The statistical methods that the sponsor has used seems to be reasonable. This reviewer assessed and re-evaluated the sponsors' results. The findings were similar to that of the Sponsor's.

Comparing the results of three different recalculations of the primary efficacy endpoints with the original evaluation, better follicular suppression is indicated with the 24 day regimen compared to the 21 day regimen."

6.1.6 Efficacy Conclusions

The efficacy conclusions for the 24-Day regimen of YAZ are the following:

- The total 28-day cycles of exposure used to calculate the Pearl Index was adequate (11,050 cycles) for efficacy determination. The division has requested that Applicants have at least 10,000 cycles.
- The Pearl Index of 1.41 is acceptable for approval for contraceptive efficacy.
- The comparative Study (protocol 308382) shows better follicular suppression with the 24-day regimen compared to the 21-day regimen.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There were four deaths reported in the clinical studies of YAZ. Two of these deaths occurred in protocol 303740 (YAZ, 24-day regimen) at the single US Study site. Neither of these deaths was related to Study medication. One death, secondary to pesticide poisoning, occurred one month following discontinuation of Study drug. The other death, occurring three months after starting Study medication, was secondary to smoke inhalation in a fire.

The clinical summaries for the two deaths reported for subjects participating in Protocol 303740 are as follows:

- **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 [redacted] 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 ——— at 2:00 a.m.

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

The other two deaths in subjects using Yaz occurred in ongoing Study protocol 308021, which is an open label non-US Study of the 24-day regimen for 13 cycles in 1010 volunteers. One of the deaths was secondary to Goodpasture's syndrome, and the other death was secondary to murder. Neither of these deaths is attributable to Study drug. The clinical summaries for these two deaths are as follows:

- **Subject 3250/Volunteer 1056 had** received Yasmin 20 (24 day regimen) for 161 days when she was murdered by shooting on ——— In agreement with the reporting investigator, the event is considered by the company as unrelated to the Study drug (none).

- **Subject 2466/Volunteer 533** died of Goodpasture's syndrome. She had started intake of Yasmin 20 (24 day regimen) on 03 Mar 2004 and died suddenly on ——— Patient's family history was unremarkable, except for type II diabetes in her father. The patient's own medical history included the fact that she was a non- smoker and that she had suffered from renal colic on 05 Jan 2005 which had been treated with cotrimoxazol 1.5 g daily. It was reported that the patient had no further relevant medical history.

  The autopsy revealed lung hemorrhage due to Goodpasture's syndrome (pulmorenal syndrome) as the cause of death in this patient.

Medical Officer's Comment:

- ***There is no indication from the scientific literature of any relationship of Goodpasture's disease with oral contraceptives. Research has focused on this disease as having an autoimmune basis related to the basement membranes found in numerous tissues.***

The following table (Table 10) lists the aforementioned deaths, SAEs and premature discontinuations due to AE in the 3 mg DRSP / 0.02 mg EE clinical studies.

Table 10: Deaths, SAEs and Premature Discontinuations due to AEs in the 3 mg DRSP / 0.02 mg EE clinical studies

Study	R*	Ph	Status	Deaths/ Drug related (yes,no)	SAEs (# of subj)	Drug related SAE & (Comment)	Subjects with Premature Discontinuation (All / Drug related)	Total YAZ subjects in Study
301780	N/A	1	Complete	0	0	0	0	18
300080	N/A	1	Complete	0	0	0	0	18
304326	N/A	1	Complete	0	0	0	0	18
305103	21	1	Complete	0	0	0	1/0	48
303741	N/A	1	Complete	0	0	0	0	24
305466	21	2	Complete	0	1	0	1/1	23
14588	21	2	Complete	0	0	0	0	30
303740	24	3	Complete	2 (no)	27	4 (migraine, depression x 2, and cholelithiasis)	77/65	1027
301888	24	3	Complete	0	0	0	3/3	29
304049	24	3	Complete	0	4	1 (cervical dysplasia)	0	231
305141	24	3	Complete	0	1	0	4/4	54
14523	21	3	Complete	0	3	0	15/13	220
303860	21	3	Complete	0	30	6 (pulmonary embolism x 2, fibrocystic breast x 2, cholecystitis, migraine	38/33	516
306946	N/A	1	Completed	0	0	0	0	24
308382	24 v. 21	3	Completed	0	2	1 (ovarian cyst)	1/1	104
308020	24 v. Mercilon	3	Draft report	0	3	0	18/18**	229
Totals				2	74	13	188/166	3149
308021	24	3	Ongoing	2 (no)	12	1 (ovarian cyst)		

* = Regimen (whether 24-day, 21-day or comparative)
** = Information derived from draft report

Medical Officer's Comment:

- ***The acne studies which are still being reviewed have not been included in this table. No deaths occurred in the acne studies. Study 308021 has been included because of the known deaths reported.***

7.1.2 Serious Adverse Events

7.1.2.1 Thrombotic and Thromboembolic Adverse Events

Clinical trials with 3 mg DRSP / 0.02 mg EE

Two cases of pulmonary embolus were reported to have occurred in women using the 21-day regimen of 3 mg DRSP / 0.02 mg EE in protocol 303860. The Applicant's clinical summaries of these two cases of pulmonary embolism are reported verbatim below:

"Volunteer number 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. Thrombosis of Vena femoralis superficialis until adductors-channel 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 sponsor as being 'possible' as a causal relationship cannot be excluded. The patient discontinued the Study drug, and fully recovered."

"Volunteer number 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 on ——— 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 phosphatidylserine 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 sponsor assessed the treatment relationship as 'possible'. The patient discontinued the Study drug, and fully recovered from the SAE."

Medical Officer's Comment

- ***The finding of two confirmed venous thromboembolic adverse events (2 cases of pulmonary emboli in the 21-day regimen Study 303860) translates to a VTE rate of 6.3 per 10,000 women-years for the (3 mg DRSP / 0.02 mg EE products (in the preliminary safety data for 24 and 21-day regimen clinical trial exposure data to date - 41,155 cycles or 3165 women years). This rate is lower than the VTE rate of the approved product Yasmin in the first year of the EURAS Study (approximately 15 cases per 10,000 women-years of use). This rate is also lower than the VTE rate in the Prescription-Event Monitoring (PEM) Study for Yasmin carried out in the UK. The VTE incidence rate in the PEM Study was 13.7 cases per 10,000 women-years.***
- ***There were no other cases of thrombotic or thromboembolic adverse events for 3 mg DRSP / 0.02 mg EE as of the 28 Oct 2005 submission where the Applicant provided the division with an update regarding these events for all clinical studies (including ongoing studies).***
- ***The VTE rate of 6.3 per 10,000 women-years is also comparable to the findings in all three arms of the EURAS Study (Yasmin, levonorgestrel based oral contraceptives and other contraceptives). Some of the highest rates for VTE in women occur in the postpartum period. A VTE rate of 51.1 per 10,000 women-years was found in the Olmstead County Minnesota 30-year population Study for women in the postpartum period (Heit et al. Trends in the Incidence of Venous Thromboembolism during Pregnancy or Postpartum: A 30-Year Population-Based Study. Annals of Internal Medicine; Volume 143, pages 697-706; Nov 15, 2005.)***

7.1.2.2 Serious Adverse Events in the 24-Day Regimen Studies

Contraceptive Studies

Protocol 303740 - In protocol 303740 (principle safety and efficacy Study for the 24-day regimen) there were 37 serious adverse events in 30 subjects (see Table 11). The drug relationship was characterized by the investigator as possible in three events (epistaxis, vascular disorder and abnormal Pap smear). The drug relationship was characterized by the investigator as probable in two events (migraine and depression)

Table 11: Serious Adverse Events in Study 303740 (Primary Efficacy and Safety Study)

PID	Country	HARTS Term	Drug Relationship	Discontinuation Due to AE
14	Austria	Migraine	Probable	Yes
		Epistaxis	Possible	Yes
		Depression	Probable	Yes
40	USA	Death, pesticide poisoning	None	-
61	USA	Death, accidental injury	None	-
193	Austria	Surgery (arthroscopy of knee)	None	No
243	Austria	Accidental injury (ruptured tendon)	None	No
244	Austria	Accidental injury (dog bite)	None	No
277	Austria	Ovarian cyst	None	No
		Surgery (chronic tonsillitis)	None	No
337	Austria	Surgery (conization)	None	No
363	Austria	Abdominal pain (pelvic inflammatory disease)	None	No
420	Austria	Surgery (appendicitis)	None	No
422	Austria	Upper respiratory infection (acute tonsillitis)	None	No
424	Austria	Surgery (appendicitis)	None	No
512	Austria	Hernia	None	No
545	Argentina	Vascular disorder	Possible	Yes
589	Argentina	Abortion	Unlikely	Yes
604	Argentina	Abortion	Unlikely	Yes
643	Argentina	Accidental injury (burns)	None	No
668	Argentina	Suicide attempt other than overdose	Unlikely	Yes
743	Argentina	Papanicolaou smear suspicious (HSIL)	Possible	No
745	Argentina	Bone fracture (not spontaneous)	None	Yes
844	Poland	Eye disorder	Unlikely	Yes
		Headache	Unlikely	Yes
		Dizziness	Unlikely	Yes
		Myasthenia	Unlikely	Yes
		Neuropathy	Unlikely	Yes
973	Austria	Surgery (chronic tonsillitis)	None	No
974	Austria	Cholelithiasis	None	No
1019	Austria	Laboratory test abnormal (creatinine increase)	Unlikely	No
1033	Austria	Laboratory test abnormal (creatinine increase)	Unlikely	No
1093	Brazil	Psychotic depression	Unlikely	Yes
1133	Brazil	Accidental injury	None	Patient lost
1143	Brazil	Allergic reaction (bronchitis)	None	No
1160	Brazil	Pyelonephritis	None	No
1196	Brazil	Pharyngitis	Unlikely	No

PID – Patient Identification number
Source: Protocol 303740, Study report page 121 of 3785 (NDA 21-676)

Medical Officer's Comment

- ***Of the serious adverse events characterized by the investigator as having no relationship or an unlikely relationship to Study drug, this reviewer feels that four events including an ovarian cyst, headache, cholelithiasis and depression are possibly related. The two events of migraine and depression listed in the probable category in the preceding paragraph***

occurred in the same subject. The vascular disorder mentioned above led to meningeal symptoms and was found to be congenital and not related to Study drug.

