Valoron, DHB, Dolantin, and ferro-Folgamma, and recovered after having mild fever of 38.5°C on 11 Apr 2001. The patient was advised to wear pressure stockings for one year. Both, investigator and applicant assessed the treatment relationship as 'possible'. The patient discontinued the study drug, and fully recovered from the SAE."

Source: Clinical Study Report No. A15129, pages 97-98 of 908

Medical officer's comments

- ***The surgery could also be contributory in this case in addition to the study drug.***

Volunteer No 160 (PID 194), 24 year-old, suffered from a suspected thrombosis in the right leg (painful lower leg) and a calf cramp 15 months after treatment start. Examination results from

the family doctor described mild warmth, pain on pressure, one prominent vein, but no difference of circumference. End of Jan 2002, the patient reported a swelling of the ankle bone on the right side after doing sports. Since the symptoms did not vanish, a phlebologist was consulted on 30 Jan 2002. A color duplex and venous occlusion plethysmography were without pathological findings for deep vein thrombosis. The possibility of very small thrombosis of veins of the right lower leg could not be excluded, but was assessed as rather unlikely by the phlebologist. The patient was nevertheless treated with Fraxiparine, heparin, Phlogenzym, and Traumeel S.

Source: Clinical Study Report No. A15129, page 98 of 908

Medical officer's comments

- ***A superficial thrombophlebitis could also be considered in this case.***

7.5.2.3 Discontinuations Due to Adverse Events

A total of 38 volunteers (7.4%, 55 AEs) had AEs that led to discontinuation of the study medication. The most common reasons for discontinuation of the study medication due to AEs were decreased libido and depression in 5 volunteers (1.0%) each, and headache and emotional lability in 4 volunteers (0.8%) each.

Source: Clinical Study Report No. A15129, page 95 of 908

Medical officer's comments

- ***Weight gain led to discontinuation in 3(0.6%) subjects. Intermenstrual bleeding led to discontinuation in only 2 (0.4%) subjects. One subject discontinued for tachycardia and restlessness. The tachycardia was not confirmed clinically.***
- ***As noted in the medical officer review of Yasmin and in the pivotal trial of Yasmin 20 (24-day regimen), the percentages for the adverse events most commonly leading to discontinuation is in the 1% range.***

7.5.2.4 Adverse Events

A total of 1399 AEs were reported in 350 out of 516 volunteers (67.8%) during the study course. The three most frequently occurring AEs were vaginal moniliasis in 89 volunteers (17.2%), upper respiratory infections in 77 volunteers (14.9%), and headache in 70 volunteers (13.6%).

A summary limited to relatively frequently occurring AEs (those occurring in at least 5% of the 516 volunteers at risk) is given in Table 29.

Table 29 AEs (>5%) for FAS (ITT) in Study Protocol 303860

HARTS TERM	AEs	N	%
Vaginal moniliasis	134	89	17.2
Upper respiratory infection	128	77	14.9
Headache	137	70	13.6
Diarrhea	82	59	11.4
Abdominal pain	53	42	8.1
Cystitis	62	40	7.8
Vomiting	40	36	7.0
Vaginitis	45	34	6.6
Breast pain	38	32	6.2
Flu syndrome	32	29	5.6

AEs = Number of events
N = Number of volunteers with selected AE
% = Volunteers with AE/ 516 Volunteers
Source: Clinical Study Report No. A15129, page 89 of 908

Medical officer's comments

- ***The percentage with headache is comparable to the 24-day regimen.***

7.5.2.5 Cervical Smear Results

Medical officer's comments

- ***The number of subjects with abnormal pap smears (0.6% at visit 4, 0.5% at visit 6, 1.7% at visit 8 and 1.6% at final visit) are all within the expected range. Typical ASCUS rates can range up to 5-6% in some labs. Dysplasia can range in the 1-2% range.***

Source: Clinical Study Report No. A15129, page 102 of 908

7.5.2.6 Vitals Signs and Body Weight

Blood Pressure. Elevated systolic blood pressure of more than 140 mmHg was reported in twenty volunteers after screening. Fifteen had an elevated measurement of systolic blood pressure only once, four (PIDs 43, 274, 296, and 181) had elevated systolic blood pressure measured twice, and one volunteer (PID 400) at three times. Only one volunteer had a systolic blood pressure of over 160 mmHg: PID 246 had a systolic blood pressure of 170 mmHg at the final examination.

Elevated diastolic blood pressure of over 90 mmHg was reported in 21 volunteers. PIDs 265, 431, 434, and 331 had elevated diastolic blood pressure measured three or more times. The highest diastolic blood pressure detected was 106 mmHg in PID 431 at Cycle 6.

Source: Clinical Study Report No. A15129, pages 104-105 of 908

Medical officer's comments:

- ***Blood pressure elevations can occur with use of COCs. The percentage of subjects showing an increase is not significant. Overall, the applicant showed slight decreases in the mean systolic and mean diastolic pressures during treatment compared to baseline. There were no significant mean changes in heart rate during treatment compared to baseline.***

Body weight. Body weight analysis in the study is listed in Table 30. There was very little in the way of mean change.

Table 30: Body Weight Findings by cycle in protocol 303860

		Weight (kg)		Change from baseline (kg)	
	N	Mean	SD	Mean	SD
Screening (Visit 1)	516	63.4	9.7		
Baseline (Visit 2)	224	62.9	9.7		
Cycle 3 (Visit 3)	504	63.2	9.7	-0.27	2.11
Cycle 6 (Visit 4)	481	63.0	9.4	-0.46	2.72
Cycle 9 (Visit 5)	466	62.6	9.1	-0.64	3.14
Cycle 12 (Visit 6)	442	62.7	9.0	-0.46	3.24
Cycle 15 (Visit 7)	429	62.9	9.0	-0.27	3.56
Cycle 18 (Visit 8)	408	62.9	8.9	-0.24	3.68
Cycle 21 (Visit 9)	396	62.9	8.9	-0.34	3.90
Cycle 24 (Visit 10)	383	63.1	9.0	-0.16	3.76
Cycle 26 (Visit 11)	367	63.3	9.0	-0.06	3.96
Final examination (Visit 12)	483	63.6	9.3	0.28	3.87

Source: Clinical Study Report No. A15129, page 103 of 908

7.5.2.7 Safety Laboratory Findings

Safety laboratory parameters were not determined in this study.

Medical Officer's Comments:

- ***Laboratory safety monitoring data obtained from Yasmin 20 (24 day dosing) and the on market product Yasmin support the safety of the 21-day active dosing regimen for Yasmin 20***

Source: Clinical Study Report No. A15129, page 100 of 908

7.5.2.8 Menstrual Cycle Control Findings (Intracyclic Bleeding)

Bleeding was evaluated based on the volunteers' daily diary entries. The length of the reference period was determined as 90 days, in accordance with the WHO recommendations. The reference period started on the 1st day of study medication intake. Treatment was carried out for 26 cycles of 28 days each. Eight reference periods were evaluated. For each woman and reference period the number of bleeding days and episodes were calculated.

In the FAS, the mean number of bleeding / spotting days decreased from 22.16 days (SD 7.81) in Reference Period 1 to 16.12 days (SD 4.55) in Reference Period 2, and was still 15.49 days (SD 4.49) in Reference Period 8.

Medical Officer's Comment:

- ***This translates into approximately 7 bleeding/spotting days in each of the first three cycles and then tapering down to 5 bleeding/spotting days in subsequent cycles. This is acceptable.***

The majority of volunteers (52.9% of the PPS, 50.4% of the FAS) had never had any intracyclic bleeding during Treatment Cycles 1 through 26. The number of volunteers with intracyclic bleeding decreased noticeably during Cycles 2 to 26 (ranging at levels from almost 5% to about 11%) as compared to Cycle 1 (about 21% in both analysis sets). The mean number of intracyclic bleeding episodes during the treatment period was low and ranged between 1.0 and 1.3 in both analysis sets.

Source: Clinical Study Report No. A15129, page 74-81 of 908

Medical Officer's Comment:

- ***A percentage of 5-10% subjects having intracyclic bleeding in cycles 2 to 26 is quite acceptable.***

A majority of 92.62% of the volunteers in the FAS experienced withdrawal bleeding in Treatment Cycle 1. Like in the PPS, the number of volunteers with withdrawal bleeding slightly increased afterwards and ranged between 96.55% in Cycle 3 and 99.08% in Cycle 5.

7.6 OTHER STUDIES SUPPORTIVE OF SAFETY (FROM (ISS, 16 OCT 2003)

The studies that provide additional supportive safety data that were included in the 16 Oct 2003 submission are listed in *Table 31.*

Table 31: Safety Findings From Supportive Studies

Study number (and type)	Dosing and number of subjects	Safety findings
301780 BA study, single dose crossover (Germany)	• 2 x 3 mg DRSP + 20ug EE (betadex clathrate)-18 subjects • 2 x 3 mg DRSP + 20ug EE (free steroid)- 18 subjects • 6 mg DRSP + 40ug EE (oral suspension)- 18 subjects	No SAEs
300080 Phase I PK Single dose (Japan)	• 3 mg DRSP + 20ug EE (betadex clathrate)- 18 subjects • 6 mg DRSP – 6 subjects • 3mg DRSP – 6 subjects • 1mg DRSP – 6 subjects	No SAEs
304326 Phase I PK Single dose (Germany)	• 3 mg DRSP + 20ug EE (betadex clathrate)- 18 subjects • 6 mg DRSP – 6 subjects • 3mg DRSP – 6 subjects • 1mg DRSP – 6 subjects	No SAEs
305103 Phase I PK Multiple dose (21 days)	3 mg DRSP + 20ug EE (betadex clathrate)- 48 subjects (24 in Germany, 24 in Japan)	No SAEs One subject withdrawn for helicobacter gastritis
303741 Phase I Interaction with simvastatin	3 mg DRSP x 14 days, 40mg simvastatin on day 14 – 24 subjects (Study performed in Germany)	No SAEs
14588 Phase 2 ovulation inhibition	3 mg DRSP + 20ug EE betadex clathrate (2 cycles, 21-day regimen)- 30 subjects (Study performed in Germany)	No SAEs
3054566 Phase 2 Ovulation Inhibition (US)	3 mg DRSP + 20ug EE betadex clathrate (2 cycles, 21-day regimen)- 23 subjects (first generation Japanese in US)	One SAE (unintended pregnancy occurred during the posttreatment cycle) One subject discontinued for irregular bleeding and abdominal discomfort
301888 Phase III lipid, hemostasis, CHO	• 3 mg DRSP + 20ug EE (24-day regimen)- 29 subjects • 0.150 mg DSG + 20ug EE (21-day regimen)- 30 subjects (7 cycles for each arm) (Netherlands)	No SAEs
14523 Phase III Comparative Cycle control and Safety	• 3 mg DRSP + 20ug EE (betadex clathrate)- 220 subjects • 0.150 mg DSG + 20ug EE - 221 subjects (7 cycles, 21-day regimen for each arm) (Belgium, Czech Republic, Italy, UK)	3 SAEs in DRSP arm (one accident and 2 surgeries) 15 premature discontinuations for AE in DRSP arm (6.8%). Four of these were for weight gain.
	• 3 mg DRSP + 30 ug EE – 566 subjects (6 cycles, 21-day regimens for both arms)	1 SAE for gastrointestinal disorder 18 premature discontinuation for AE of which 4 were for headache/migraine, 3 for acne and 3 for depression

Medical Officer's Comment:

- ***No worrisome adverse events were noted in these studies.***

7.7 4-MONTH SAFETY UPDATE

The reporting interval for this Safety Update is March 31, 2003 – February 14, 2004. These dates correspond to the cut-off date for inclusion of data into the NDA and the cut-off date established for inclusion of data into this update, respectively.

Reports for 5 Phase 3 clinical studies (one final report for completed (Protocol 303860) and 4 on-going studies were included in the Safety Update. The safety and efficacy findings from Protocol 303860 (the pivotal safety and efficacy trial for Yasmin 20 [21-day dosing regimen]) has been previously described in this review in Section 6.4 and Section 7.5, respectively. A brief description of the 4 Phase 3 studies that were ongoing in the United States during the reporting period and critical safety findings from these studies follow below.

1. *Protocol 304049: "Multicenter, Double-Blind, Randomized, Placebo Controlled, Parallel Group Study to Evaluate the Efficacy of a Monophasic Oral Contraceptive Preparation, Containing Drospirenone 3 mg Ethinyl Estradiol 20 μg (as Beta-Cyclodextrin Clathrate), in the treatment of Premenstrual Dysphoric Disorder (PMDD)".*

Status: Clinical phase recently completed. Database not yet locked.