Protocol 308020 - In protocol 308020 (comparative Study with Mercilon), there were 4 serious adverse events in 3 subjects in the YAZ, 24-day regimen arm (broken finger, abnormal Pap smear, tonsillitis and peritonsillar abscess). Five serious adverse events occurred in five Mercilon subjects (abscess, enteritis, gastroenteritis, optic neuritis and abnormal Pap smear). None of these events were considered to be related to Study drug (Medical officer concurs).

PMDD Trials

There were a total of five serious adverse events (SAEs) in the two trials (see Table 12). Three occurred in subjects randomized to DRSP /EE in Study 304049: incarcerated incisional hernia, abnormal Pap and spinal bone spurs. Two occurred in subjects taking placebo (one in each trial): appendicitis and miscarriage following a pregnancy diagnosed during the placebo exposure period. The overall rates of SAEs in the two exposure groups were therefore 1.1% in the DRSP /EE-exposed subjects and 0.7% in the placebo-exposed subjects. For the individual trials, the SAE rate was 1.3% in the DRSP /EE group and 0.5% in the placebo group of Study 304049, and 0% during DRSP /EE exposure and 2.0% during placebo exposure in Study 305141.

Table 12: Serious Adverse Events during Treatment

SAE (Subject #)	Treatment	Causality	Timing	Intensity	Resolution
Lower abdominal pain (incarcerated incisional hernia) (510008)	DRSP /EE	Unrelated	5 weeks after first dose	Moderate	Recovered following surgery
Lower back bone spurs (190004)	DRSP /EE	Unrelated	5 weeks after first dose	Severe	Recovered following surgery
Severe dysplasia on Pap (HSIL) (560002)	DRSP /EE	Possibly related	12 weeks after first dose (Visit 7)	Severe	Unknown – colposcopic dx and LEEP pathology unknown
Appendicitis (380066)	Placebo	Unrelated	8 weeks after first dose	Severe	Recovered following surgery
Miscarriage (231002)	Placebo	Unrelated	59 days after starting placebo	Severe	Recovered

Source: Table 91, a21566.pdf, Section 16, p 219 and Table 90, a07545.pdf, Section 14, p 306 (NDA 21-676)

7.1.2.3 Serious Adverse Events in the 21-Day Regimen Studies

Protocol 303860 - In protocol 303860 (principal safety and efficacy Study for the 21-day regimen) there were 34 serious adverse events in 30 subjects (see Table 13). The drug relationship was characterized by the investigator as possible in three events (ovarian cyst/back pain; pain in extremity and pulmonary embolus/pelvic vein thrombosis). The drug relationship was characterized by the investigator as probable in four events (fibrocystic breast; pulmonary embolus/left leg; abnormal vision and migraine).

Table 13: Listing of Serious Adverse Events in 21-Day Regimen Protocol 303860

PID	HARTS Code/ Diagnosis	Drug Relation	Discontinued
10	Surgery / appendectomy	None	No
6	Fibrocystic breast / fibroadenoma left breast Skin hypertrophy / keloid scar	Probable None	Yes
118	Surgery / right knee	None	No
156	Surgery / appendectomy	None	No
149	Surgery / tonsillectomy	None	No
163	Pulmonary embolus / + thrombosis left leg	Probable	Yes
215	Fibrocystic breast / fibroadenoma right breast	Unlikely	No
194	Pain in extremity	Possible	Yes
268	Gastroenteritis	Unlikely	No
262	Surgery / gnathoplasty (deviated maxilla)	None	No
306	Constipation	None	No
329	Accidental injury / smoke intoxication	None	No
189	Surgery plastic surgery (nasal septum)	None	No
317	Ovarian cyst / pain in back and abdomen	Possible	No
313	Surgery / appendectomy	None	Yes (wt. gain)
60	Bone fracture / left leg	None	No
671{	Abnormal vision / sudden visual disturbance Migraine	Probable Probable	Yes
655{	Tooth disorder / teeth correction Tooth disorder / teeth correction	None None	No No
96	Surgery / appendectomy	None	No
115	Cholecystitis	None	No
94	Encephalitis	None	No
75	Surgery / plastic surgery (nasal septum)	None	No
70	Surgery / breast reduction	None	No
371{	Pulmonary embolus / + pelvic vein thrombosis Surgery / appendectomy	Possible None	Yes
355	Surgery / appendectomy	None	No
399	Infection / erysipelas	None	No
450	Surgery / appendectomy	None	No
462	Skin melanoma / superficial spreading melanoma (abdominal skin right, level III, 0.7cm depth)	Unlikely	Yes
486	Abdominal pain	None	No
512	Cervix carcinoma in situ / (cervix uteri)	None	Yes

Brackets in the table refer to the fact that some subjects had two events
Source: Study Report for Protocol 303860, page 94 of 1143 (NDA 21-676)

Medical Officer's Comment

- ***Of the serious adverse events characterized by the investigator as having no relationship to Study drug, this reviewer feels that a case of cholecystitis is possibly related. The cases of pulmonary emboli were fully described in section 7.1.2.1.***
- ***The case of the painful extremity had imaging studies performed to rule out deep vein thrombosis (DVT). The studies were negative for DVT. The abnormal vision and migraine events occurred in a single subject and can be related solely to migraine.***

Protocol 14523 - In protocol 14523 (21-day regimen compared to Mercilon) there were three serious adverse events in the 21-day regimen arm (accidental injury and two surgeries). There was one serious adverse event in the Mercilon arm (gastroenteritis). None of these events was considered to be related to drug use.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Adverse Events Associated With Dropouts in the 24-Day Regimen

Contraceptive Trials

Protocol 303740 - In Study protocol 303740 (principle safety and efficacy Study for the 24-day regimen) a total of 125 AEs in 77 of 1027 volunteers (7.5%) led to discontinuation of the Study medication. The most common reasons for discontinuation of the Study medication due to AEs were headache in 14 volunteers (1.4%), intermenstrual bleeding and nausea in 7 volunteers (0.7%) each, and decreased libido and depression in 6 volunteers (0.6%) each. A total of 65 volunteers prematurely discontinued the Study medication due to treatment-related AEs. A more complete description is found in Table 14 that follows.

Table 14: Most Common Reasons for Discontinuation of Study Medication Due to AEs in Study Protocol 303740

HARTS TERM	N = 1027	
	AEs	(%)
Headache	14	1.4
Intermenstrual bleeding	7	0.7
Nausea	7	0.7
Libido decreased	6	0.6
Depression	6	0.6
Emotional lability	5	0.5
Vomiting	5	0.5
Dysmenorrhea	5	0.5
Breast pain	4	0.4
Weight gain	4	0.4
Abdominal pain	4	0.4
Rash	3	0.3
Acne	3	0.3
Migraine	3	0.3
Back pain	2	0.2
Asthenia	2	0.2
Abnormal laboratory test	2	0.2
Edema	2	0.2
Sweating increased	2	0.2
Dizziness	2	0.2
Somnolence	2	0.2
Menorrhagia	2	0.2

Source: Study Report A12007, page 116 of 3785 (NDA 21-676)

Protocol 308020 - In protocol 308020 (comparative Study with Mercilon), a total of 18 volunteers prematurely discontinued the Study because of AEs in the YAZ-24 day regimen. All

AEs that led to discontinuation were considered related to the Study medication. The most common reasons were headache (3 of 229 or 1.3%); mood changes (3 of 229 or 1.3%) and irregular bleeding (3 of 229 or 1.3%)

Medical Officer's Comment

- ***These adverse events are commonly seen with all combination oral contraceptives and may lead to drug discontinuation. These percentages are not increased above expected rates.***

PMDD Trials

Forty subjects terminated prematurely across the two clinical trials because of one or more adverse events that occurred during DRSP /EE exposure (14.0 %), as did 11 subjects during their exposure to placebo (4.1%). For the individual trials, the rate of withdrawal due to adverse events was 15.5% in the DRSP /EE group and 4.1% in the placebo group of Study 304049, and 7.4% during DRSP /EE exposure and 4.1% during placebo exposure in Study 305141. Adverse events leading to withdrawal (>1%) are listed in Table 15.

Table 15: Adverse Events (>1%) Leading to Withdrawal in the PMDD trials

Preferred Term	DRSP /EE N=285		Placebo N=267	
	N	%	N	%
Nausea	13	4.6	3	1.1
Intermenstrual bleeding	8	2.8	0	0
Asthenia	7	2.5	1	0.4
Breast pain/tenderness	5	1.7	0	0
Depression	4	1.4	0	0
Nervousness	4	1.4	2	0.7
Headache	3	1.1	2	0.7
Emotional lability	3	1.1	0	0
Increased appetite	3	1.1	0	0
Menorrhagia	3	1.1	0	0
Vomiting	3	1.1	0	0

Source: Text Table 35, a21566.pdf, p 119 and Table 91, Section 14, a07545.pdf, p 307 (NDA 21-676)

7.1.3.2 Adverse Events Associated With Dropouts in the 21-Day Regimen

Protocol 303860 - Of a total of 38 volunteers in protocol 303860 (21-day regimen safety and efficacy) that had AEs leading to discontinuation of the Study medication, 33 volunteers prematurely discontinued the Study medication due to treatment related AEs. The most common reasons for discontinuation of the Study medication due to AEs were decreased libido and depression in 5 volunteers (1.0%) each, headache and emotional lability in 4 volunteers (0.8%) each and acne and weight gain in 3 volunteers (0.6%) each.