Medical Officer's Comment:

- ***Four SAEs have been reported in this study (surgery for bone spur, appendectomy, incisional hernia, and high grade cervical dysplasia)***

2. *Protocol 305141: "A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Crossover Study to Evaluate the Efficacy of a Monophasic Oral Contraceptive Preparation, Containing Drospirenone 3 mg/Ethinyl Estradiol 20 μg (as Beta-Cyclodextrin Clathrate), in the treatment of Premenstrual Dysphoric Disorder (PMDD)"*

Status: Clinical phase completed. Database locked.

Medical Officer's Comment:

- ***One SAE has been reported in this study (spontaneous abortion for subject in placebo arm))***

3. *Protocol 306820: "A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Efficacy of an Oral Contraceptive Preparation, Containing Drospirenone 3 mg/Ethinyl Estradiol 20 μ g (as Beta-Cyclodextrin Clathrate) for 6 Treatment Cycles in Women with Moderate Acne Vulgaris"*

Status: Clinical phase ongoing.

Medical Officer's Comment:

- ***One SAE has been reported in this study (possible missed abortion)***

4. *Protocol 306996: "A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Efficacy of an Oral Contraceptive Preparation, Containing Drospirenone 3 mg/Ethinyl Estradiol 20 μg (as Beta-Cyclodextrin Clathrate) for 6 Treatment Cycles in Women with Moderate Acne Vulgaris"*

Status: Clinical phase ongoing.

Medical Officer's Comment:

- ***One SAE has been reported in this study (epileptic seizure in subject with a history of these in the past)***

Source: 4-Month Safety Update, 18 March 2004 Submission.

7.8 POSTMARKETING PHASE 4 YASMIN SAFETY DATA – THROMBOTIC AND THROMBOEMBOLIC ISSUES

Global postmarketing safety data obtained with Yasmin (3 mg DRSP/0.03 mg EE) is very relevant in assessing the potential thrombotic/thromboembolic risks associated with the use of Yasmin 20. The most comprehensive discussion of this issue was in the applicant's 17 Aug 2004 submission. This section will describe the findings from 3 postmarketing safety studies, (the EURAS study, the Ingenix study, and the PEM study).

7.8.1 BACKGROUND

Until recently, a background rate of about 0.5 to 1 events per 10,000 woman-years (WY) in women not exposed to OCs and a rate of about 2-4 events per 10,000 WYs during OC use has been accepted. However, recent work suggests that the background rate for VTE, and thus the rate seen in OC users as well, may be higher than previously believed. For instance, obesity is an important risk factor for VTE; therefore the increase prevalence of obesity in the US will impact the background incidence of VTEs.

VTE in the form of deep venous thrombosis or pulmonary embolism may have severe clinical consequences; however, most cases of VTE present with minimal symptoms. For example, in a prospectively designed study of 2177 passengers of long-haul flights and control subjects, only 3 out of 39 subjects with venous thrombosis, as confirmed by venous compression ultrasonography, were symptomatic (isolated calf pain). This observation suggests that VTE may be substantially underdiagnosed in the general population.

In contrast to this finding in the normal population, the widespread awareness of the association between VTE and OC usage may result in VTE being selectively more frequently identified in

users of these products (detection bias). Given the scientific and public discussion on the VTE risk associated with third generation OCs, this effect appears to be more pronounced in users of any new or innovative OC. In addition, the increased awareness of OC-associated VTE has the effect that health professionals may assume a causal link, and are therefore more likely to spontaneously report VTEs to health authorities and/or pharmaceutical companies when they occur.

Spontaneous worldwide reporting revealed a VTE reporting rate of in the magnitude of 5.0/100,000 women-years during Yasmin use. In contrast, results from a large, controlled, prospective post-marketing surveillance study (EURAS) suggest a VTE rate of 61/100,000 women-years for Yasmin, compared with rates of 60/100,000 and 73/100,000 women-years for levonorgestrel-containing OCs and other OCs, respectively. Overall, the VTE rate reported with Yasmin use was similar to that for LNG-containing OCs or other OCs. The VTE rates with Yasmin are reassuring when placed in context with potential biases and confounding factors that would inflate the perceived risk of VTE with a novel OC. Furthermore, the risk of VTE with Yasmin or other OCs is less than that associated with pregnancy and delivery.

Source: Applicant's 17 Aug 2004 submission, pages 5-6 of 37

7.8.2 CLINICAL TRIALS IN THE OC POPULATION

VTEs in young women are too rare to be precisely quantified within a regular clinical development program for market authorization of an OC.

Only one suspected case of pulmonary embolism (PE) was reported in Yasmin's extensive clinical development program. In the program that led to registration, over 30,000 treatment cycles were assessed in non-obese Yasmin users up to the age of 35 years (or for smokers up to the age of 30). Two additional confirmed cases of DVT were reported in Phase III clinical studies in Canada and the United Kingdom. In NDA 21-676, no VTE was reported in the clinical development of Yasmin 20 (24-day regimen). Two VTEs were reported during the [redacted] asmin 20 (21-day regimen); both cases had a confirmed PE. In another Yasmin 20 (21-day regimen) treated volunteer, a thrombosis was initially suspected, but not confirmed by a phlebologist. These 3 cases in Yasmin 20 users were previously reviewed.

If the data from all development studies from Yasmin and Yasmin 20 are pooled, approximately 5000 WY were collected. When considering the 5 confirmed/suspected VTEs, the VTE incidence is approximately 10 per 10,000 WY. A robust estimate of the VTE incidence is not possible on the basis of 5000 WY; however, it appears to be on the same order of magnitude seen in the extensive post marketing surveillance data gathered in the EURAS and PEM studies.

Source: Applicant's 17 Aug 2004 submission, pages 6-7 of 37

7.8.3 POSTMARKETING SAFETY STUDIES

7.8.3.1 European Active Surveillance (EURAS) Study

The EURAS post-marketing, prospective, observational study compares the occurrence of rare events, such as VTE and ATE, in Yasmin users with the occurrence in LNG-containing OC users and all other OC users. EURAS study uses a non-randomized, comparative 'noninterference approach' which allows study inclusion of new OC users who are prescribed an OC based upon standard medical practice. The EURAS is being conducted, under a grant provided by Schering AG, by Prof. L. Heinemann, ZEG (Centre for Epidemiology and Health Research) with oversight by an Advisory Council.

At the latest update of the EURAS database on June 9, 2004, approximately 50,000 women were enrolled in the study representing 64,000 WY of observation, including 19,530 WY of exposure to Yasmin. The study is planned to be completed in 2006. The current number of enrolled women and women-years per cohort are given in Table 32

Table 32: EURAS Study: Women enrolled, Women-years of Observation and Mean Ages

	Yasmin		LNG-containing OCs		Other OCs		Total Study	
	N	%	N	%	N	%	N	%
Number of women	15,020	(30.4)	14,630	(29.7)	19,692	(39.9)	49,342	(100)
Women-years	19,530	(30.5)	18,476	(28.8)	26,097	(40.7)	64,103	(100)
Mean Age (SD)	26.3	(8.2)	25.2	(8.8)	25.1	(8.0)	25.5	(8.3)

Source: Applicant's 17 Aug 2004 submission, page 8 of 37

Participants are queried for occurrence of adverse events by questionnaire every six months over a period of several years. The diagnosis of VTE or ATE is established with a follow-up/assessment algorithm including follow-up with the treating physician and written verification of the reported diagnostic and therapeutic procedures. The follow-up procedure has resulted in a low lost to follow-up rate that is evenly distributed among the cohorts (currently overall: 1.7%; Yasmin: 1.6%, LNG-containing OCs: 1.7%, and Other OCs: 1.8%).

A total of 10 deaths were reported in the study by the June 9, 2004 cutoff date. This equates to ten deaths during approximately 64,000 women-years corresponding to a rate of 16/100,000 women-years. Two of ten deaths reported were considered related to the treatment. Both were reported in the LNG-containing OC cohort, one was related to a VTE and one to an ATE.

The two fatalities in the Yasmin cohort were due to rupture of an aortic aneurysm and liver failure secondary to liver metastasis from a neuroendocrine cancer. Since the last update on June 9, 2004 one new death, due to suspected chronic myocarditis (PE and DVT ruled out by autopsy according to the applicant), was reported in the Yasmin cohort. Causality assessment by the treating physician concluded there was no causal relationship between any of the fatalities in the Yasmin cohort and Yasmin use.

Source: Applicant's 17 Aug 2004 submission, page 9 of 37

Table 33 provides the rates for confirmed VTEs and ATEs in all cohorts, as well as an overview of the fatal VTE/ATE rates.

Table 33 EURAS Study: Confirmed Thromboembolic AEs – Number of Events, Incidence, 95% Confidence Intervals

Event Category	Yasmin (19,530 WY)			LNG-containing OCs (18,476 WY)			Other OCs (26,097 WY			Total
	N	Per 104 WY	95% CI	N	Per 104 WY	95% CI	N	Per 104 WY	95% CI	N
All VTE & ATE	13	6.7	3.5 - 11.4	14	7.6	4.1 – 12.7	23	8.8	5.6 – 13.2	50
All VTE	12	6.1	3.2 - 10.7	11	6.0	3.0 – 10.7	19	7.3	4.4 – 11.4	42
of which PE	3	1.5	0.3 – 4.5	2	1.1	0.1 – 3.9	2	0.8	0.1 – 2.8	7
All ATE	1	0.5	0.0 – 2.9	3	1.6	0.3 – 4.8	4	1.5	0.4 – 3.9	8
of which AMI	0	0.0	0.0 – 1.9	1	0.5	0.0 – 3.0	2	0.8	0.1 – 2.8	3
of which CVA	1	0.5	0.0 – 2.9	2	1.1	0.1 – 3.9	2	0.8	0.1 – 2.8	5
All Fatal VTE/ATE	0	0.0	0.0 – 1.9	2	1.1	0.1 – 3.9	0	0.0	0.0 – 1.4	2

VTE = venous thromboembolic event, ATE = arterial thromboembolic event, AMI = acute myocardial infarction, CVA = cerebrovascular accident, WY = women-years
Source: Applicant's 17 Aug 2004 submission, page 10 of 37

All deaths reported through June 9, 2004 in the EURAS Study are listed with a brief description in Table 34. A listing of the cases of thromboembolic events is provided in Section 6 of the Appendix.

Table 34: Deaths Reported from the EURAS Study

Case Number	Age/BMI Smoking	Entered study	Incident date	Comments
Yasmin				
1000156088	34yr/ 19	Jun 2001	[redacted]	Death secondary to ruptured aortic aneurysm Her father died secondary to ruptured artery
1006657017	45yr/26 Smoker	Jun 2002	[redacted]	Death secondary to neuroendocrine cancer. No OC use for 6 months prior to death (last Yasmin intake Jan 2003
Levonorgestrel (LNG)-Containing OC				
1000010153	21yr/20	Oct 2001	[redacted]	Death secondary to Waterhouse Friderichsen Syndrome
1000072256	32yr/24 Smoker		[redacted]	Death secondary to septic multi-organ failure after liver transplantation. Liver failure was caused by phenprocoumon, which was given for a DVT, which was initially diagnosed in Dec 2001. She had been on her LNG OC for 14 years.
1000072309	32yr/24	Oct 2001	[redacted]	Death secondary to cervical cancer. Last OC use Jun 2002
OCs containing other progestins				
1000069066	35yr/19	Jan 2001	[redacted]	Death following surgery for cerebral aneurysm Using desogestrel OC
1000534002	16yr/19 Smoker	May 2002	[redacted]	Death secondary to motor vehicle accident Using desogestrel OC
1000156023	37yr/22	Apr 2001	[redacted]	Death secondary to viral encephalitis Using chlormadinone OC

Medical Officer's Comments

- ***The incidence for all thromboembolic events are similar in all three cohorts (Yasmin: 6.7 per 10,000 WY; LNG-containing OCs: 7.6 per 10,000 WY; and Other OCs: 8.8 per 10,000 WY). Separate evaluation of VTEs and ATEs results in similar point estimates for all three cohorts.***
- ***Compared with other OCs, VTE/ATE occurrence was not increased during Yasmin use.***

7.8.3.2 Ingenix Study

The Ingenix study is a prospective; cohort study based on claims data from United Health Care (UHC), a major US health care provider. This study is being conducted as part of a Phase IV commitment for Yasmin. The study was initiated in July 2001 to evaluate hyperkalemia risk and was modified in December 2003 to include VTEs and ATEs. Final results are expected in 2006. Pharmacy claims are being used to identify a cohort of Yasmin and other OCs users with follow-up using the ICD-9 codes reported for billing purposes. The cohorts are matched through propensity scoring. The computerized codes for possible cases of VTE or ATE were added and searched at the request of the Division. The medical records for these potential cases are then abstracted and reviewed by trained personnel to adjudicate the cases. Also, the protocol was amended on February 27, 2004 [Serial No. 088] to include a validation (nested case control) study to better understand potential differences in the study cohorts.

Medical Officer's Comment:

To date, no Yasmin-related deaths have been detected in this study.

On 7 Oct 2004, the applicant submitted chart summaries of subjects suspected of developing thromboembolic adverse events. These summaries include subjects taking Yasmin and other oral contraceptives. The following summary table (Table 35) was derived from the applicant's information. Listing of Cases of suspected thromboembolic events in users of other OCs (based on Chart analysis) are provided in Section 6 of the Appendix. There is a 1:2 ratio for Yasmin: Other OCs. From quarter #3, 2001 to Quarter 3, 2003 there were 14,295 Yasmin initiators and 28,509 "other OC" initiators.

Table 35: Ingenix Study Results: Chart Confirmed Cases of Thrombotic and Thromboembolic Events (Cohorts Quarter 3, 2001 Through Quarter 3, 2003)

Outcome (a)	Yasmin Initiators (n=14,295)			Other OC Initiators (n=28,590)		
	Claims-Based	Chart Confirmed	Chart Not Found	Claims-Based	Chart Confirmed	Chart Not Found
Number of Charts Requested	20			58		
Pulmonary embolism	4	1	0	11	9	1
Venous thrombosis	12	8	1	27	20	3
Arterial embolism	1	1	0	8	0	1
Stroke	2	0	0	7	3	1
TIA	0	0	0	0	0	0
Thrombotic thrombocytopenic purpura	0	0	0	1	1	0
Other diagnoses	4	0	0	9	0	0
Not specified (b)	2	0	0	4	0	0

(a) A woman can have multiple events in multiple categories
(b) Women with claims for procedures or anticoagulant therapy only
Source: Applicant submission 7 Oct 2004

Medical Officer's Comment:

- ***Although this report still represents interim study data, there is no signal of increased thromboembolic risk.***

7.8.3.3 Prescription-Event Monitoring (PEM) Study

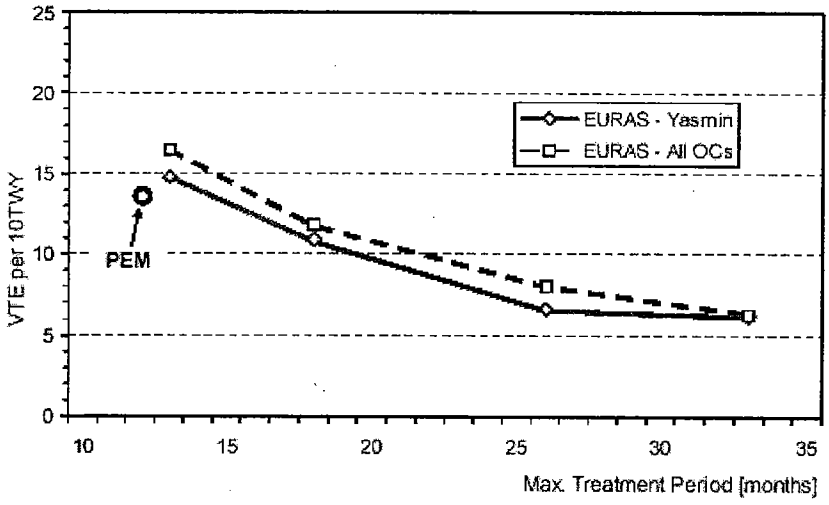
An observational, non-controlled cohort Prescription-Event Monitoring (PEM) Study on venous thromboembolism was conducted in Yasmin users in the UK by an independent investigator (Prof. F. Shakir, Drug Safety Research Unit). Data were collected on safety-related events after 6 to 12 months of use in Yasmin users who were given prescriptions during Yasmin's initial 8 months in the UK market (from May 2002 until December 2002). Of the 30,797 distributed questionnaires, 17,877 (58%) were returned. Of these, 15,684 (51%) contained sufficient clinical data to be included in the analysis. These data totaled 9,482 women-years of observation. The average treatment period was 0.6 women-years per woman.

A total of 13 women with venous thromboembolism (VTE) were identified, of these, five cases were deep vein thrombosis (DVT) and eight cases were pulmonary embolism (PE). The crude incidence rate in this cohort is 13.7 cases per 10,000 women-years (95% CI: 7.3-23.4). Each of the cases had one or more risk factors for VTE.
The authors stated that incidence rates appeared to be at the upper end of incidence rate reported in other OC observational studies. The authors, however, highlighted the difficulty of interpretation: VTE rates significantly vary during OC use and may be affected by case identification criteria, recent market introduction, age and other risk factors, diagnostic suspicion and referral bias.

Medical Officer's Comments

- ***The reported VTE risk is highest during the first year of use of estrogen/progestogen combinations. Obviously, women predisposed to VTE (e.g., by genetic factors) develop VTE quite soon after commencing OC use. The PEM study included only users during their first year of use. In the first interim analysis of the EURAS study, where the average treatment duration and maximum length of treatment (<13 months) were comparable to the PEM study, the VTE rates were similar to those reported in the PEM study. It is important to note that in the first year of the EURAS study the VTE rate was 2 to 3 times higher than the rate seen 20 months later after a treatment period of up to 33 months. (See the Figure that follows below). Based on both the EURAS study results and literature it can be expected that the VTE incidence reported in the PEM study seen for Yasmin users in the UK will decrease with the number of years on the market.***

Figure 1 Time dependent decline of the VTE rate for Yasmin and all oral contraceptives (OCs) user cohorts in the EURAS study compared to VTE rate reported at the end of the PEM study



7.8.3.4 Postmarketing Spontaneous Reporting of Adverse Events for Yasmin

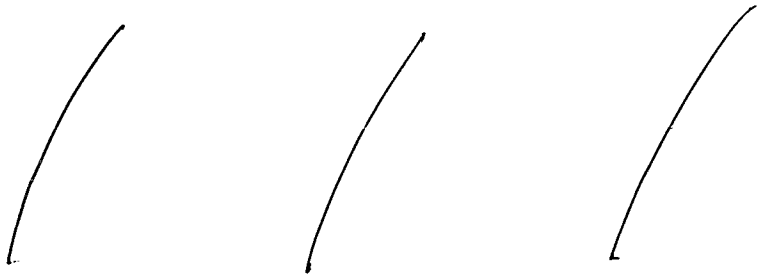
Spontaneous reporting of adverse events (through AERS database) has shown thrombotic and thromboembolic adverse events. The reporting rates are shown in an analysis by the Office of Drug Safety in Section 8 of the appendix. There have been 6 US reported deaths in patients taking Yasmin. In most of the cases a pulmonary embolism is suspected to be the immediate cause of death. The deaths are listed in detail in the Section 8 of the appendix. The number of reported deaths is similar to another combination hormonal contraceptive that was marketed over the same time period and shares similar marketing number. Although any postmarketing reports of any deaths are of concern and bear further careful monitoring, the prospective safety data for Yasmin appears similar to that for other combination oral contraceptives investigated in the EURAS and Ingenix Studies. The thrombosis/thromboembolism risks for combination oral contraceptives ultimately need to be compared to the higher risk for similar events in pregnant women.

There have been no large prospective clinical trials that have compared 20 microgram ethinyl estradiol combination oral contraceptives with similar products containing 30-35 micrograms in regard to safety risk. Based on the reduction seen for the thromboembolic risks from the very high dose oral contraceptives used in the 1960s there is a theoretical basis to think the 20 microgram products may be safer. Both the Yasmin 20 regimens (24-day and 21-day) reduce the amount of ethinyl estradiol to the 20 microgram level. The 24-day regimen slightly increases the amount of progestin compared to the approved product, while the 21-day regimen keeps the progestin amount the same. The 21-day regimen would be the preferred regimen if only dosing level is considered, especially since there has been no definite clinical benefit demonstrated to date for the 24-day regimen.

7.9 PROPOSED PHASE 4 POSTMARKETING SURVEILLANCE STUDY

The Applicant has proposed a prospective, cohort study similar in design to the European Active Surveillance Study (EURAS), a large non-interventional long-term cohort study that permits safety monitoring of Yasmin and other oral contraceptives (OC), reliable identification of study outcome, and incidence estimates. Overall, the proposed phase IV study is similar in design to the EURAS study but also incorporates surveillance of US as well as international prescribing behavior and cardiovascular outcome associated with Yasmin 20 (24-day dosing regimen) and other oral contraceptives.

The Division of Drug Risk Evaluation (DDRE) was asked to review the Applicant's proposed Phase 4 active surveillance study. The following comments are taken from the DDRE review.



Medical Officer's Comments:

- *The proposal for a prospective postmarketing safety surveillance study is very welcome because it adds significant numbers of subjects to assess rare adverse events. It appears from interim data in the EURAS study that the thrombotic and thromboembolic risks appear similar when comparing Yasmin to levonorgestrel based OCs and other OCs.*
- *Further assessment of the DRSP 3mg/ EE 0.02mg product in a well designed study of sufficient size will add additional safety information that will be much more informative than spontaneous reporting of postmarketing adverse events.*
- *The applicant estimated that the surveillance study should evaluate*

7.10 OVERALL SUMMARY OF SAFETY FINDINGS

7.10.1 24-DAY REGIMEN (PROTOCOL 303740)

- *There is adequate exposure of patients to study drug to assess safety in the 24-day regimen (1027 subjects, 746 subjects completing 13 cycles, 11,480 total cycles of exposure, and 883 women-years exposure)*
- *The two deaths in protocol 303740 are not related to study drug. One was secondary to smoke inhalation and the other was secondary to pesticide poisoning. The pesticide poisoning occurred about one month after study drug discontinuation.*
- *Three of the SAEs in study 303740 are felt to be probably related to study drug (migraine, depression, and cholelithiasis) These are not unexpected adverse events related to combination oral contraceptives.*
- *The adverse event contributing to the greatest number of drug discontinuation was headache (14 incidents, 1.3%). This is similar to other combination oral contraceptives.*
- *Headache was also the most common adverse event occurring in 13.3% of subjects.*
- *Endometrial biopsies showed no abnormalities in the subgroup analyzed.*
- *There were no significant mean changes in vital signs or body weight.*
- *Increased mean levels of total cholesterol, HDL, LDL and triglycerides were seen. This is comparable to other combination oral contraceptives.*

- *All of the elevated potassium levels identified in the study are felt to be secondary to hemolysis or transport problems. Repeat values were normal. The elevated levels centered at three study sites. There were no concurrent adverse events reported at the time of the "elevated" potassium readings.*

- *The product demonstrates an acceptable level of intracyclic bleeding/spotting (10-15% range).*

7.10.2 21-DAY REGIMEN (PROTOCOL 303860)

- *There is adequate exposure of patients to study drug to assess safety in the 21-day regimen (516 ITT subjects, 11,510 study cycles for safety, 885 women-years of safety exposure, 438 subjects completing cycle 13 and 375 subjects completing cycle 26)*

- *There were no deaths in this study*

- *There were two cases of pulmonary embolism occurring in this study. There is no reason to suspect that these adverse events are more likely to occur in a 21-day regimen rather than 24-day regimen. There have been other approved oral contraceptives that have shown a similar number of thromboembolic events occurring in the clinical trials. Based on the three large clinical trials of Yasmin 20 (3 mg DRSP/ 0.02 mg EE) there are at least 1,878 (excluding small phase 1 and 2 studies) women years of exposure. With caveats regarding rate estimations of rare events derived from typical Phase 3 registry studies for oral contraceptives, two venous thromboembolic adverse events (in study 303860) translates to a rate of 10.6 per 10,000 women years. This rate is similar to the findings of Yasmin in the first year of the EURAS study (approximately 15 per 10,000). This rate is similar to the applicant's estimation of 10 per 10,000 WY using pooled data from Yasmin, Yasmin 20 (24-day regimen) and Yasmin 20 (21-day regimen) namely, 5 events in 5,000 WY.*

- *The other SAEs possibly related to drug in this study include one case each of migraine, ovarian cyst, and cholecystitis.*

- *The most common reasons for study discontinuation in the 21-day regimen were decreased libido and depression in 5 volunteers (1.0% each) and headache and emotional lability in 4 volunteers (0.8% each).*

- *Vaginal moniliasis constituted the highest number of anytime adverse events occurring in 17.2% of subjects. Headache was found in essentially the same percentage as the 24-day regimen (13.6%).*