Protocol 14523 -Twenty-four (5.4%) volunteers discontinued Study protocol 14523 (21-day regimen compared to Mercilon) due to AEs, i.e., 15 (6.8%) from the 21-day group (incl. one

SAE, subj. no. 649, accidental injury) and 9 (4.0%) from the Mercilon group. The most frequent AE leading to a discontinuation of the Study medication was weight gain (four volunteers from the 21-day group and two from the Mercilon group). Other events, which occurred more than once, were headache, depression, menorrhagia, skin disorder/acne and emotional lability.

7.1.5 Common Adverse Events

7.1.5.1 Common Adverse Events in the 24-Day Regimen Studies

Contraceptive Studies

Protocol 303740 - In protocol 303740 (principle safety and efficacy Study for the 24-day regimen) signs and symptoms most frequently reported as AEs were headache for 137 volunteers (13.3%) assessed as treatment related for 67 volunteers (6.5%), upper respiratory tract infections for 137 volunteers (13.3%) all of which were assessed to be without treatment relationship, and breast pain for 71 volunteers (6.9%) assessed as treatment related for 65 volunteers (6.3%). A more complete listing is presented in Table 16 derived from the medical officer's review during the first review cycle.

Table 16: Adverse Events (>2% of subjects) in Protocol 303740 (Total N = 1027)

HARTS term	N	%	Considered Treatment Related	
			N	%
Headache	137	13.3	67	6.5
Upper respiratory infection	137	13.3	0	0
Breast pain	71	6.9	65	6.3
Vaginal moniliasis	67	6.5	12	1.2
Leukorrhea	58	5.6	5	0.5
Diarrhea	52	5.1	2	0.2
Nausea/ Vomiting	47	4.6	38	3.7
Vaginitis	45	4.4	2	0.2
Abdominal pain	42	4.1	10	1.0
Flu syndrome	39	3.8	0	0
Dysmenorrhea	38	3.7	9	0.9
Allergic reaction	33	3.2	0	0
Accidental injury	32	3.1	2	0.2
Urinary tract infection	32	3.1	0	0
Cystitis	31	3.0	0	0
Tooth disorder	29	2.8	0	0
Sore Throat	28	2.7	0	0
Infection	26	2.5	0	0
Fever	24	2.3	0	0
Surgery	23	2.2	0	0
Sinusitis	23	2.2	0	0
Back pain	21	2.0	3	0.3

Source: Clinical Study Report No. A12007, pages 1470-1476 of 3206 (NDA 21-676)

Medical Officer's Comment

- ***These adverse events are commonly seen in combination oral contraceptive trials. There are no safety signals in the percentages found for these events.***

Protocol 308020 - In protocol 308020 (comparative Study with Mercilon), the most common AEs (≥ 5% of all volunteers) are listed in Table 17.

Table 17: Comparative Study 308020 – Frequent Adverse Events ≥ 5%

Adverse Event	YAZ 24-Day Regimen		Mercilon	
	N (229)	%	N (220)	%
Headache	29	12.7	23	10.5
Nasopharyngitis	16	7.3	16	7.3
Influenza	14	5.2	15	5.9
Cystitis	7	3.1	14	5.0

Source: Study Report A29551 submitted to NDA 21-676 on November 22, 2005

7.1.5.2 Common Adverse Events in the 21-Day Regimen Contraceptive Studies

Protocol 303860 - Table 18 lists the most common adverse events in a comparative fashion between the pivotal Phase 3 studies for the 24-day and 21-day regimens of 3 mg DRSP / 0.02 mg EE, respectively..

Table 18: Comparison of most frequent AEs (≥ 5% of subjects) 24 versus 21 – Day Regimen

Adverse Event	**24-Day Regimen Protocol 303740**		**21-Day Regimen Protocol 303860**	
	N (1027)	**%**	**N (516)**	**%**
Headache	137	13.3	70	13.6
Upper respiratory infection	137	13.3	77	14.9
Breast pain	71	6.9	32	6.2
Vaginal moniliasis	67	6.5	89	17.2
Leukorrhea	58	5.6	5	1.0
Diarrhea	52	5.1	59	11.4
Abdominal pain	42	4.1	42	8.1
Flu syndrome	39	3.8	29	5.6
Vaginitis	45	4.4	34	6.6

Source: Clinical Study Report No. A12007, pages 1470-1476 of 3206 and Clinical Study Report No. A15129, page 89 of 1143 (NDA 21-676)

Medical Officer's Comment

- ***The common adverse event profile is similar in these two regimens except for moniliasis and leukorrhea. This may just be a recording discrepancy. There is no theoretic reason that a 21-day regimen should be associated with more yeast infections.***

Protocol 14523 - In protocol 14523 (21-day YAZ regimen compared to Mercilon) the most common treatment related adverse events in the 21-day regimen were metrorrhagia (n = 9, 4.1%); headache and weight gain (each n=7, 3.2%) and alopecia & emotional lability (n = 3,

1.4% for each). The most common treatment related adverse events in the Mercilon arm were headache (n =21, 4.8%); metrorrhagia (n =20, 4.5%) and weight gain (n =8, 1.8%).

7.1.6 Cycle Control

Intracyclic Bleeding

The numbers (%) of subjects with intracyclic bleeding during each cycle in Study protocols 303740 (24-day regimen) and 303860 (21-day regimen) are shown respectively in Table 19 and Table 20.

Table 19: Intracyclic Bleeding Analysis for Protocol 303740 (24-day regimen)

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 (NDA 21-676)

Table 20: Intracyclic Bleeding Analysis for Protocol 303860 (21-day regimen)

Cycle	Intracyclic Bleeding			
	No		Yes	
	N	%	N	%
1	287	78.6	78	21.4
2	325	91.8	29	8.2
3	319	89.6	37	10.4
4	327	90.8	33	9.2
5	348	94.8	19	5.2
6	334	90.0	37	10.0
7	344	93.2	25	6.8
8	339	93.6	23	6.4
9	336	93.8	22	6.2
10	333	92.7	26	7.2
11	340	93.4	24	6.6
12	331	92.2	28	7.8
13	341	94.2	21	5.8
20	314	95.1	16	4.9
26	258	93.4	18	6.5

Source: Clinical Study Report No. A15129, pages 552-553 of 1143 (NDA 21-676)

The numbers (%) of subjects with intracyclic bleeding in each treatment cycle are directly compared by treatment cycle for the 21- and 24-day dosing regimens (see Table 21).

Table 21 Number (%) of Subjects with Intracyclic Bleeding in Studies 303860 and 303740

Cycle	Number (%) with No Intracyclic Bleeding			
	24-day regimen		21-day regimen	
	N	%	N	%
1	704	25	287	21
2	768	14	325	8
3	753	14	319	10
4	757	14	327	9
5	766	10	348	5
6	727	14	334	10
7	748	9	344	7
8	713	11	339	6
9	687	10	336	6
10	678	10	333	7
11	674	8	340	7
12	645	10	331	8
13	442	15	341	6

Source: Modified from Table 19 and Table 20 of this review (NDA 21-676)

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. Intracyclic or "mid-cycle bleeding" is a common side effect of many combination oral contraceptives. Intracyclic bleeding may increase slightly when the estrogenic component of the pill is lessened. There were 7 (0.6%) incidents of intermenstrual bleeding leading to discontinuation of YAZ in protocol 303740 (24-day regimen). There were 2 (0.4%) incidents of intermenstrual bleeding leading to discontinuation in the 21-day regimen. The pattern of intracyclic bleeding appears slightly better in the 21-day protocol, but both products overall have a very acceptable bleeding profile.***
- ***In comparative Study 308020, intracyclic bleeding percentages for Mercilon were 12.5%, 9.4% and 11.1% for cycles 2, 4 and 6, respectively. Intracyclic bleeding percentages for YAZ in this comparative Study were 15.3%, 16.5% and 8.8% for cycles 2, 4 and 6, respectively.***

Withdrawal Bleeding (Protocol 303740 (24-day regimen)

A majority (89.6%) of the volunteers in the full analysis set (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.

Medical Officer's Comment

- ***The absence of a withdrawal bleeding episode may disturb some patients and make them think that they have become pregnant.***

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 is small. The mean length of withdrawal bleeding is acceptable as well as the percentage of subjects who reported somewhat heavier withdrawal bleeding (8-12%)***
- ***In Study 308020 the overall cycle control pattern appeared similar to Mercilon. There was no evidence of significant irregular bleeding with either product.***

7.1.7 Laboratory Findings

7.1.7.1 Potassium Monitoring

Because of a potential for drospirenone products to cause retention of potassium, potassium measurements and assessment for hyperkalemic symptoms have been undertaken, first for Yasmin and also for YAZ.

Contraceptive Trials

Protocol 303740 - The section on potassium monitoring in protocol 303740 (pivotal Study for 24-day regimen for contraception) in the Medical Reviewer's first cycle clinical review is reproduced below:

"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 mEq/L. The mean and median values along with the mean changes from baseline are listed in Table 22

Table 22: Mean Potassium Levels During Protocol 303740

Visit	Mean/median absolute value (mEq/L)				Mean change from baseline (mEq/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 (NDA 21-676)

Single potassium values above 5 mEq/L were reported for 65 volunteers. In most of theses cases, values were only slightly increased and did not exceed the Applicant's alert range (>5.75 mEq/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 reported that were 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 or a subsequent 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, preanalytical 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 suggest 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 23.

Table 23: Subject Listing for Serum Potassium Values >5.5 mEq/L (Study 303740)

PID	Site #	Study Day	Potassium mEq/L	Re-Test Potassium 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	5.5			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	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

Source: Lab dataset for Study 303740 (NDA 21-676)

Medical Officer's Comment

- ***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. 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 potassium values 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 mEq/L 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.***
- ***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.***

Protocol 308020 - In European Study 308020 (YAZ vs Mercilon) hyperkalemia (serum potassium above the normal range of 5.3 mEq/L) occurred at least once in post baseline samples in 5 of 229 (2.2%) women in the YAZ group and in 5 of 220 (2.3%) subjects in the Mercilon group. Of the 10 subjects with elevated potassium, only 2 had elevated values on treatment (one each in the YAZ and Mercilon treatment groups). In the YAZ group, the on treatment serum K+ value was > 6.0 mEq/L (subject 500249). However, the blood sample was assessed as hemolytic. The remaining 8 values were measured in the YAZ (n=4) and Mercilon (n=4) groups during follow up 10 to 17 days after last tablet intake. There was one case of dizziness among the subjects in the YAZ group with post-baseline serum potassium values >5.5 mEq/L which was not an SAE. None of the other selected cardiovascular events potentially related to elevated potassium (arrhythmia, bradycardia, syncope, tachycardia, and palpitations) were reported. Hyponatremia was not seen in any of the subjects during the treatment phase of the Study,

Protocol 308382 - In the Applicant's complete response to NDA 21-676 (15 June 2005), there was only one subject (PID# 307) in the ovarian suppression Study (protocol 308382) with a potassium value of 5.6 mEq/L which is slightly above the upper limit of the reference range (upper limit of the reference range in this Study was: 5.3 mEq/L).

PMDD Studies

The major focus of the analysis of chemistry laboratory values was to assess the potential effect of DRSP /EE, as an antimineralocorticoid, on potassium concentrations. The number of subjects

with potassium levels above 5.4 mEq/L is shown in Table 24 . The proportions in each treatment group were similar (1.4% of DRSP /EE subjects, 1.1% of placebo subjects). None of these subjects experienced any of the cardiovascular adverse events potentially associated with hyperkalemia, and only one subject in each treatment arm was taking a concomitant medication (NSAID) thought to affect potassium levels. All except two of the placebo subjects normalized their values while remaining on treatment. Only one elevated value (subject #380112 in Study 304049, assigned to DRSP /EE, who increased from a baseline level of 4.4 mEq/L to 6.0 at Cycle 2, and then returned to normal, by the end of treatment) was considered by the investigator to be clinically relevant.

Table 24: Subjects with Elevated Post-treatment Potassium Values – Pooled Data

Report Number	Treatment	Subject	Visit	Postbaseline Serum Potassium ≥5.5 mEq/L	Serum Creatinine (mg/dL)	Creatinine Clearance (mL/min)	Creatinine Clearance Category*
A21566	YAZ	200056	Treatment Cycle 2 (31 days)	5.5	1.0	69.1	mild
	YAZ	380122	Treatment Cycle 2 (26 days)	6.0	0.9	81.6	normal
	YAZ	510008	Treatment Cycle 2 (30 days)	5.7	0.6	129.9	normal
	Placebo	840058	End of Treatment Cycle (127 days)	5.6	0.6	145.2	normal
A07545	YAZ	80001	End of Treatment Cycle (87 days)	5.6	1.0	67.2	mild
	Placebo	80021	Treatment Cycle 2 (140 days)	5.7	0.7	116.0	normal
	Placebo	80039	End of Treatment Cycle (246 days)	6.2	4.2	27.6	severe

*Creatinine clearance categories: >80 mL/min = normal; 50 to ≤80 mL/min = mild; 30 to ≤50 mL/min = moderate; ≤30 mL/min = severe.

Source: Text Table 21, iss.pdf, p 61 (NDA 21-873)

Change from baseline in potassium level was minimal, and similar between treatment arms, as shown in Table 25

Table 25 Change from Baseline in Potassium Level – Pooled Data

Treatment	Number of Subjects[a]	Baseline Mean ± SD	Change from Baseline in Postbaseline Maximum[b] Mean ± SD	Change from Baseline in Postbaseline Average[b] Mean ± SD
YAZ	255	4.27 ± 0.374	0.17 ± 0.431	0.04 ± 0.394
Placebo	245	4.23 ± 0.359	0.18 ± 0.393	0.04 ± 0.360

SD = standard deviation.
Note: Normal ranges of serum potassium are 3.4 – 5.4 mEq/L for Report A21566 and 3.6 - 5.2 mEq/L for Report A07545.
[a]Number of subjects who had a baseline and at least 1 postbaseline serum potassium value.
[b]All serum potassium values, including results from unscheduled and repeat visits, were used in the calculation of average and maximum serum potassium values.

Source: Text Table 22, iss.pdf, p 65 (NDA 21-873)

The percent of subjects with transitions in potassium values from normal findings at baseline to values outside the normal range over all treatment visits was greater in the DRSP /EE group (2.8%) than the placebo group (1.6%) (See Table 26).

Table 26 Transitions* in Potassium Values with Treatment – Pooled Data

Parameter	Treatment Cycle	Treatment Group	Baseline Value (%)	Low (%)	Normal (%)	High (%)	Total (%)
Potassium	All	DRSP /EE	Low (%)	0	1 (0.4)	0	1 (0.4)
			Normal (%)	1 (0.4)	245 (96.1)	7 (2.8)	253 (99.2)
			High (%)	0	1 (0.4)	0	1 (0.4)
			Total (%)	1 (0.4)	247 (96.9)	7 (2.8)	255 (100)
		Placebo	Low (%)	0	2 (0.8)	0	2 (0.8)
			Normal (%)	2 (0.8)	237 (96.7)	4 (1.6)	243 (99.2)
			High (%)	0	0	0	0
			Total (%)	2 (0.8)	239 (97.6)	4 (1.6)	245 (100)

* Normal range varied slightly over the two studies, with an upper limit of normal of 5.4 mEq/L in Study 304049 and of 5.2 mEq/L in Study 305141 (NDA 21-873)
Source: Table 38, ise.pdf, pp 472

Medical Reviewer's Comment:

- ***The difference in numbers of YAZ patients in Table 26 compared to Table 24 is due to difference in the cut points between the two studies. A small but increased percent of DRSP /EE subjects as compared to placebo subjects had increases in potassium level outside of the normal range over the course of treatment. However, these elevated potassium levels were not associated with cardiovascular sequelae in any case, and tended to resolve without discontinuation of DRSP /EE. The overall mean change in potassium level with treatment was minimal and similar to that experienced in the placebo group.***

In addition, creatinine clearance was assessed as a measure of renal function that may affect potassium balance (see Table 27). In the DRSP /EE group, 2.3% of subjects experienced a shift from normal function to mild renal impairment (as estimated by serum creatinine levels), compared to 3.3% of placebo subjects.

Table 27 Transitions in Creatinine Clearance with Treatment – Pooled Data

Parameter	Treatment Cycle	Treatment Group (N)	Baseline Value (%)	Normal (%)	Mild (%)	Moderate (%)	Severe (%)
Creatinine Clearance	EOT	DRSP /EE (256)	Normal (%)	243 (94.9)	6 (2.3	0	0
			Mild (%)	6 (2.3	1 (0.4)	0	0
			Moderate (%)	0	0	0	0
			Severe (%)	0	0	0	0
		Placebo (242)	Normal (%)	226 (93.4)	8 (3.3)	0	1* (0.4)
			Mild (%)	3 (1.2)	4 (1.7)	0	0
			Moderate (%)	0	0	0	0
			Severe (%)	0	0	0	0

* This subject, #80039 in the placebo group, had elevations in creatinine clearance, creatinine and potassium that were determined to be spurious
Source: Table 41, ise.pdf, pp 481 (NDA 21-873)

Medical Reviewer's Comment:

- ***There does not appear to be an increased risk of renal impairment with DRSP /EE use.***

7.1.7.2 Postmarketing Potassium Monitoring of Yasmin

Ingenix Study. A postmarketing safety surveillance of Yasmin was undertaken for the theoretical possibility of hyperkalemia developing with drospirenone. There has been no safety signal regarding hyperkalemia or symptoms secondary to hyperkalemia to date. According to the Applicant, safety advisory board reviewing this data last reported no safety issues on June 7, 2005 regarding data presented in a April 30, 2005 report. A table (Table 28) below shows ten quarters worth of safety data in the Ingenix Study regarding hyperkalemia and associated symptoms.

Table 28: Hyperkalemia and Hyperkalemia Symptoms - Ingenix Ten Propensity Matched Cohorts from Quarter Three, 2001 through Quarter Four, 2003

	Yasmin Initiators (n=15,767)			Other Oral Contraceptive Initiators (31,534)	
Outcome	Chart Confirmed	Not Found *		Chart Confirmed	Not Found *
Syncope	57	23		141	43
Arrhythmia	36	60		54	95
Hyperkalemia	1	1		4	1
Other Electrolyte Disturbance	21	23		45	24
Dialysis	0	0		4	0
Myocardial Infarction	0	1		3	6

* In these cases the chart was not found to verify the insurance claim diagnosis.
Source: Applicant's October 28, 2005 submission to NDA 21-676 and NDA 21-873, page 14 of 98.

Medical Officer's Comment

- ***Although there appears to be more arrhythmias identified in the Yasmin initiators there is no evidence of increased hyperkalemia in the Yasmin initiators. The safety advisory board evaluated the arrhythmia cases and found a large number with a preexisting diagnosis. There were no cases of hyperkalemia when potassium was recorded in the arrhythmia cases.***

Spontaneous Postmarketing Safety Reports.