- *Safety laboratory determinations were not performed in this protocol. The findings from the 24-day regimen did not raise any safety concerns and also are relevant to this dosing regimen.*

- *As in the 24-day regimen, there were no significant changes in vital signs or body weight.*

- *Cycle control (amenorrhea, intracyclic bleeding) was similar to the 24-day regimen and acceptable.*

7.10.3 OTHER STUDIES SUBMITTED TO NDA 21-676

- *There were no deaths, thromboembolic events or hyperkalemia in any of the other studies submitted to this NDA.*

- *Although there are many limitations to hemostatic laboratory testing, there did not appear to be any significant differences between Yasmin 20 and the comparator oral contraceptives in two studies (Mercilon and Marvelon)*

7.10.4 POST MARKETING SAFETY STUDIES

EURAS Study

- *Multiple interim reports from this prospective ongoing safety surveillance study have shown that the incidence rates for Yasmin for both venous and arterial thromboembolic events are similar to levonorgestrel containing oral contraceptives and other non-levonorgestrel containing contraceptives. There have been no treatment-related deaths to date attributable to Yasmin in the EURAS study.*

- *Interim findings from the EURAS study has not indicated any difference between Yasmin and other contraceptives in regard to heart symptomatology that may indicate potassium problems.*

Ingenix Study

- *Interim reports from this study also indicate that the risks for venous and arterial adverse events are similar for users of Yasmin compared to those for users of other oral contraceptives prescribed in the US.*

- *Interim reports from the Ingenix study have not indicated any difference for users of Yasmin versus those for users of other oral contraceptives in regard to symptoms that may be associated with hyperkalemia (syncope, arrhythmia etc.)*

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

The principal issue regarding dosing relates to consideration of the 24-day dosing regimen versus a 21-day dosing regimen. The applicant has submitted data that is adequate to allow for a decision on approval for either regimen. The applicant seeks approval only for the 24-day regimen. Their overall drug development program is focusing on the 24-day regimen in regard to possible future secondary indications for the 24-day regimen including prevention of PMDD (premenstrual dysphoric disorder) and treatment of acne.

Comparing the 24-day regimen to the 21-day regimen in regard to cycle control revealed approximately the same number of days of bleeding/spotting (4-5). The adverse event pattern for both regimens was similar. The two thromboembolic adverse events occurred in the 21-day regimen study, but this is felt to be secondary more to chance since less hormone per year is being provided in the 21-day regimen. The clinical efficacy in regard to pregnancy protection in both regimens was acceptable. The 21-day regimen study showed a better Pearl Index, but this could be accounted for by better compliance of medication usage in Germany and Switzerland.

The applicant submitted their rationale for the 24-day regimen with their 21 Oct 2004 submission. This submission contained literature references and a consultative note from Dr. Mishell. Although the literature suggests potential benefit for extending the days of active treatment (via surrogates of hormonal analysis and sonography), there have not been any significant head to head comparative clinical trials of these regimens to prove clinical benefit.

9. USE IN SPECIAL POPULATIONS

9.1 EVALUATION OF APPLICANT'S GENDER EFFECTS ANALYSES AND ADEQUACY OF INVESTIGATION

This product is only intended for use in women.

9.2 EVALUATION OF EVIDENCE FOR AGE, RACE, OR ETHNICITY EFFECTS ON SAFETY OR EFFICACY

The product is intended for reproductive age women. The pharmacologic class is well characterized. There are no separate race or ethnicity considerations in regard to safety or efficacy.

9.3 EVALUATION OF PEDIATRIC PROGRAM

A separate pediatric program is not required. Combination oral contraceptives are safe and effective in postpubertal females. This product is not intended for pre-pubertal use.

9.4 COMMENTS ON DATA AVAILABLE OR NEEDED IN OTHER POPULATIONS

No additional data is required in other populations.

10. CONCLUSIONS AND RECOMMENDATIONS

10.1 KEY LABELING ISSUES

10.2 RECOMMENDATION ON APPROVABILITY

Approval is recommended for both the 24-day active dosing regimen and the 21-day active dosing regimens of drospirenone 3 mg/ethinyl estradiol betadex 0.020 mg tablets based on the contraceptive efficacy and safety data submitted to the NDA (21-676). This approval recommendation is contingent on acceptable labeling for each dosing regimen

Approval of the 21-day active dosing regimen is preferable from a safety perspective because it provides the same efficacy with less hormonal exposure than the 24 day active dosing regimen. Based on presently submitted data, there is no proven added clinical benefit associated with the use of the 24-day regimen. Although further developmental work is in progress to demonstrate added benefits of the 24-day regimen for supplemental indications, this data has not yet been submitted. This approval recommendation is contingent on acceptable labeling.

10.3 RECOMMENDATION ON PHASE 4 STUDIES AND/OR RISK MANAGEMENT STEPS

The general outlines of the applicant's proposed Phase 4 safety surveillance study for the 24-day regimen are acceptable. The final protocol should be submitted to the Division for review and agreement within 90 days of the approval of this application

A Phase 4 safety surveillance study is not required for the 21-day dosing regimen.

APPEARS THIS WAY
ON ORIGINAL

Appendix

Section 1: Abbreviations and Definitions

AC = Advisory Council
ACE = Angiotensin-converting enzyme
AE = Adverse event
AERS = Adverse Event Reporting System
ALAT (SGPT) = Alanine aminotransferase
AMI = Acute Myocardial Infarction
ASAT (SGOT) = Aspartate Aminotransferase
ATE = Arterial Thromboembolic Event
BMI = Body Mass Index (definition = body weight (kg)/body height (m^2)
BP = Blood Pressure
CBC = Complete blood count
CI = Confidence Interval
CRF = Case Report Form
COC = Combination Oral Contraceptive
CT = Computed Tomography
CVA = Cerebrovascular accident
DSG = Desogestrel
dL = Deciliter
DRSP = Drospirenone
DVT = Deep Vein Thrombosis
E2 = Estradiol
EDC = Electronic data capture
EE = Ethinyl estradiol
EMEA = European Agency for the Evaluation Of Medicinal Products
EOSM = End of Study Medication
EURAS = European Active Surveillance Study
EMB = Endometrial biopsy
FAS = Full Analysis Set
FT4 I = Free thyroxin (T4) index
GCP = Good Clinical Practice
GGT = Gamma-glutamyl Transferase
HARTS = Hoechst Adverse Reactions Terminology System
HCG = Human chorionic gonadotropin
HDL = High Density Lipoprotein
HPF = High-power Field
HPV = Human Papillomavirus
HR = Hazard Ratio
HSIL = High grade Squamous Intraepithelial Lesion
ICH = International Conference on Harmonization
IEC = Independent Ethics Committee
IMS = IMS Health Inc. global provider of pharmaceutical market intelligence

IRB = Institutional review board
ISE = Integrated Summary of Efficacy
ITT = Intent-to-treat
IUCD = intrauterine contraceptive device
IUPAC = International Union of Pure and Applied Chemistry
LNG = Levonorgestrel
MEB = Medicine Evaluation Board (Dutch health authorities)
MEDDRA = Medical Dictionary FOR Regulatory Activities
Mercilon = 0.150 mg desogestrel + 0.02 mg ethinyl estradiol
ug= Microgram
mg = Milligram
NDA = New Drug Application
NDI = National Death Index
NDTI = National Disease and Therapeutic Index
NHS = National Health Service
NOS = Not Otherwise Specified
OC = Oral Contraceptive
PE = Pulmonary Embolism
PEM = Prescription-Event Monitoring study
PI = Pearl Index
PI c = Adjusted PI
Pk = Pharmacokinetics
PMDD = Premenstrual Dysphoric Disorder
PPS = Per-protocol Set
PPI = Patient Package Insert
Pramino = Ortho Tri-Cyclen = 0.18/0.215/0.250 mg norgestimate + 0.035 mg ethinyl estradiol
RMP = Risk Management Program
SAE = Serious Adverse Event
SD = Standard Deviation
T_{half} = Terminal Elimination Half-life
T_{max} = Time of Maximum Concentration
TESS = Treatment-emergent signs and symptoms
TURX = Therapeutic Unit Prescriptions
UA = Urinalysis
UHC = United Health Care
VTE = Venous Thromboembolic Event
WBC = White Blood Count
WNL = Within Normal Limits
WY = Women-years
Yasmin = drospirenone 3mg/ ethinyl estradiol 0.03 mg
YAZ = drospirenone 3mg/ ethinyl estradiol 0.02 mg (24-day regimen)
ZEG = Zentrum für Epidemiologie und Gesundheitsforschung

Section 2: Electronic Submission Listings in Original NDA

Table 36: Folders and Included Items in the Original NDA Electronic Submission

Included folders	Specifics
Clinstat	• ISE and ISS • Integrated summary of risks and benefits • Final study report A12007 for the pivotal trial 303740 • Statistical Overview • [redacted] eport no. A07148 • Commercial Marketing Experience • Table of Studies and List of Investigators List of INDs and NDAs • Background and Overview of Clinical Investigations • Risk Management • Literature Review/Publications • Overdose and Drug Abuse Information • Lipid, hemostatic, CHO study report for protocol 301888 • Cycle control study report for protocol 14523
CMC	See Chemistry Review
CRF	Covers study reports: • A03328 (multiple dose pk) • A07148 • A09151 (lipid, hemostatic, CHO) • A09372 (ovulation inhibition) • A09653 (cycle control) • A11401 (ovulation inhibition) • A12007 (pivotal phase 3)
CRT	Datasets are submitted for the following study reports: • A03328 (multiple dose pk) • A07148 • A09151 (lipid, hemostatic, CHO) • A09372 (ovulation inhibition) • A09653 (cycle control) • A11401(ovulation inhibition) • A12007 (pivotal phase 3) • A01222 (single dose escalation pk) • A03773 (single dose pk) • 1999 Contraceptive Study • b862 (Bioavailability) • bd09 (Drug interaction with Simvastatin) • ISS
Hpbio	Please see Clin pharm review
Labeling	• Brief summary patient • PI • Detailed patient • Carton label • Container label
Other	• Debarment certification • Exclusivity request • Field Certification • Financial Information • Patent Certification/ Information • Pediatric Waiver • User fee cover sheet and Form 365h • Cover letter and NDA Table of Contents
Pharm	See Pharm Tox and Biopharm review
Summary	

Section 3: Study Centers for Protocol 303740

Table 37: Principal Investigators and Sites, Protocol 303740

Center	Principal Investigator	CCC	Site Location	No. Subjects (ITT)
1	W and G. Bartl	712	Vienna, Austria	40
2	Boeckl	713	Salzburg, Austria	34
3	Heytmanek	714	Vienna, Austria	25
4	Hosmann	715	Vienna, Austria	6
5	Huber	8	Vienna, Austria	24
6	Kahr	716	Graz, Austria	80
7	Lassmann	717	Salzburg, Austria	13
8	Mayr	718	Kufstein, Austria	15
9	Neunteufel	719	Dornbirn, Austria	48
10	Poetsch	720	Leibnitz, Austria	30
11	Rogan	721	Vienna, Austria	30
12	Sacher	722	Vienna, Austria	10
13	Schmidl-Amann	723	St. Polten, Austria	40
14	Staudach	702	Salzburg, Austria	27
15	Stiglbauer	724	Wiener Neustadt, Austria	50
Austria subgroup				472
31	Alfonsin	678	Ginecología, Argentina	23
32	Badano	804	Ginecología, Argentina	32
33	Bellmann	808	Rosario, Argentina	45
34	Gurucharri	809	Buenos Aires, Argentina	25
35	Morozovsky/Orrico	810	Córdoba, Argentina	9
36	Sala	807	Nac. de La Plata, Argentina	21
37	Tozzini	679	Nac. de Rosario, Argentina	14
Argentina subgroup				169
51	Diogenes Yazlle	785	São Paulo, Brazil	24
52	Baracat	786	São Paulo, Brazil	23
53	Camargos	787	Minas Gerais, Brazil	37
54	Pinto Costa	788	Rio de Janeiro, Brazil	5
55	Ferriani	785	São Paulo, Brazil	25
56	Nakagava	789	Brasilia, Brazil	5
57	Pereira de Andrade	790	Curitiba, Brazil	32
58	Petracco	791	Porto Alegre, Brazil	39
Brazil subgroup				190
71	Drews	725	Poznan, Poland	48
72	Kaminski	828	Katowice, Poland	27
73	Radowicki	726	Warsaw, Poland	25
74	Woyton	827	Wroclaw, Poland	20
Poland subgroup				122
90	Bachmann	708	New Brunswick, NJ	76
US subgroup				76
35 totalsites				1027 subjects (ITT)

CCC = Center computer code in datasets
Source: A12007a study report pp 21-25 and the November 18, 2003 submission by the applicant

Section 4: Study Centers for Protocols 14523 and 303860

Table 38: Principal Investigators and Sites for Protocol 14523

Center	Principle Investigator	CCC	Site Location (Country)	No. Subjects (ITT)
11	De Bock	291	Belgium	9
12	Pauwels	294	Belgium	39
23	Skrivanek	774	Czech Republic	46
25	Kalousek	840	Czech Republic	19
21	Hlavackova	775	Czech Republic	47
22	Smrhova-Kovacs	773	Czech Republic	44
24	Dvorak	776	Czech Republic	48
35	Scarselli	833	Italy	31
33	Falsetti	831	Italy	12
36	Masellis	841	Italy	13
32	Rattazzi	830	Italy	8
40	Buscaglia	844	Italy	7
31	Melis	829	Italy	29
39	Fedele	543	Italy	9
34	Petraglia	832	Italy	27
37	Volpe	842	Italy	17
38	Affronti	843	Italy	20
41	Venturoli			
8	Maksimczyk	914	UK	5
3	Patchett	68	UK	1
2	Rees	278	UK	1
1	Stagg	71	UK	8
4	Richardson			
5	Briggs			
7	Starr	277	UK	5
				Total =445

Medical officer's comments: Three investigators did not enroll any subjects.