The Applicant submitted an updated report on hyperkalemia found through spontaneous postmarketing safety reporting. Table 29 lists these cases:

Table 29: Postmarketing Reports of Hyperkalemia in Women Using Yasmin

Case number	Potassium level	EKG changes	Symptoms	Comment
01/00187-GBD	Mild (value unknown)	None reported	None reported	Treatment duration unknown. Laboratory error suspected by physician
US-2005-009728	Elevated (value unknown)	None reported	None reported	Value measured after 3 days of use
FR-2004-031662	5.0	None reported	weight increase, increased triglycerides and aldosterone	Hyperaldosteronism suspected (not in line with hyperkalemia), adrenal adenoma ruled out by US, positive de-challenge
US-SHR-04-022934	5.9 (nl range unknown)	None reported	None reported	Blood glucose 56 mg/dl. No concurrent drugs mentioned. No info on Yasmin discontinuation, physician refused to provide additional information
US-SHR-03-015436	K 5.6 and 5.9 (normal range 3.5-5.3)	None reported	None listed	K values during the 1st month of use Serum Creatinine 1.3 (baseline unknown) No concurrent drugs, Renal insufficiency since age of 1 year
US-SHR-03-008562	"over 5.5"(nl range and baseline unk)	None reported	None reported	Treatment duration unknown
US-SHR-03-004094 (consumer)	"high end of normal"(baseline and normal range unknown)	None reported	None reported	Treatment duration approx. 8 months. Indication: HT and ovarian cyst suppression. Fluid retention for which triamterene-HCTZ was described. Thereafter weakness and dizzy spells. Diuretic changed to HCTZ alone. In addition, ovarian cyst rupture was reported. Symptoms abated, Yasmin continues.
USA-2002-007308	"elevated K level"(not specified)	None reported	None reported	Treatment duration unknown. No case details available
02/05035-USE	"hyper-kalemia" (value unk)	None reported	None reported	Treatment duration 2 weeks. H/o aldosterone disorder. No case details available
02/04297-USE	"slight elevation" ,(no values prior to or during use)	None reported	Breast enlargement, 8-10 lb weight gain	Finding during the month of initiation. H/o slightly elevated K prior to Yasmin due to chronic ibuprofen use (800 mg tid).
02/02398-USE	"elevated"	None reported	None reported	Treatment duration unknown. Test performed more than once with different results (unspecified). No case details available.
02/01905-USE	"high"	None reported	None reported	Treatment duration unknown. No case details available.
02/01883-USE	"high"	None reported	None reported	Treatment duration unknown. No case details available.
02/00406-USE	5.5-5.6 (normal range not provided)	None reported	Fatigue, near syncope	Value measured during the first month of use. Conc.drugs:Zoloft, Cafergot, Vicodin, OTC NSAIDS.
01/07332-USE	5.6 mEq/l (3.6-5.0)	None reported	None reported	Treatment duration 3 weeks. Until 2 wks prior to Yasmin start spironolactone had been used for ***acne*** (K 4.8)
01/06273-USE	5.0 mEq/l, "increased " (nl: 3.6-5.0)	Ventricular ectopics in EKG	Palpitation	Treatment duration approx. 1 month. No treatment initiated, symptoms continued 1.5 months after Yasmin was stopped.
01/05736-USE	5.6 mEq/l (nl: 3.6-5.3)	None reported	None reported	Treatment duration 2 months

Source: The 10 Jan 06 submission to both NDA 21-873 and NDA 21-676

Medical Officer's Comment

- ***Most of the listed cases lack evidence of any symptomatic sequelae. Only one case (01/06273-USE) had EKG alterations and this case had symptoms continue past discontinuation of Yasmin. In most of the cases the potassium elevation appears to be mild, but the normal range for the determination is missing. It appears that other medical conditions and concurrent drugs may be also playing a role. The evidence to date does not suggest any alteration to our present labeling and safety monitoring for Yasmin. This reporting information does not preclude an approval recommendation for YAZ.***

7.1.7.3 Other Laboratory Findings

Medical Officer's Comment:

- ***In Study 303740 standard hematological and chemistry safety labs either showed normal findings or laboratory changes consistent with class effects known for combination oral contraceptives.***

7.1.8 Vital Signs

In the pivotal contraceptive Study 303740, there were no significant mean changes in heart rate or blood pressure. Rare subjects had slight elevations in blood pressure which is a known side effect of combination oral contraceptives.

7.1.17 Postmarketing Experience with Yasmin

The Applicant has provided data from two large ongoing postmarketing safety surveillance trials supporting the safety of the presently marketed DRSP product Yasmin:

7.1.17.1 EURAS Study

The European Active Surveillance Study (EURAS) was initiated for Yasmin in March 2001. This surveillance Study is part of a European effort to perform postmarketing safety on contraceptive formulations with new progestins and/or estrogen. Reporting for this Study was last updated on 15 June 2005. At that time, 59,510 women were enrolled representing 117,153 women-years of observation including 34,310 women-years of exposure to Yasmin. The comparative data (see Table 30) shows the thrombotic/thromboembolic adverse event rates for Yasmin, levonorgestrel-based oral contraceptives and "other" oral contraceptives. The results demonstrate that Yasmin does not have a thrombotic/thromboembolic rate that is statistically higher than other COCs that do not contain DRSP.

Table 30: EURAS Study: Confirmed Thromboembolic AEs – Number of Events, Incidence, 95% CI

Event Category	Yasmin (34,310 WY)			LNG-containing OCs (32,415 WY)			Other OCs (50,428 WY			Total
	N	Per 104 WY	95% CI	N	Per 104 WY	95% CI	N	Per 104 WY	95% CI	N
All VTE & ATE	28	8.2	5.4 –11.8	25	7.7	5.0-11.4	48	9.5	7.0-12.6	101
All VTE	25	7.3	4.7 - 10.8	20	6.2	3.8-9.5	42	8.3	6.0-11.3	87
PE	7	2.0	0.8 – 4.2	5	1.5	0.5-3.6	8	1.6	0.7-3.1	20
All ATE	3	0.9	0.2 – 2.6	5	1.5	0.5-3.6	6	1.2	0.4-2.6	14
AMI	0	0.0	0.0 – 1.1	2	0.6	0.1-2.2	4	0.8	0.2-2.0	6
CVA	3	0.9	0.2 – 2.6	3	0.9	0.2-2.7	2	0.4	0.0-1.4	8
All Fatal VTE/ATE	0	0.0	0.0 – 1.1	2	0.6	0.1-2.2	0	0.0	0.0-0.7	2

VTE = venous thromboembolic event, ATE = arterial thromboembolic event, AMI = acute myocardial infarction,
CVA = cerebrovascular accident, WY = women-years
Source: Applicant's 18 Aug 2005 submission, page 7 of 13 (NDA 21-676)

7.1.17.2 Ingenix Study

The US postmarketing surveillance Study (Ingenix Study of United Health Care Patients) was initially designed to monitor adverse events related to hyperkalemia. The Ingenix Study was later modified to monitor thrombotic and thromboembolic adverse events. The most recent interim analysis of the Ingenix Study (see Table 31) does not show a higher risk for Yasmin, compared to other oral contraceptives, for thrombotic and thromboembolic adverse events.

Table 31: Ingenix Study Results (Confirmed Cases of Thrombotic and Thromboembolic Events)

	Yasmin Cohorts (N=15,767)				Other OC Cohorts (N=31,534)					
Thromboembolism Subgroup	N	PY	IR [1]	95% CI	N	PY	IR	95% CI	RR	95% CI
Pulmonary embolism	5	13,160	0.4	0.1-0.8	7	25,361	0.3	0.1-0.5	1.4	0.3-5.0
Venous thrombosis	12	13,160	0.9	0.5-1.5	22	25,361	0.9	0.6-1.3	1.1	0.5-2.2
Venous thrombosis and pulmonary embolism	1	13,160	0.1	0.0-0.4	4	25,361	0.2	0.1-0.4	0.5	0.0-4.9
Stroke [2]	1	13,160	0.1	0.0-0.4	4	25,361	0.2	0.1-0.4	0.5	0.0-4.9

PY = Person-years; IR= Incidence rate; RR= Rate ratio
1 Incidence rates expressed as events per 1,000 person-years
2 TIA outcomes also counted in stroke.
Source: Applicant's 18 Aug 2005 submission, page 7 of 13 (NDA 21-676)

7.1.17.3 AERS Database

The office of drug safety recently reported on thromboembolic adverse events in selected contraceptive products. The estimated figures for Yasmin are shown in Table 32:

Table 32: Vascular Adverse Events and Deaths for Yasmin in AERS Reporting Data Since U.S. Product Launch.

	Yasmin (May 2001-May 2004)		Yasmin (May 2001-Aug 2005)	
Estimated Total Prescriptions	[redacted]		[redacted]	
Person-Years of Exposure	749,844		1,906,838	
	N	Reporting Rate (per 100,000)	N	Reporting Rate (per 100,000)
All Embolism & Thrombosis	89	11.9	123	6.5
Pulmonary Embolism	43	5.7	53	2.7
Cerebrovascular Events	16	2.1	23	1.2
Myocardial Infarction	Not assessed		2	0.1
All Deaths	6	0.8	6	0.3

Source: ODS reports of August 31, 2004 and November 1, 2005

Medical Officer's Comment:

- ***Post marketing reporting rates can only provide limited data regarding the true incidence of adverse events compared to similar products due to marketing influences and increased reporting after media attention. It is noteworthy that the reporting rates for all embolism and thrombosis have dropped since the analysis in 2004. The rates listed for Yasmin are less than some other marketed products. It is anticipated that spontaneous reporting for YAZ will show lower numbers since the product contains one third less ethinyl estradiol per tablet.***

7.2 Adequacy of Patient Exposure and Safety Assessments

Table 33 lists the completed phase 2/3 studies comprising the safety exposure database for 3 mg DRSP / 0.02 mg EE. There were another 101 subjects in phase 1 and phase 2 studies with limited treatment duration.