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Table 39: Principal Investigators and Sites for Protocol 303860 – German sites

Center	Principal Investigator	CCC	Site Location	No. Subjects (ITT)
1	Karck/Fittkow	31	Freiburg/Stuttgart, Germany	17
2	Diegritz	765	Freiburg ,Germany	10
3	Harsk	766	Freiburg ,Germany	14
4	Hemberger-Theegarten	767	Karlsruhe, Germany	14
5	Hoffman	768	Karlsruhe,Germany	8
6	Kohoutek	246	Karlsruhe,Germany	21
7	Lieder	769	Mannheim,Germany	6
8	Soder	770	Ettlingen,Germany	18
9	Weidenhammer	771	Freiburg,Germany	13
10	Weihe	777	Ansbach,Germany	14
11	Gramatte	778	Berlin,Germany	14
12	Heger-Mahn	427	Berlin,Germany	41
13	Koniger	640	Berlin,Germany	14
14	Weber	779	Berlin,Germany	14
15	Wernecke	259	Berlin,Germany	14
16	Brach	238	Dietzenback,Germany	14
17	Clauss-Hoffmann	780	Frankfurt,Germany	14
18	El Tobgui-Jensen	781	Frankfurt,Germany	14
19	Feldmann	782	Seligenstadt,Germany	11
20	Frohns	754	Dreieich,Germany	14
21	Gottker-Schnetmann	241	Frankfurt,Germany	21
22	Rahmig	783	Langen,Germany	13
23	Reinhardt	784	Rodgau,Germany	14
24	Rosenkranz	759	Langen,Germany	21
25	Schwaner	253	Frankfurt,Germany	30
26	Tyagi	255	Goettingen,Germany	17
27	Wuttke	260	Goettingern,Germany	14
				Total= 429

Table 40: Principal Investigators and Sites for Protocol 303860- Switzerland Sites

Center	Principal Investigator	CCC	Site Location	No. Subjects (ITT)
28	Grandi	727	Lausanne, Switzerland	14
29	Fehr-Kuhn	728	Frauenfeld, Switzerland	11
30	Hotz-Amati	729	Frauenfeld, Switzerland	6
31	Koenig	731	Bern, Switzerland	21
32	Kunz	732	Zollikerberg, Switzerland	14
33	Stucki	735	Fribourg, Switzerland	21
				Total = 87

Section 5: Additional Clinical Efficacy Data

Protocol 14523 (Report A09653)

Report A09653 is a multicenter, open-label, randomized, parallel-group comparison of cycle control and safety of DRSP 3 mg/EE 0.020 mg in a 21-day regimen compared with Mercilon (0.150 mg desogestrel [DSG]/0.020 mg EE). A total of 441 women were treated for 7 cycles (220 in DRSP group, 221 in Mercilon group) Three pregnancies were reported during treatment: 1 subject in the DRSP 3 mg/EE 0.020 mg group and 2 subjects in the Mercilon group. **The Pearl Index for the one pregnancy in the DRSP group (based on 1,372 cycles without back-up contraception) was 0.95.**

Source: ISE, 16 Oct 2003 submission

Medical Officer's Comment:

- ***This provides additional efficacy support for the 21-day regimen. There were 1435 total cycles studied for Yasmin 20 (21-day active dosing regimen) in this protocol (1,372 without back-up contraception)***

Protocol 301888 (Report A09151)

Protocol 301888 is a single-center, open-label, randomized study to investigate the effect of DRSP 3 mg/EE 0.020 mg in a 24-day regimen on plasma lipids, hemostatic variables, and carbohydrate metabolism compared with a 21-day regimen of Mercilon (0.150 mg DSG/ 0.020 mg EE). A total of 59 women were treated for 7 cycles. There were 29 subjects in the DRSP arm and 30 subjects in the Mercilon arm. There were no pregnancies reported in this smaller study.

Source: ISE, 16 Oct 2003 submission

Medical Officer's Comment:

- ***This study is too small to comment on contraceptive efficacy. Safety comments from this study are addressed in the integrated summary and the coagulation consult review in Section 9 of the appendix.***

Protocol 14588 (Report A09372)

The aim of the study was to assess the ovulation inhibitory effect of SH T 00186 D containing 0.02 mg ethinyl estradiol betadex and 3 mg drospirenone. The majority of volunteers showed a strong suppression of the ovarian activity, i.e. a low Hoogland score.

For 2 volunteers (PID 105, 128), potential ovulations were assessed in treatment cycle 2 according to the Hoogland score. For these 2 volunteers, the drospirenone levels were measured in all blood samples taken under treatment to check the compliance and to facilitate the interpretation of the ultrasound findings and hormone levels with regard to the Hoogland score assessment.

For PID 105, drospirenone was not detectable in the blood samples taken in treatment cycle 2, being suggestive of completely omitting the intake of study medication in this cycle.
For volunteer PID 128, a slightly irregular intake of study medication was documented in the diary. She was also found to have a history of developing cysts under OCs, which was not recorded in her gynecological history at screening. For PID 128, a follicle size of >13 mm was observed during the whole treatment cycle 2, except for day 7. However, the hormone pattern was not characteristic of an ovulatory cycle. There was no LH peak in the middle of the cycle, no FSH decrease in the second half, and the progesterone levels were low during the whole cycle. A comparison of the hormone patterns in the pre-cycle and the post-treatment cycle with that in treatment cycle 2 revealed apparent differences, especially with regard to the LH and progesterone levels, not being suggestive of enabling and/or supporting a pregnancy. Moreover, the contraceptive efficacy of an oral contraceptive is not solely provided by the follicular suppression, but other factors, e.g. viscosity of cervical mucus contribute to it.

Medical Officer's Comment:

- ***This ovulation inhibition study was performed in Germany using a 21-day regimen.***

Section 6: Case Listings for Thrombotic/Thromboembolic Adverse Events from EURAS and Ingenix Post Marketing Safety Studies

EURAS

The following Tables provide additional information about each of the cases of thrombotic/thromboembolic events that have been reported in the on-going European Post Marketing Surveillance Study.

Table 41: Yasmin Group: Reported VTE and ATE Events in EURAS Study

#	Case Number	Age/BMI	Comments
1	1000033018	21yr/20 Smoker	DVT (phlebography) DRSP OC x 2months prior to event
2	1000053119	44yr/23 Smoker	DVT (duplex sonography) DRSP OC x 1.5-2.0 yrs use
3	1000058097	26yr/24	DVT following femur fracture DRSP OC x 2months prior to event
4	1000118025	23yr/30	DVT and PE Began DRSP OC Oct 2001, DVT symptoms began 10 days later, but had calf and pulmonary symptoms in the postpartum period prior to OC intake Patient = heterozygous for factor V Leiden
5	1000187056	36yr/32	Family history of VTE DRSP OC x 2 years prior to event DVT (phlebography)
6	1000201050	42yr/25 Smoker	DVT (phlebography and sonography) DRSP OC x 18 months prior to event
7	1000201146	34yr/25 Smoker	DVT (sonography-doppler) Prior history of venous thrombosis, family history of DVT DRSP OC x 6 months prior to event
8	1000318009	21yr/19 Smoker	DVT (phlebography) Family history of thrombosis DRSP OC x 21 months prior to event
9	1000320145	31yr/35	Prior history of venous thrombosis after c-section DVT (phlebography) DRSP OC x 4 months prior to event
10	1000491248	23yr/34	DVT and PE DRSP OC x 7 months prior to event
11	1000465011	43yr/26 Ex-smoker	CVA (MR and CT) DRSP OC x 6 months prior to event
12	1000122041	34yr/24	DVT (duplex sonography) DRSP OC x 9 months prior to event
13	1000277205	23yr/18	DVT and PE (duplex sonography) and (spiral CT) DRSP OC x 23 months, stopped for PID which was about 2-3 weeks prior to VTE event

Table 42: LNG-OC Group : Reported VTE and ATE Events in EURAS Study

#	Case Number	Age/BMI	Comments
1	1000020051	43yr/26 Smoker	DVT (US doppler) LNG OC x 6 months prior to event
2	1000053068	41yr/22	DVT and PE developed after knee surgery LNG OC x 18 months prior to event
3	1000055013	25yr/23	DVT (US-doppler) Factor V Leiden mutation LNG OC x 2 months prior to event DRSP OC x 7 months prior to LNG OC
4	1000072256	32yr/24	Death – this case described in table of deaths
5	1000097046	41yr/21 Smoker	DVT and PE after varicose vein surgery one month before LNG OC x 12 months prior to event
6	1000192046	18yr/20	DVT (duplex sonography) Slept in car prior to having symptoms LNG OC x 1-2years prior to event
7	1000390001	20yr/24 Smoker	DVT (duplex sonography) right arm LNG OC x 1 months prior to event, other nonspecified OCs used prior
8	1000800053	43yr/31	DVT (phlebography) LNG OC x 1 months prior to event, other nonspecified OCs used prior
9	1000003132	47yr/24 Smoker	DVT (duplex sonography)
10	1000042196	29yr	CVA (MR) LNG OC x 6 months prior to event
11	1000050305	18yr/19 Ex-smoker	CVA (CT and EEG) LNG OC x 5 months prior to event
12	1000205080	40yr/22	DVT (sonography) after arthroscopy of knee LNG OC x 23 months prior to event
13	1000320109	37yr/26	DVT (phlebography) LNG OC x 21 months prior to event
14	1000405032	43yr/25 Ex-smoker	DVT (phlebography and sonography) Recent LNG OC use

Table 43: "Other Combination Oral Contraceptive" Group: VTE and ATE Events in EURAS Study

#	Case Number	Age/BMI	Comments
1	1000003132	47yr/24 Smoker	DVT (duplex sonography) DSG OC x 19 months prior to event
2	1000021054	23yr/17 Smoker	DVT (duplex sonography) Factor V deficiency dienogest OC x 9 months prior to event
3	1000023175	43yr/21 Smoker	DVT (phlebography) one week following hysterectomy Family history positive for DVT chlormadinone OC x 6 months prior to event
4	1000066086	36yr/27	DVT (duplex sonography) one week post accident Dienogest OC x 8 months prior to event
5	1000077202	44yr/25	DVT (sonography) Possible family history of thrombosis Desogestrel OC x 8 months prior to event
6	1000143087	24yr/22	DVT (phlebography) Factor V-Leiden mutation Dienogest OC x 12 months prior to event
7	1000160021	18yr/23	DVT (phlebography and sono doppler) after knee surgery Desogestrel OC x 2 months prior to event
8	1000201096	50yr/24 Smoker	DVT (duplex sonography) Dienogest OC x 7 prior to the event
9	1000327005	30yr/22 Smoker	DVT (duplex sonography) Desogestrel OC x 8 months prior to the event
10	1000485002	32yr/27 Smoker	DVT (phlebography) Chlormadinone OC x 4 months prior to the event
11	1000485007	39yr/28 Smoker	DVT (phlebography) NETA OC x 14 years prior to the event
12	1010709038	20yr/28	Possible DVT (suspicious imaging) Family history positive Desogestrel OC x 12 months prior to the event
13	1013732115	25yr/33 Smoker	DVT (duplex sonography) Cyproterone acetate OC for a few days prior to event DRSP OC x 6 months prior to cyproterone OC
14	1000010339	27yr/30	PE (V/Q mismatch) Desogestrel OC x 6 months prior to event
15	1000081075	26yr/43 Smoker	PE (pulmonary perfusion scintigraphy Desogestrel OC x 3 months prior to event
16	1000072062	46yr/27 Ex-smoker	AMI (enzymes and ECG, anterolateral) Desogestrel OC x 18 months prior to event
17	1000320125	45yr/35 Smoker	AMI (enzymes) History of hypertension, hyperlipidemia, and diabetes On sequostat OC x 30 years which is 50ug EE pill
18	1000014162	21yr/19	CVA Norgestimate OC x 15 months prior to the event
19	1000311580	25yr/38	Vertebrobasilar ischemia (CT and MR) Depomedroxyprogesterone x 4 months prior to event Last oral contraceptive was Yasmin
20	1000327010	26yr/21	Cerebral hemorrhage associated with brain mets from skin cancer Desogestrel use x 4 months then stopped for one month then event occurred
21	1000177011	38yr/24	DVT (duplex sonography) Cyproterone OC recent use
22	1000180160	44yr/23	DVT (duplex sonography) Gestodene OC recent use
23	1000382090	38yr/24	DVT (sonography) Dienogest x 18 months