Table 33: Subject Exposure Completed studies of 3 mg DRSP / 0.02 mg EE (24 and 21 day regimens)

Study No. (Regimen)	Purpose of Study	No. Subjects on DRSP /EE	Treatment Duration (cycles)	No. Treatment Cycles	No. Subjects treated for ≥ 1 yr
24 day active dosing regimen					
303740	Contraception (24-day)	1027	13	11,480	746
301888	Lipid, hemostatic and CHO	29	7	182	0
304049	PMDD	231	3	579	0
305141	PMDD	54	3	140	0
308020	Cycle control comparative	227	7	1354	0
306996	Acne	270	6	~1407*	0
306820	Acne	266	6	~1346*	0
Subtotal		1341	NA	16,488	746
21 or 24 day active dosing regimens					
308382	Ovarian suppression 24-day vs 21-day	104	3	311	0
21 day active dosing regimen					
303860	Contraception (21-day)	516	26	11,510	438
14523	Cycle control	220	7	1,435	0
305466	Ovarian suppression (21-day)	23	2	43	0
14588	Ovarian suppression (21-day)	30	2	58	0
Subtotal		789	NA	13,046	438
All completed 24 and 21 day active dosing regimens					
Total of all		***2232***	***NA***	***29,845***	***1184***

* = Derived from multiplying #subjects x mean days on drug/ 28 days
Source: Tables of studies and individual Study reports (NDA 21-676 and NDA 21-873)

Medical Officer's Comment

- ***Additional review of the safety data in the acne studies and the Applicant's ongoing Study 308021 (open label safety and efficacy of YAZ) is being performed. The Applicant stated that 870 subjects in Study 308021 (Phase 3 contraceptive Study) have completed 13 cycles of treatment which would add 11,310 additional cycles for safety evaluation. The Applicant has stated that in these additional cycles there have been no reports of thrombotic or thromboembolic adverse events (VTE, PE, MI or CVA). Based on the additional cycles the present safety database includes approximately 41,155 cycles of exposure.***
- ***The overall exposure in terms of numbers of subjects and duration of exposure is acceptable.***

8 ADDITIONAL CLINICAL ISSUES

8.7 Postmarketing Safety Surveillance Study

The Applicant's planned postmarketing safety Study is presented in this section:

8.7.1 Study Protocol Title:

International Active Surveillance Study of Women taking Yaz® (INAS Yaz)

8.7.2 Introduction

Based on the lower estrogen dose of Yaz®, it can be assumed that a 21-day regimen of Yaz® would not be associated with a higher risk of venous thromboembolism (VTE) than Yasmin® which contains 10ug more of ethinyl estradiol per tablet. Though the 24-day regimen of Yaz® is not anticipated to have a negative impact on the risk of VTE and arterial embolism (ATE) compared to a 21-day regimen, a Study to assess this impact was deemed appropriate.

The Yasmin® EURAS Study is an example of a large, prospective, controlled, non-interventional, long-term cohort Study that is suitable for safety monitoring of an oral contraceptive and identification of relevant clinical outcomes. The Study described in this protocol has a similar Study design but the procedures for recruitment, informed consent and follow-up are modified to comply with US regulations and to ensure good recruitment rates and low loss to follow-up in the US environment.

8.7.3 Study Objectives

The main clinical outcomes of interest for the short and long-term follow-up are:

- Deep Venous Thrombosis (DVT)
- Pulmonary Embolism (PE)
- Acute Myocardial Infarction (AMI)
- Cerebrovascular Accidents (CVA)

Secondary objectives are

- To analyze the drug utilization pattern of Yaz® and established OCs in a Study population that is representative for typical use of the individual preparations under routine medical conditions. Interference of Study-specific requirements and measures with the normal drug utilization pattern should be minimized by using a non-experimental Study design.
- To characterize the baseline risk of users of the individual formulations (lifetime history of co-morbidity, risk markers, co-medication, socio-demographic and lifestyle data).

8.7.4 Study Design

This is a large, multinational, prospective, controlled, non-interventional, long-term cohort Study that follows a series of cohorts. The cohorts consist of new users (first ever users or switchers) of two different groups of OCs: OCs containing DRSP (Yaz® or Yasmin®) and OCs containing other progestagens. In this Study, regular contacts with the cohort members (= active surveillance) should provide all necessary information on health-related events or changes in health status during new OC use.

There will be active contacts with all cohort members (= *active surveillance*) at baseline and then every 6 months with a planned follow-up for an individual patient between 3 and 5 years. Patient adverse outcomes will be verified by contacting the relevant physicians and by reviewing source documents. Under routine medical conditions, diagnosis of a VTE it is not always confirmed by an imaging procedure. Therefore, reported VTEs have to be classified as "confirmed" or "not confirmed" according to a predefined algorithm.

Recruitment of the cohort members will be conducted via a network of approximately —— OC prescribing physicians (= Study centers) in the US and approximately —— prescribing physicians in Europe.

The combined cohort will include 50,000 women recruited in the United States and Europe. The sequence for starting the Study in individual European countries will depend upon the sequence of Yaz® launches in Europe. Patients should undergo follow-up for at least 3 years.

Baseline data are to be recorded on a self-administered questionnaire containing queries relating to the participant's state of health and potential risk factors. Medical history, including medication history and history of OC use, as well as the addresses, e-mail addresses and phone numbers of the patient, relatives or friends, and the primary care physician are to be provided. In compliance with data protection regulations names, addresses and phone numbers are to be documented on a separate sheet. A follow-up assessment for each woman is scheduled 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months after recruitment.

In order to minimize loss to follow-up a multi-faceted, four-level follow-up process will be established. Level 1 activities include mailing of the follow-up questionnaire and – in case of no response – two reminder letters. If level 1 activities do not lead to a response, multiple attempts are to be made to contact the woman, friends, relatives and the Gynecologist/Primary Care Physician per phone. In parallel to these level 2 activities searches in national and international telephone and address directories are started (level 3 activities). If this is not successful, an official address search via the respective governmental administration will be conducted in the European countries. This level 4 activity can provide information on new addresses (or emigration or death). If necessary, a search in the national death registers could be started at the end of the Study to clarify the vital status of patients who are lost to follow-up after level 4 activities. Overall, the loss to follow-up of the combined cohort should be kept at less than 10% of the recruited population. The follow-up questionnaires will address the occurrence of adverse events. Reasons for switching to another OC or discontinuation will be requested if applicable.

8.7.3 VTE Algorithm

Under routine medical conditions, diagnosis of a VTE it is not always confirmed by an imaging procedure. Therefore, reported VTE have to be classified as "confirmed" or "not confirmed" according to the following predefined algorithm:

Definite VTE: Confirmed by imaging procedure

- DVT: phlebography, duplex sonography
- PE: pulmonary angiography, ventilation-perfusion scan, spiral computed tomography

Probable VTE:

- Absence of confirmation by an imaging test, but a clinical diagnosis is confirmed by a health professional or is supported by a non-imaging test (such as US doppler, plethysmography, D dimer for VTE or typical ECG/blood gas tests for PE).

- These cases are usually characterized by a subsequent specific therapy (such as fibrinolysis or long-term anticoagulant therapy). However, if the attending physician confirms that the diagnosis is correct, the event is classified as a VTE, even if a specific treatment was not given.

VTE not confirmed:

- VTE excluded by an imaging procedure
- Other medical condition diagnosed by the attending physician
- Woman does not contact a health professional to clarify her symptoms and no diagnostic measures are performed that could clarify the diagnosis

A VTE will be classified as "confirmed" if the diagnosis is categorized as definite or probable according to the above criteria, regardless of hospital admission or type of treatment provided.

At the end of the Study this classification will be checked by blind independent adjudication. The Advisory Council will appoint three independent medical experts who will review all available information on the reported VTE. However, brand names, dose, regimen and composition of the OC(s) used by the reporting woman will be rendered anonymous. The adjudicators will perform the review independently of each other and without knowing the judgment of the other adjudicators. If at least one adjudicator classifies a report as confirmed VTE, the reported event will be considered a confirmed VTE.

8.7.3 Study Size and Data Analyses

Based on the EURAS results the estimated VTE and ATE incidence rates in the young Study population are ~ 6/10,000 women years for VTE and ~ 1/10,000 WY for ATE.

The Study was designed to analyze rare events (according to the CIOMS classification 1 – 10 events per 10,000 women years). The 3 to 5 years of follow-up of 50,000 women should result in at least 100,000 documented women-years. Exact power calculations based on actual incidences and drop-out rates should be done one year after start of the Study. If these calculations do not confirm the assumed incidences and drop-out rates the independent Advisory Council (AC) may discuss the need for adapting patient numbers and follow-up times.

Safety monitoring during Study conduct will be based primarily on the ITT analysis of crude data. The final analyses will be based on ITT and "as treated" data sets using Cox regression models. The appropriate confounding variables will be built into the model. The analysis plan will be approved by the independent AC before the first interim analysis.