Ingenix Study

Table 44: Listing of Cases of Suspected Thromboembolic Events in Yasmin Users (Ingenix Cases)

Patient Number	Age	Reviewer Classification	Reviewer's Comments
Y102108	38	DVT	Probable DVT, Ultrasound of extremities performed
Y102109	35	DVT	Post knee surgery, FH of VTE Left lower extremity DVT confirmed with venous doppler ultrasound
Y102110	46	DVT	Developed right lower extremity DVT after injury to right foot Documented by ultrasound
Y203103	26	CVA	MRI confirmed CVA, history of migraines and Imitrex use
Y301114	19	DVT	DVT of arm develops post IV during ER visit for asthma Ultrasound confirmation
Y303105	31	DVT	Leg DVT confirmed with venous doppler, FH positive for DVT
Y303106	17	DVT	History of lupus, DVT diagnosed but no location specified Short of breath, but VQ was low probability
Y303108	47	Superficial Thrombo-phlebitis	Treated with aspirin and heat
Y401109	31	DVT	Right arm DVT, which recurred after 6 months of coumadin ? underlying factor
Y401113	42	DVT	Left lower extremity DVT, obese
Y402101	48	Superficial Thrombo-phlebitis	Secondary to IV
Y402103	20	?	Chart not found
Y402107	39	PE	PE documented by CT, No apparent risk factors
Medical Officer's Totals = 8 DVT only, 2 Superficial thrombophlebitis, 1 PE)			

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Table 45: Listing of Cases of Suspected Thromboembolic Events in "Other" OC Users (Ingenix Cases)

Patient Number	Age	Reviewer Classification	Reviewer's Comments
O102123	37	?	Developed right sided hemiparesis and aphasia, Diagnosis of TTP, CT negative for CVA
O102135	37	DVT	Ultrasound confirmed RUL DVT
O102141	49	DVT	Duplex confirmed LUL 4 days after total hip revision
O102166	45	DVT	DVT developed after admission for pneumonia and respiratory failure
O103127	23	DVT PE	Developed DVT and PE after admission of idiopathic pulmonary hemorrhagic syndrome
O103135	22	DVT	Doppler confirmed DVT – Strong FH of TE problems "On double dose of OCs for endometriosis)
O103139	38	DVT	MRI confirmed dural venous sinus thrombosis
O103140	24	DVT	LUL DVT confirmed by doppler, Obese +for Factor V mutation
O103155	44	?	Transient loss of vision – migraine versus retinal artery embolus
O202125	38	DVT PE	Multiple carcinoid tumors
O202126	20	DVT	RUL DVT – Down syndrome recent admission for congestive heart failure and pneumonia
O202137	38	DVT	Duplex positive for DVT
O202144	36	DVT	Sagittal sinus thrombosis
O202175	32	PE	V/Q scan positive obesity as risk factor
O203121	38	PE	4 days after bladder surgery
O203137	40	PE	Hysterectomy 10 days prior, Family history of DVT
O203139	41	?	Chart not found
O203146	38	DVT	Femoral and iliac vein thromboses, Obesity risk factor
O203152	24	PE	V/Q scan positive Obesity risk factor
O301121	19	DVT	Confirmed by doppler, FH of TE disease
O302120	21	DVT	Right subclavian DVT two weeks following blood donation
O302127	36	?	Chart not found
O302142	30	Superficial thrombophle bitis	Sono ruled out DVT- Family history of DVT
O302147	50	PE	V/Q scan positive
O302156	27	DVT	Doppler positive popliteal vein, Heterozygous Factor V Leiden
O302159	53	?	DVT one month after colectomy but no definite mention of oral contraceptive use in the record
O303123	34	?	Chart not found
O303125	22	?	History of Hodgkin's and Hickman catheter, may not have been on OCP at the time
O303136	43	?	Chart not found
O401129	41	?	Chart not found
O401143	38	DVT PE	Smoker, recent bruise right thigh CT confirmed PE, sono confirmed DVT
O401146	40	DVT	Sono confirmed DVT, 6 weeks post gastric bypass Family history positive for DVT in two brothers
O402121	37	DVT	Saphenous vein clot
O402138	47	PE	CT confirmed. Mother had history of DVT
Medical Officer's Totals = (15 DVT only, one superficial thrombophlebitis, 9 PEs)			

Section 7: EDR Submissions (bolded) and FDA - Applicant Interactions During Review Cycle

- **16-Oct-2003 = Original submission**
- 3-Nov-2004 = NDA acknowledgement letter
- **18-Nov-2003 = ITT concerning study sites = complete case report tabulations for the pivotal study 303740**
- **25-Nov-2003 = Chemistry submission**
- **4-Dec-2003 = Study site numbering guide**
- 24-Dec-2003 = 74 day letter (questions regarding Brazil site closures, request for interim EURAS report by early July 2004, Updated overall safety extending through early July 2004
- 20-Jan-2004 = Chemistry information request
- **29-Jan-2004 = Chemistry submission**
- 20-Feb-2004 = Request for plan regarding risk management for YAZ and assessment of VTE risks compared to other contraceptives.
- **18 Mar-2004 = Safety Update (reporting period is 3-31-03 to 2-14-04) and Final study report for using YAZ in a 21 day regimen (protocol 303860 in report # A15129)**
- **8-Apr-2004 = Interim EURAS report and response about site closures in Brazil**
- **16-Apr-2004 = Chemistry submission**
- **19-Apr-2004 = United Health Care (numbers of VTE claims Quarter 3, 2001 to Quarter 1, 2003)**
- **21-Apr-2004 = Applicant's initial response regarding their risk management plans for YAZ**
- **23-Apr-2004 = Comparison of Evra and Ortho Tri-Cyclen Lo numbers to Yasmin**
- **28-Apr-2004 = Chemistry submission**
- 30-April-2004 = Applicant's Fax regarding chemistry issues
- 3-May-2004 = Tradename and labeling comments sent to applicant
- **6-May-2004 = Chemistry submission**
- **14-May-2004 = Carton labeling**
- 14-May-2004 = Applicant's letter regarding Tradename
- **21-May-2004 = Tradename issues**
- 21-May-2004 = FDA request for VTE line listings from Ingenix study
- 21-May-2004 = Request for applicant to correlate adverse events with potassium levels ≥5.5 mmol/L and to provide Ingenix line listings for VTEs and ATEs
- 21-May-2004 = Biopharm information request concerning bioequivalence
- **26-May-2004 = Response to line listing and potassium questions in United Health Care**
- **27-May-2004 = Biopharm submission**
- 7-Jun –2004 = Chemistry information request regarding amount of clathrate.

- **9-Jun-2004 = Chemistry submission**
- **10-Jun-2004 = United health care line listing submission**
- **11-Jun-2004 = Chemistry submission**
- 17-Jun-2004 = Request for applicant to submit coagulation study from Yasmin NDA (protocol 92038)
- 23-Jun-2004 = Chemistry information request concerning stability
- **24-Jun-2004 = Submission of hemostasis study 92038 of Yasmin, YAZ and Marvelon**
- **29-Jun-2004 = Response to stats for efficacy dataset**
- **30-Jun-2004 = Short information letter regarding AERS reporting numbers and Dr. Walker's participation**
- **1-Jul-2004 = Chemistry submission**
- 2-Jul-2004 = Agency letter extending PDUFA goal date to 17-Nov-2004 based on 10-Jun-2004 submission of major amendment
- **8-Jul-2004 = Reference to the March and April safety and Euras submissions**
- **9-Jul-2004 = Biopharm submission**
- 13-Jul-2004 = Information request sent to applicant concerning Ingenix and EURAS (requests for information on assessing deaths and summary reports of VTE and ATE in Ingenix, information regarding case of probable VTE in EURAS)
- **22-Jul-2004 = EURAS follow-up algorithm, updated EURAS tables for VTE, PEM abstract**
- 27-Jul-2004 = Industry meeting to discuss EURAS and Ingenix
- 30-Jul-2004 = Biostatistical request for a specific dataset required for efficacy analysis (protocol 303740)
- **3-Aug-2004 = Discussion of the member European state changing the label in regard to Yasmin's unknown influence regarding VTE**
- **4-Aug-2004 = Applicant's response to United Health Care questions – SAS transport file of VTE claims.**
- **6-Aug-2004 BC = Chemistry submission**
- 6-Aug-2004 MR = Meeting request
- **11-Aug-2004 = EURAS cases (June 9, 2004 cut-off)**
- **13-Aug-2004 = Response to stats request**
- **17-Aug-2004 = Meeting request discussion and discussion of Phase IV surveillance study**

- 17-Aug-2004 = Biostatistical request for a specific dataset required for efficacy analysis (protocol 303860)
- **23-Aug-2004 = Response to stats request**
- **8- Sept-2004 = Patent information**
- 24-Sept-2004 = Applicant's FAX regarding Ingenix procedures, individual case reviews and response to ODS questions related medical conditions and demographics of Yasmin initiators
- **24-Sept-2004 = Submission related to decisions concerning chart retrieval in Ingenix study**
- **7-Oct-2004 = Ingenix Study Chart Reviews**
- **21-Oct-2004 = Applicant's Rationale for 24-day regimen**
- **4-Nov-2004 = Applicant's safety update for clinical studies, recalculation of Pearl Indices and life table analysis**

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Section 8: Office of Drug Safety Consultations Regarding Yasmin

The Office of Drug Safety (ODS) has periodically reviewed safety issues related to Yasmin. Their consultative reviews have addressed issues related to spontaneous adverse event reporting the ongoing prospective postmarketing safety surveillance programs (EURAS and Ingenix)and the applicant's proposal for postmarketing surveillance of the 24-day regimen Yasmin 20.

In their most recent review (Aug 31, 2004), they provide the following information related to spontaneous reporting of thrombotic/thromboembolic adverse events and corresponding prescription information.

Table 46: Postmarketing Spontaneous Adverse Event Reporting and Number of Prescriptions for Yasmin

Yasmin Data (May 2001-May 2004)	Number	Reporting Rate (RY) (per 100,000)
Estimated Total Prescriptions*	[redacted]	
Person-Years of Exposure (PY)**	[redacted]	
All Embolism & Thrombosis (ALL)	89	11.9
Pulmonary Embolism (PE)	43	5.7
Deep Vein Thrombosis (DVT) ***	23	3.1
Venous Thromboembolism (VTE)	66	8.8
Cerebrovascular Events (CVE)	16	2.1
All Deaths	6	0.8

* Estimated total Rxs obtained from IMS HEALTH's National Prescription Audit Plus™ - DATA NOT TO BE SHARED OUTSIDE OF FDA OR WITH non-FDA STAFF WITHOUT PRIOR CLEARANCE BY IMS HEALTH.
** 21 average days on therapy assumed for all combined oral contraceptives evaluated.
*** Excludes DVT with PE.
Source: DDRE memo, August 31, 2004

It is difficult to compare these reporting rates to the rates found in the prospective postmarketing safety surveillance studies(EURAS and Ingenix) due to the inherent problems in spontaneous reporting. These rates however are about 6-fold lower than those found in the prospective studies. ODS used 21 days to calculate cycles and subsequent women years as opposed to the 28 days used in the analysis of exposure in the clinical trials. The IMS prescription data does not take into account product samples that are provided in an office setting.

I reviewed the AERS database for analysis of the reported US deaths on Yasmin. They are listed in the following table.

Table 47: US Deaths Reported for Yasmin

ISR/Mfr #	Mfr #	Age	Wt.	FDA Rcvd Date	Comments
3986107	02/ 003887 -US	40	81.6 kg	02 Oct 2002	On Yasmin for premenstrual symptoms for approximately 6 weeks before fatal pulmonary embolism
4095319	03/ 005078 –US SHR	43	UNK	15 Apr 2003	History of polycystic ovaries Autopsy performed
4172180	03/ 007063 – US SHR	22	119 kg	18 Aug 2003	History of obesity, polycystic ovaries, hirsutism and acne Concomitant use of spironolactone Autopsy confirmed massive pulmonary embolism
4117961 and 4123256	03/ 007389 – US SHR	?45 or 46	? 81 or 115 kg	27 May 2003	Patient's past medical history includes deep venous thrombosis Used Yasmin for cycle control and polycystic ovaries Diagnoses = Multiple pulmonary emboli, cardiac arrest Not known if autopsy performed
4132566 and 4101089	03/ 008004 – US SHR	33	103.4 kg	18 June 2003	No family history of VTE Negative for Factor V Leiden, prothrombin mutation and MTHFR Diagnoses = Pulmonary embolism, DVT
4361375	04/ 024911 US SHR	34	UNK	17 May 2004	Reported as normal weight, no patient or family risk factors Pulmonary embolism diagnosed

Noteworthy in the previous table is the fact that five out of six of these individuals were older than age 30 and at least 4 were overweight (the weight for the other two was unknown). Although not autopsy-confirmed in all cases, pulmonary embolism is suspected to be the primary etiology for cause of death in these cases.

Section 9: Division of Gastrointestinal and Coagulation Drug Products Consultation (HFD-180)

The following narrative is taken directly from the Consultation Response by Dr. George Shashaty of the Division of Gastrointestinal and Coagulation Drug Products.

Purpose of the Consult

The Division of Reproductive and Urologic Drug Products poses the following two questions:

1. Please assess if there are any significant differences in regard to hemostatic variable changes between SH T 00186DA (YAZ) and Mercilon treatment arms in Clinical Report A09151.
2. Do any of these hemostatic variables predict thromboembolic risk to patients? If so, which ones are the most important?

The applicant has submitted a study (Clinical Study Report A09151) in which the effects of the oral administration of YAZ on hemostatic variables were compared to those of the oral contraceptive, Mercilon (0.02 ethinyl estradiol/0.150 desogestrel). In this study, 60 healthy female volunteers were randomized into an open-label, single center, randomized trial. The primary endpoint was the effect of these 2 agents on the lipid profile, and a secondary endpoint was the absolute and relative change in a number of hemostatic parameters from baseline to the end of the treatment period, which was 7 cycles.

A previous study (Study 92038) was also made available. Study 92038 was an open-label, randomized trial of the influence of the oral contraceptives SH T 470 FA (Yasmin) and SH T

470 IA (YAZ) on hemostasis in comparison with Marvelon (identical to Mercilon, except that it contains 0.030 mg of ethinyl estradiol). This study was conducted in 1993-94.

Conclusions

The availability of laboratory tests to measure changes in the coagulation system exceeds our knowledge of the relationship between various laboratory changes and thromboembolic events (3). Of the coagulation tests performed in these studies, increased risks of venous thromboembolism occur with increased Factor VIII activity, and inherited deficiencies of anti-thrombin III, Protein C and Protein S. Other clinical states that appear to confer a heightened likelihood of venous thromboembolism (31), including inherited Factor V Leiden and its variants, the prothrombin gene mutation (G20210A) and elevated levels of Factors IX and XI, were not evaluated in these studies. The remainder of the tests performed, which may by theory be believed to predict thrombotic risk, have not been studied sufficiently to warrant their use in the assessment of such risk.

Assays of coagulation factors are problematic because most have large deviations around the mean in apparently healthy persons, are affected by age and sex, and are often both acute and chronic phase reactants.

Because of this variability, the changes seen in the coagulation tests in the women on the various forms of oral contraceptives, although raised above baseline levels, continue to remain within the normal range in most of the subjects. The only exceptions were higher than normal values for Factor VII activity and activated Factor VII and plasminogen, and lower than normal values for total protein S and plasminogen activator inhibitor 1 antigen. The relationship between these out of range values and the risk of thrombosis is not known.

An additional problem in interpreting the coagulation changes is whether or not there is a causal link between the changes and the development of thrombosis. It is possible that many of the coagulation changes are simply epiphenomena that signal risk but do not participate in the clotting process.

The increased risk of thromboembolic events in women receiving oral contraceptives is compounded in the face of an inherited coagulation defect (21, 24, 31, 33). Although it is possible for a woman with an inherited coagulation defect to use oral contraceptives, particularly if she has no personal or family history of symptomatic thrombosis, there may be as high as a 10-15 fold increase in the risk of thromboembolism when a coagulation defect is present.

The findings in these studies are interesting. There seems to be little difference between YAZ and Mercilon in their effects on the laboratory assessment of changes in coagulation. The results do not provide a basis for the suggested differences in thromboembolic risk among women taking oral contraceptives containing different doses and forms of estrogens and progestins. The changes described cannot be used to reliably predict thromboembolic risks to women who use these contraceptive drugs.

Recommendations

1. To help clarify the relationship between coagulation parameters and clinical thromboembolic events, it would be useful to determine the rates of thromboembolism in a prospective manner in women whose coagulation profiles have been performed. Regression analysis

would then permit correlations to be made between each of the laboratory tests and the risk of thromboembolism, as well as odds ratios for specific levels of changes. The most important women upon whom to focus would be those whose laboratory values are most distant from the mean. The assumption is that such women would be both most and least likely to experience thromboembolic events.

2. In the event that such studies cannot be done, a registry of treated women should be considered as a post-marketing commitment to provide some correlation of thromboembolism with coagulation parameters which would allow a prediction of the likelihood of thrombosis in a given person receiving the drug. Women admitted to the registry would have blood collected and analyzed for hemostatic parameters at baseline and again at cycle 7. Those with antithrombin III, protein C and protein S deficiency, and with Factor V Leiden would be either excluded from the trial or analyzed separately, as there is reasonable documentation that these persons would have a higher rate of thromboembolism. The remaining subjects would be followed for the development of thromboembolism, and correlations, if any, would be established for each hemostatic parameter. At some point, a statistically significant relationship between a change(s) in specific parameter(s) would emerge if it exists. Such a relationship would not necessarily prove causality between the parameter and thromboembolism, but would be a useful surrogate for risk.

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/s/

Gerald Willett
11/16/04 11:57:16 AM
MEDICAL OFFICER

Scott Monroe
11/17/04 03:29:18 PM
MEDICAL OFFICER
I concur with Dr. Willett that both dosing regimens for Yasmin 20 are approvable. However, Yasmin 20 (24-day regimen) should not be approved until the Applicant demonstrates a clinical advantage for this regimen, over that for the 21-day regimen.

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SEREVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: July 8, 2004

From: George G. Shashaty, M.D.
Medical Reviewer, Hematology, HFD-180

Subject: Consultation Request dated June 15, 2004
NDA 21676
Berlex SH T 00186 DA (YAZ)

To: Charlene Williamson
Project Manager
Division of Reproductive and Urologic Drug Products, HFD-580

Through: Kathy Robie Suh,M.D., PhD
Medical Team Leader, Hematology
and
Robert Justice, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Background

YAZ is a new oral contraceptive that contains both an estrogen (0.020 mg of ethinyl estradiol) and a synthetic progestational agent (3.0 mg of drosperinone). YAZ is nearly identical to Yasmine, an oral contraceptive already marketed by the sponsor, except that the latter contains 0.030 mg of ethinyl estradiol.

The sponsor has submitted a study (Clinical Study Report A09151) in which the effects of the oral administration of YAZ on hemostatic variables were compared to those of the oral contraceptive, Mercilon (0.02 ethinyl estradiol/0.150 desogestrol). In this study, 60 healthy female volunteers were randomized into an open-label, single center, randomized trial. The primary endpoint was the effect of these 2 agents on the lipid profile, and a secondary endpoint was the absolute and relative change in a number of hemostatic parameters from baseline to the end of the treatment period, which was 7 cycles.

A previous study (Study 92038) was also made available. Study 92038 was an open-label, randomized trial of the influence of the oral contraceptives SH T 470 FA (Yasmine) and SH T 470 IA (YAZ) on hemostasis in comparison with Marvelon (identical to Mercilon, except that it contains 0.030 mg of ethinyl estradiol). This study was conducted in 1993-94.

Purpose of the Consult

The Division of Reproductive and Urologic Drug Products poses the following two questions:

1. Please assess if there are any significant differences in regard to hemostatic variable changes between SH T 00186DA (YAZ) and Mercilon treatment arms in Clinical Report A09151.
2. Do any of these hemostatic variables predict thromboembolic risk to patients? If so, which ones are the most important?

Review of the Submission

The review examined the following materials:

- Clinical Study Report A09151, dated January 30, 2003, Pages 1-112
- Research Report AE91, Study Report ME92038, dated August 25, 1995, Pages 34630-34688
- Literature references listed

In the current study (A09151), coagulation parameters were measured in women treated with either YAZ or Mercilon. Hemostatic studies were performed on study subjects in both arms of the trial immediately prior to administration of study drug (referred to as baseline) and immediately following the termination of study drug which was at the end of menstrual cycle #7. Blood for these determinations was drawn in the fasting state, stored and transported under appropriate conditions, and analyzed in a central laboratory

Of 60 women randomized, 7 had premature discontinuation of the study drug (equivalently in both arms) and an additional 6 stopped medication because of adverse events (equal in both arms). The full analysis set (FAS) for safety included 59 women, and the full analysis set for efficacy included 53 women, equally distributed between the 2 arms. The per-protocol analysis set (PPS) included 22 women in the SH T 00186DA arm and 25 in the Mercilon arm. A review of the results of the hemostatic parameters shows little difference between the FAS (efficacy) and the PPS populations. Therefore, this report focuses on the results of the PPS since it provides observations on subjects with the longest duration in the study.

The following categories of hemostatic functions were performed:

1. Activation markers of thrombin and fibrinogen turnover:
    a) Prothrombin fragments 1 + 2
    b) D-dimer
    c) Thrombin-antithrombin complexes
    d) Soluble fibrin
2. Procoagulatory variables:
    a) Factor VII antigen
    b) Factor VII activity

c) Activated Factor VII
d) Factor VIII activity
e) Fibrinogen

3. Anticoagulatory variables:
   a) Anti-thrombin antigen and activity
   b) Protein C antigen and activity
   c) Free Protein S
   d) Total Protein S
   e) APC resistance
4. Profibrinolytic variables:
   a) Plasminogen
   b) t-plasminogen activator antigen
   c) t-plasminogen activator activity
   d) Plasmin-antiplasmin complex
5. Antifibrinolytic variable:
   a) Plasminogen activator inhibitor-1

Table 1 shows the results of the changes in hemostatic variables associated with each drug. For simplicity, only the ratio of the cycle 7/baseline values is listed. For comparison, the shaded areas of the table show the results from a previous study (ME92038) performed in 1992-93, and which included YAZ, Yasmine (same formulation as YAZ except that it contains 0.030 mg of ethinyl estradiol) and Marvilon (which is the same as Mercilon except that it contains 0.030 mg of ethinyl estradiol).

Table 1. Hemostatic Parameters after Administration of YAZ and Mercilon (current study) and YAZ, Marvilon and Yasmine (1992-93 study). Values listed are ratios of Cycle #7 to baseline.