9 OVERALL ASSESSMENT

9.1 Conclusions

YAZ 24-day regimen combination oral contraceptive is efficacious as a contraceptive. The Pearl Index of 1.41 in Study protocol 303740 is acceptable. Supportive efficacy data has been submitted by the Applicant for the 24-day regimen by showing improved ovarian suppression compared to the 21-day regimen (in Study 308382) by Hoogland scoring. Safety data reviewed to date indicate that the safety profile of YAZ is satisfactory for a highly effective hormonal contraceptive product. However, a final determination of the safety profile cannot be made until additional safety data submitted within 90 days of the PDUFA goal date (notably the acne studies and the Applicant's large safety and efficacy Study 308021) are reviewed. Review of these latter data cannot be completed during the present review cycle

9.2 Recommendation on Regulatory Action

An approvable action is recommended by this reviewer for the contraceptive indication of YAZ (24-day active dosing regimen of drospirenone 3 mg/ethinyl estradiol betadex 0.020 mg tablets) under NDA 21-873. Approval is contingent on (1) a determination that the overall safety profile is acceptable (which will require review of supportive safety data submitted within 90 days of the PDUFA goal date and not reviewed during this cycle) and (2) acceptable labeling.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Product labeling will include, in additional to the standard class warnings for combination oral contraceptives, a Bolded Warning (similar to that for Yasmin) that informs healthcare providers and consumers about the risk of hyperkalemia associated with the use of drospirenone. The Applicant also has committed (letter date 17-Nov-2005) to conducting an educational program for healthcare providers, similar to that conducted for the approved

drospirenone containing product, Yasmin. This program should stress the contraindications to its use and additional risks related to its potential for producing clinically significant hyperkalemia. The education program will continue and a risk management plan, similar to that conducted for the presently marketed DRSP-containing product (Yasmin) for 3 years after the launch of YAZ in the U.S.

9.3.2 Required Phase 4 Commitments

In additional to the risk management activities described above, the Applicant has committed to a large prospective Phase 4 postmarketing safety Study of YAZ called the International Active Surveillance Study of Women taking Yaz® (INAS Yaz). The amended protocol is found in the Applicant's 18-Aug-2005 submission. This Study is designed in a similar manner to the ongoing European Active Surveillance Study (EURAS) which is assessing vascular adverse events for Yasmin users compared to users of other combination oral contraceptives. These vascular adverse events include deep vein thrombosis, pulmonary embolism, myocardial infarction and cerebrovascular accident. The INAZ Study will have a U.S. component in addition to Europe (—prescribing physicians in the US and approximately —in Europe). It will compare drospirenone combination oral contraceptives (YAZ and Yasmin) to those which contain other progestagens. The Study will recruit 50,000 women and follow them every 6 months for three years.

9.4 Labeling Review

Product labeling will be completed during the next review cycle. The following are preliminary comments. The product labeling for YAZ will be very similar overall to that of the approved product Yasmin and the labeling will incorporate recently used class labeling for combination oral contraceptives.

The consult from the Division of Drug Marketing, Advertising, and Communication (DDMAC) regarding the YAZ was reviewed in detail. A number of their recommendations were incorporated into the labeling for YAZ.

Clinical note is taken of the following sections:

Pharmacodynamics:

Notation is made that the clinical significance of the antiandrogenic effects seen in animals has not been fully studied for hyperandrogenic conditions in humans.

Special Populations:

- There is limited data on ethnic group differences with YAZ. A small comparative Study between Japanese and Caucasian women is noted in this section.

- Similar to Yasmin this section mentions the contraindications for YAZ in those patients with hepatic dysfunction and renal insufficiency.

Indications and Usage:

Medical Officer's Comment:

Contraindications:

This section contains all the contraindications included in class labeling in addition to those specific for drospirenone (renal insufficiency, hepatic dysfunction and adrenal insufficiency).

Warnings:

- The Applicant desired to remove NSAIDs from those drugs that may increase serum potassium. NSAIDs should remain on this list.
- Inherited thrombophilias were added to the list of risk factors for taking oral contraceptives.
-
- The following paragraph was added to the *Cerebrovascular diseases* section of Warnings:

- The paragraph describing the risk related to breast cancer has been changed to read:

  "Although the risk of having breast cancer diagnosed may be slightly increased among current and recent users of combined oral contraceptives (RR=1.24), this excess risk decreases over time after combination oral contraceptive discontinuation and by 10 years after cessation the increased risk disappears. The risk does not increase with duration of use and no consistent relationships have been found with dose or type of steroid. The patterns of risk are also similar regardless of a woman's reproductive history or her family breast cancer history. The subgroup for whom risk has been found to be significantly elevated is women who first used oral contraceptives before age 20, but because breast cancer is so rare at these young ages, the number of cases attributable to this early oral contraceptive use is extremely small."

- In the blood pressure section of warnings the following sentence has been added:

  "Women with significant hypertension should not be started on hormonal contraceptives."

Precautions:

- Under Lipid Disorders the following paragraph has been added:

  "In patients with familial defects of lipoprotein metabolism receiving estrogen-containing preparations, there have been case reports of significant elevations of plasma triglycerides leading to pancreatitis."

- Under Emotional Disorders the following paragraph has been added:

  "Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug related. Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree."

10 APPENDICES

10.1 Ovarian Suppression Study

10.1.1 Entry Criteria for Study Protocol 308382

10.1.1.1 Inclusion Criteria

1. Signed informed consent

2. Age: 18 - 35 years (inclusive), smokers aged 30 years (inclusive) at visit 1

3. Willingness to use non-hormonal methods of contraception (e.g., condoms, diaphragms, spermicidal vaginal suppositories, or abstinence) during pretreatment, treatment, and follow-up cycles

4. Laboratory test results without clinically relevant abnormalities

5. Non-suspicious Papanicolaou (Pap) smear taken at screening (visit 1) or within the last six months before Study entry and written result available

6. Follicular diameter $\geq$ 15 mm at visit 6 (admission to treatment) or observed ovulation during pretreatment cycle

10.1.1.2 Exclusion Criteria:

1. Pregnancy or lactation (less than 3 cycles following delivery, abortion, or lactation before start of pretreatment cycle)

2. Substantial overweight, i.e., body mass index (BMI) > 30, where BMI = body weight in kilograms / (body height in meters squared)

3. Known hypersensitivity to any of the Study drug ingredients

4. Any known disease or condition that compromised the function of the body systems and could result in altered absorption, excessive accumulation, impaired metabolism, or altered excretion of the Study medication

5. Any disease that may worsen under hormonal treatment or might interfere with the conduct of the Study, or the interpretation of the results (e.g., herpes gestationis or idiopathic icterus during

a previous pregnancy; middle-ear deafness [otosclerosis]; Sydenham chorea, porphyria, disturbances in the bile flow (presence or history of cholestasis, gallstones, systemic lupus erythematosus)

6. Diagnosed or suspected malignant or pre-malignant disease

7. Liver diseases: presence and / or history of severe hepatic diseases including benign or malignant tumors. There should be an interval of at least 3 months between the start of Study medication intake, and the return of liver function values to normal

8. Vascular diseases: presence and / or history of venous thromboembolic diseases (deep vein thrombosis, pulmonary embolism), presence of history of arterial thromboembolic diseases (myocardial infarction, stroke), and / or any condition which could increase the risk to suffer from any of the above mentioned disorders, e.g., a positive family history (an event that occurred in a sibling or a parent at an early age) or a suspected hereditary predisposition

9. Other diseases: chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis), hemolytic uremic syndrome, migraine with focal neurologic symptoms (complicated migraine)

10. Undiagnosed vaginal bleeding

11. Uncontrolled thyroid disorder

12. Severe dyslipoproteinemia

13. Pancreatitis or a history thereof, if associated with severe hypertriglyceridaemia

14. Uncontrolled arterial hypertension: confirmed systolic blood pressure > 140 mm Hg or confirmed diastolic blood pressure > 90 mm Hg

15. Diabetes mellitus with vascular involvement

16. Sickle-cell anemia

17. Current or history of clinically significant depression

18. Current or history of alcohol or drug abuse

19. Prohibited concomitant medication: use of additional steroid hormones; anticoagulants (e.g., heparin, coumarin), antiepileptics / hydantoin derivatives (e.g., phenytoin), carboxamid derivatives, (e.g., carbamazepin, oxcarbamazepin), other anti-epileptics (e.g., felbamate, topiramate), hypnotica and sedativa / barbiturate derivatives (e.g., primidone), tuberculostatics, (e.g., rifampicin), oral antimycotics (e.g., griseofulvin, ketoconazole), virostatic agents (e.g., ritonavir), products containing the herbal remedy St. John's Wort, and continuous systemic use of antibiotics over a period of more than 10 days

20. Subject is a dependent person, (e.g., a relative, family member and/or is a member of the investigator's staff)

21. Intake of an experimental drug within 1 month before inclusion in the Study.

10.1.2 Treatment Protocol for Study 308382

Table 34: Treatment Dosages in Protocol 308382

	Investigational products	
Regimen	24-day regimen	21-day regimen
Package	Blister pack containing 28 tablets	
Dosage form	Film coated tablets	
Dosage in Cycle 1,2	24 tablets of SH T 00186 D each with 3 mg DRSP / 0.02 mg EE , and 4 placebo tablets of SH T 00186 PB	21 tablets of SH T 00186 D each with 3 mg DRSP / 0.02 mg EE , and 7 placebo tablets of SH T 00186 PB
Dosage in Cycle 3	21 tablets of SH T 00186 D each with 3 mg DRSP / 0.02 mg EE , and 7 placebo tablets of SH T 00186 PB	18 tablets of SH T 00186 D each with 3 mg DRSP / 0.02 mg EE, and 10 placebo tablets of SH T 00186 PB

Source: Page 31 of 5895, Study report A25848 (NDA 21-676)

Missed tablet management was based on the following 2 basic rules:
1. Tablet intake was not to be discontinued at any time in cycles 1 to 3.
2. Seven days of uninterrupted hormone-containing tablet intake were necessary to attain adequate suppression of the hypothalamic-pituitary-ovarian axis.