	YAZ (current)	Mercilon (current)	
Prothrombin Frag 1/2	1.22	1.34	
D-dimer	1.76	1.58	
T-AT Complex	1.24	1.31	
Soluble Fibrin	1.09	1.23	
Factor VII Activity	1.57	1.36	
Factor VII, activated	2.13	1.58	
Factor VII Antigen	1.55	1.38	
Factor VIII Activity	1.23	1.09	
Fibrinogen	1.19	1.13	
AT-III Antigen	0.98	0.94	
AT-III Activity	0.97	0.93	
Protein C Antigen	1.25	1.15	
Protein C Activity	1.31	1.18	
Protein S, free	0.91	0.99	
Protein S, total	0.81	0.87	
APC Resistance	0.85	0.91	

Protein S Antigen			
Plasminogen	1.38	1.32	
t-PA Antigen	0.63	0.52	
t-PA Activity	8.29	5.84	
PAP Complex	1.77	1.49	
PAI-1 Antigen	0.35	0.28	
PAI-1 Activity			

Empty boxes indicate that the particular assay was not performed. Unshaded areas are results from the current study (A09151). Shaded areas are results from 1992-93 study (ME92038)

The data in the table may generally be summarized as follows:

1. Blood levels of prothrombin fragment 1 + 2, D-dimer, T-AT complex and soluble fibrin are increased, suggesting activation of the coagulation pathway.
2. Blood levels of Factor VII (activity, activated and antigen), Factor VIII and fibrinogen are increased. This increase may be due to the stimulatory effect of estrogen on protein synthesis in general. Nonetheless, the reported values for some of these factors actually underestimates the rate of anabolism, since the rate of catabolism is probably raised because of the apparent activation of the coagulation system.
3. Blood levels of the intrinsic inhibitors of coagulation (anti-thrombin III, protein C and protein S) are variable. Anti-thrombin III is unchanged, protein C is increased and protein S is diminished. APC resistance is diminished. Such inhibitors are usually decreased when coagulation has been activated, so an easy explanation for these results is not available.
4. Blood levels of components of the fibinolytic pathway, a process that would be a response to the deposition of fibrin, are also variable. Levels of plasminogen and plasminogen-antiplasmin complex are increased, whereas the level of tissue plasminogen activator antigen is considerably reduced. Tissue plasminogen activator activity is markedly increased. These findings suggest activation of the fibrinolytic system.
5. Blood levels of plasminogen activator inhibitor reflect a curbing of the anti-fibrinolytic response with a marked fall in PAI-1 antigen with a smaller fall in PAI-1 activity.
6. The levels of all these components of coagulation appear to be similarly raised or lowered in both the YAZ treated patients and the Mercilon treated patients except for somewhat higher relative increases in the Factor VII related moieties in the YAZ treated women.
7. Tests of coagulation performed in 1992-93 on YAZ treated women show changes similar to YAZ treated women in the current study except for a much lower relative increase in t-PA activity. How much of this may be due to methodological differences or the different laboratories that performed the tests is uncertain.
8. There are some differences in coagulation tests between YAZ and Yasmine in the 1992-93 study that would, in general, suggest that YAZ has a somewhat lesser

effect on activation of coagulation and the body's native response to that perturbation. For example, the levels of D-dimer, thrombin-antithrombin complex formation and fibrinogen are lower and the levels of total protein S are higher in YAZ treated women than they are in Yasmine treated women

9. Although the levels of the coagulation factors increase and decrease as described above, the majority of values continue to remain within the normal range. The reason for this is that the range of normal for most of these factors is very wide.
10. The wide standard deviations around the mean or median of the level of the coagulation factors indicates that some persons had very high or very low levels of these factors. It is possible that persons who had these extreme values may behave differently from those who had only a modestly higher or lower value.
11. The uncertain effect of the difference in the site of performance of the laboratory tests (the original tests were performed at [redacted], and the different time and methodologies of test performance (the original tests were done in 1992-93) on the results listed in the Table 1 make direct comparisons between the studies difficult.

Background

Balance between bleeding and clotting depends on the interaction among 3 entities: the blood vessel, platelets and liquid phase components of the coagulation system. Each of these factors possesses multiple procoagulatory and anticoagulatory functions. In general, it is believed that thrombotic events that occur on the venous side of the circulatory system, where pressures and flow are low, are more related to changes in coagulation factors. Thus, drugs that affect coagulation factors, such as heparin and warfarin, are particularly useful in the prevention and treatment of venous thromboembolic disease. Thrombotic events that occur on the arterial side of the circulation, where pressures and flow are high, are more related to platelets and the vessel wall. Thus, drugs that affect platelets, such as aspirin and clopidogrel, are useful in coronary syndromes and cerebrovascular disease. Although such divisions of pathological processes may be useful in the overall considerations of thrombosis, there is also significant overlap between changes in vessels, platelets and coagulation factors and both arterial and venous thrombotic disease.

The study under consideration did not investigate any platelet or vascular characteristics, and this review will be confined to a discussion of changes in coagulation factors and their relation to thrombosis.

Review

The increased frequency of thromboembolic complications in women taking oral contraceptives was noted from the earliest days of their use (1). Subsequently,

coagulation studies performed on women taking oral contraceptives showed changes in the coagulation system (2). Since then, large bodies of data relevant to perturbations in the coagulation system have been gathered as new knowledge and methods of analysis of this system have been acquired (3). Despite this information, the relationship of the specific changes in coagulation to the causation of thromboembolic complications has never been established.

What does seem clear is that the use of oral contraceptives containing any of a myriad of different estrogens and progesterones elicits an in vivo state of accelerated fibrinogen catabolism that in turn provokes a reactionary response of the fibrinolytic system or a state of "compensated clotting". In addition, it appears that oral contraceptives upregulate the synthesis of many or all of the individual coagulation factors that have been associated with an increased incidence of both venous and arterial thromboembolic events in persons not receiving oral anticoagulants.

In a recent study by the Oral Contraceptive and Hemostasis Study Group (4), the effects of 7 monophasic oral contraceptive regimens on hemostatic variables revealed the following changes:

1. Activation of coagulation demonstrated by a rise in prothrombin fragment 1 + 2, and increases in the level of D-Dimer, fibrinogen degradation products and soluble fibrin.
2. Increases in the plasma levels of fibrinogen, Factor VII (coagulant, antigen and activated), Factor VIII and von Willebrand factor.
3. Diminution of native anticoagulation capability demonstrated by a fall in the levels of antithrombin and protein S (although there was an increase in protein C).
4. Some increase in resistance to activated protein C, but in only one of two assays, and in a manner that is not associated with an increased risk of thrombosis in women.
5. Diminution in free and total protein S.
6. Increases in plasminogen, plasmin-antiplasmin complex formation and tissue plasminogen activator activity with decreases in tissue plasminogen activator and plasminogen activator inhibitor.

These effects on hemostatic variables were dependent on both the estrogen and progesterone components of the drug. The magnitude of the changes was small and their relationship to thromboembolic risk in healthy women could not be defined. A number of other studies (5,6,7,8,9,10,11) have shown similar or nearly similar results, and have not been able to correlate the changes noted with the ability to predict an increased thromboembolic risk.

Table 2 lists the nature and/or function of each studied variable, the state of knowledge of its association with thrombosis and references. For some variables, although a test is available, there is no reasonable literature to indicate any association with thrombosis.

Table 2. Hemostatic variables and the relation to thrombosis.

	Nature/Function	Relation to Thrombosis	Reference
Prothrombin Frag 1/2	Activation of prothrombin	Uncertain	12,13,14
D-dimer	Fibrin degradation product	Uncertain	14,15
T-AT Complex	Thrombin binding/inactivation	Uncertain	12,13
Soluble Fibrin	Early product of thrombin activation	Uncertain	
Factor VII Activity	Pro-coagulant	Uncertain	16,17,18
Factor VII, activated	Tissue factor co-factor	Uncertain	16,17,18
Factor VII Antigen	Quantitation of protein form	Uncertain	16,17,18
Factor VIII Activity	Pro-coagulant	Increased risk for >90th compared to <90th percentile	19,20
Fibrinogen	Substrate of thrombin	Uncertain for VTE; higher risk of stroke and myocardial infarction as fibrinogen increases	21,22
AT-III Antigen	Quantitation of protein form	Uncertain	
AT-III Activity	Anti-coagulant	Increased thromboembolism with inherited deficiencies	23,24
Protein C Antigen	Quantitation of protein form	Uncertain	
Protein C Activity	Anti-coagulant	Increased thromboembolism with inherited deficiencies	24,25
Protein S, free	Anti-coagulant	May be increased	24
Protein S, total	Quantitation of protein form	Uncertain	
APC Resistance	Ability to neutralize V_a and $VIII_a$	Increased thromboembolism with Factor V Leiden	25,26,27
Protein S Antigen	Quantitation of protein form	Uncertain	
Plasminogen	Degrades fibrinogen and fibrin	Uncertain	28,29
t-PA Antigen	Quantitation of protein form	Uncertain	
t-PA Activity	Converts plasminogen to plasmin	Uncertain	30
PAP Complex	Inactivator of plasmin	Uncertain	
PAI-1 Antigen	Quantitation of protein form	Uncertain	
PAI-1 Activity	Inactivates plasminogen activator	Uncertain	

Empty cells reflect absence of significant information to comment

Conclusions

The availability of laboratory tests to measure changes in the coagulation system exceeds our knowledge of the relationship between various laboratory changes and thromboembolic events (3). Of the coagulation tests performed in these studies, increased risks of venous thromboembolism occur with increased Factor VIII activity, and inherited deficiencies of anti-thrombin III, Protein C and Protein S. Other clinical states that appear to confer a heightened likelihood of venous thromboembolism (31), including inherited Factor V Leiden and its variants, the prothrombin gene mutation (G20210A) and elevated levels of Factors IX and XI, were not evaluated in these studies. The remainder of the tests performed, which may by theory be believed to predict thrombotic risk, have not been studied sufficiently to warrant their use in the assessment of such risk.

Assays of coagulation factors are problematic because most have large deviations around the mean in apparently healthy persons, are affected by age and sex, and are often both acute and chronic phase reactants. Table 3 shows the normal range of values for common coagulation tests for an apparently healthy population of adults (32). Similar broad ranges are reported for the other tests reported in the studies examined.

Table 3. Normal values for coagulation tests
(in U/ml, except as otherwise noted)

Coagulation Test	Range (U/ml)
Fibrinogen	1.50-3.50 (g/dl)
Factor II	0.79-1.31
Factor V	0.62-1.39
Factor VII	0.50-1.29
Factor VIII	0.50-1.50
Factor IX	0.65-1.50
Factor X	0.77-1.31
Factor XI	0.65-1.50
Factor XII	0.50-1.50
Von Willebrand Factor	0.43-1.50
Antithrombin III	0.85-1.22
Protein C	0.78-2.32
Protein S	0.58-1.46
Plasminogen	0.74-1.24
T-PA	3.0-12.0 (ng/ml)
PAI	2.0-15.0
α_2-antiplasmin	4.4-8.5 (mg/dl)

Because of this variability, the changes seen in the coagulation tests in the women on the various forms of oral contraceptives, although raised above baseline levels, continue to remain within the normal range in most of the subjects. The only exceptions were higher than normal values for Factor VII activity and activated Factor VII and plasminogen, and

lower than normal values for total protein S and plasminogen activator inhibitor 1 antigen. The relationship between these out of range values and the risk of thrombosis is not known.

An additional problem in interpreting the coagulation changes is whether or not there is a causal link between the changes and the development of thrombosis. It is possible that many of the coagulation changes are simply epiphenomena that signal risk but do not participate in the clotting process.

The increased risk of thromboembolic events in women receiving oral contraceptives is compounded in the face of an inherited coagulation defect (21, 24, 31, 33). Although it is possible for a woman with an inherited coagulation defect to use oral contraceptives, particularly if she has no personal or family history of symptomatic thrombosis, there may be as high as a 10-15 fold increase in the risk of thromboembolism when a coagulation defect is present.

The findings in these studies are interesting. There seems to be little difference between YAZ and Mercilon in their effects on the laboratory assessment of changes in coagulation. The results do not provide a basis for the suggested differences in thromboembolic risk among women taking oral contraceptives containing different doses and forms of estrogens and progesterones. The changes described cannot be used to reliably predict thromboembolic risks to women who use these contraceptive drugs.

Recommendations

1. To help clarify the relationship between coagulation parameters and clinical thromboembolic events, it would be useful to determine the rates of thromboembolism in a prospective manner in women whose coagulation profiles have been performed. Regression analysis would then permit correlations to be made between each of the laboratory tests and the risk of thromboembolism, as well as odds ratios for specific levels of changes. The most important women upon whom to focus would be those whose laboratory values are most distant from the mean. The assumption is that such women would be both most and least likely to experience thromboembolic events.
2. In the event that such studies cannot be done, a registry of treated women should be considered as a post-marketing commitment to provide some correlation of thromboembolism with coagulation parameters which would allow a prediction of the likelihood of thrombosis in a given person receiving the drug. Women admitted to the registry would have blood collected and analyzed for hemostatic parameters at baseline and again at cycle 7. Those with antithrombin III, protein C and protein S deficiency, and with Factor V Leiden would be either excluded from the trial or analyzed separately, as there is reasonable documentation that these persons would have a higher rate of thromboembolism. The remaining subjects would be followed for the development of thromboembolism, and correlations, if any, would be established for each hemostatic parameter. At

some point, a statistically significant relationship between a change(s) in specific parameter(s) would emerge if it exists. Such a relationship would not necessarily prove causality between the parameter and thromboembolism, but would be a useful surrogate for risk.

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