Therefore, the following advice was given in daily practice:

- If the subject was more than 12 hours late in taking the table, the general recommendation was to take the last missed tablet as soon as remembered, even if this meant taking 2 tablets at the same time. After this, tablet intake was to be continued as usual.
- Not more than 2 tablets were to be taken on a given day.
- If the subject vomited within 4 hours after tablet intake, absorption may have been incomplete. In such an event, another hormone tablet was to be taken from the reserve blister. The same procedure applied for diarrhea.

If the woman missed tablets and subsequently had no withdrawal bleeding, the possibility of a pregnancy was to be considered and ruled out immediately by a human chorionic gonadotropin (HCG)-urine test.

Non-hormonal back-up contraception was to be used during the whole Study period, from pretreatment until the end of the follow-up cycle.

10.1.3 Study Flowcharts for Study 308382

AA, BB, and CC list the flowcharts for screening, pretreatment, treatment and follow-up.

Table 35: Screening and Pretreatment Cycle Flowchart

Assessment	Screen	Pretreatment Cycle						
Visit	1	2	3	4	5	6 Adm (1)	7 (2)	8 (2)
Day	1-6	7	11	15	19	23	27	31
Subject information Informed consent	X							
Demographics, smoking, alcohol	X					Update		
Entry criteria	X							
Medical history	X							
Vitals, weight	X					X		
Physical exam	X							
Gyn exam	X							
Cervical smear	X	Check						
Transvaginal ultrasound	X	X	X	X	X	X	X	X
Hormones	X	X	X	X	X	X	X	X
Safety lab	X	Check						
Update medical history		X	X	X	X	X	X	X
Randomization						X		
Medication dispensed						X		
Diary cards dispensed						X		
Condoms dispensed	X	X	X	X	X	X	X	X
HCG urine test dispensed						X		

(1) Admission to treatment only after follicular diameter ≥ 15 mm or ovulation was observed
(2) Visits 7 and 8 were to be skipped if menstruation started earlier, if no menstruation occurred until day 31, additional visits may have been scheduled
(3) Cycle started with first bleeding day
(4) If necessary
(5) Cervical smear could be waived if a normal result from the last 6 months before visit 1 was available
(6) Boxes for first and second cycle treatment and reserve blister
(7) Human chorionic gonadotropin (HCG)-urine test was to be performed by the subject before first tablet intake
Source: Page 23 of 5895, Study report A25848 (NDA 21-676)

Table 36: Flowchart for Cycles 2 and 3

Assessment	Treatment cycle 2			Treatment cycle 3			
Visit	9	10-16	17	18	19-24	25	26
Day	3	5,8,11,14,17,20,23	26	2	5,8,11,14,17,20	23	26
Transvaginal sonogram	X	X	X	X	X	X	X
Hormonal evaluation	X	X	X	X	X	X	X
Safety Lab						X	Check (1)
Adverse events (7)	X	X	X	X	X	X	X
Medication dispensed			X (3)				
Blister collection	X			X			
Diary collected (2,6)	X	X	X	X	X	X	X
Condoms dispensed (5)	X	X	X	X	X	X	X
HCG urine test (4)	X	If required					

(1) If result not yet available, checked during follow-up cycle, at the latest on visit 35
(2) Diary cards for cycle 2 were to be filled in until the last tablet intake in cycle 2
(3) Boxes for third treatment cycle and reserve blister
(4) In the absence of monthly bleeding a HCG-urine pregnancy test was to be performed (including cycle 1)
(5) If required
(6) As soon as a calendar month was complete, the diary card was to be collected
(7) Also for cycle 1
Source: Page 24 of 5895, Study report A25848 (NDA 21-676)

Table 37: Study Flowchart of Follow-up Cycle

Assessment	Follow-up cycle								
Visit	27	28	29	30	31	32	33	34	35
Day	3	7	11	15	19	23	27	31	**
Vitals, weight									X
Physical exam, Gyn exam, Cervical smear (3)									X
TVU	X(6)	X(6)	X(6)	X(6)	X(6)	X(6)	X(6)	X(6)	X
Hormonal testing	X(7)	X(7)	X(7)	X(7)	X(7)	X(7)	X(7)	X(7)	X
Safety lab									X (9)
AEs	X	X	X	X	X	X	X	X	X
Blister collection	X								
Diary card collection	X (3,8)								X (3,8)
Condoms dispensed	X	X	X	X	X	X	X	X	X
End of Study evaluation									X (1,4)

** = Day of first scheduled visit after ovulation has been observed
1. To be performed also in the event of premature discontinuation of Study medication / Study course
2. Visit(s) may have been skipped if menstruation had already started earlier
3. Diary cards were to be filled in until last tablet intake in cycle 3
4. End of Study documentation on subject's last visit
5. If required
6. Until ovulation was observed
7. Until the visit after ovulation was observed
8. Diary cards of cycle 3 to be collected; check whether all diary cards were collected
9. In the event of premature discontinuation before visit 25
Source: Page 25 of 5895, Study report A25848 (NDA 21-676)

10.2 Associated INDs and NDAs

Table 38: Associated INDs and NDAs

INDs	
60,738	Submitted to Division of Reproductive and Urologic Drug Products on August 22, 2000 for drospirenone 3 mg/ ethinyl estradiol betadex 0.020 mg tablets; indication is for prevention of pregnancy (Principal IND related to this NDA submission)
61,304	Submitted to the Division of Neuropharmacological Drug Products on November 20, 2000 for drospirenone 3 mg/ ethinyl estradiol betadex 0.020 mg tablets; indication is for prevention of premenstrual dysphoric disorder
65,370	Submitted to the Division of Dermatological and Dental Drug Products on October 28, 2002 for drospirenone 3 mg/ethinyl estradiol betadex 0.020 mg tablets; indication is for treatment of acne
[	]
51,693	Submitted to Division of Reproductive and Urologic Drug Products on October 7, 1996 for drospirenone 3 mg/ ethinyl estradiol 0.030 mg tablets; indication is for prevention of pregnancy
[	]

NDAs	
21-098	Yasmin - drospirenone 3 mg/ ethinyl estradiol 0.030 mg, developed from IND 51,693, submitted to DRUDP on May 14, 1999 and approved on May 11, 2001 for contraception
21-355	Angeliq - drospirenone 3 mg /estradiol 1 mg, developed from IND 53,842, submitted to DRUDP on December 14, 2001 and approved on September 28, 2005.
21-676	YAZ - drospirenone 3 mg/ ethinyl estradiol 0.020 mg (Contraceptive indication)

APPEARS THIS WAY
ON ORIGINAL

10.3 Executive Summary from Medical Officer's Review of YAZ in the First Review Cycle (NDA 21-676)

EXECUTIVE SUMMARY

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 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.

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. It is recommended that 40,000 subjects be studied for two years rather than 30,000 for three years, since venous and arterial thrombotic and thromboembolic events tend to occur earlier rather than later in treatment.

No Phase 4 safety surveillance Study is required for the 21-day dosing regimen.
Berlex seeks approval of a second drospirenone based combination oral contraceptive, hereafter referred to as Yasmin 20 (24-day). This contraceptive contains two-thirds the daily level of ethinyl estradiol (EE) that is found in the Applicant's approved product Yasmin (0.02 mg compared to 0.03 mg per tablet) and the same amount of drospirenone (3 mg DRSP) per tablet. The product also differs from Yasmin in that the dosing regimen consists of 24 days of active tablets followed by 4 days of placebo tablets compared to 21 days of active tablets followed by 7 days of placebo tablets for Yasmin

In the present NDA, the Applicant also has submitted safety and efficacy data from a second combination oral contraceptive that contains 0.02 mg EE and 3 mg DRSP (hereafter referred to as Yasmin 20 (21-day). The dosing regimen for this product consists of one active tablet daily for 21 consecutive days followed by 7 tablet–free days. The Applicant has not requested approval of this product, which is being developed for selected non-U.S. markets.
The Applicant's protocol for establishing contraceptive efficacy is similar to other product submissions in this class. Over ten thousand 28-day cycles were studied in both the 24-day regimen (protocol 303740) and the 21-day regimen (protocol 303860). More than 200 women completed 13 cycles of use in both protocols.

The primary efficacy endpoint was the number of "during treatment" pregnancies defined as all pregnancies with an estimated date of conception after the onset of treatment with Study drug and through 4 days (Applicant's definition) or 14 days (DRUDP's definition) after the last dose of Study drug. The primary efficacy analysis was the Pearl Index, which is the number of

"during treatment" pregnancies per 100 women-years of use. The efficacy for the 24-day and 21-day dosing regimens, expressed in terms of the Pearl Index is listed in Table A. The values for the Pearl Index in Table A are based on the Medical Officer's determination of the number of "during treatment" pregnancies and exclude cycles where backup contraception was used, cycles for women over age 35, and cycles for women listed as sexually inactive

Table A. Efficacy of the 24 and 21-day Regimens of DRSP 3 mg/ EE 0.02 mg*

24-day regimen (protocol 303740)					
Total days of exposure	Total 28-day cycles of exposure	Total Number Pregnancies		Pearl Index **	2-sided 95% confidence interval
		Applicant's Determination	FDA's Determination		
309,386	11,050 *	11	12	1.41	0.73-2.47
21-day regimen (protocol 303860)					
Total days of exposure)	Total 28-day cycles of exposure	Total Number Pregnancies		Pearl Index *	2-sided 95% confidence interval
		Applicant's Determination	FDA's Determination		
309,136	11,040	2	3	0.35	0.07-1.04

* Calculated by dividing number of days of exposure by "28".
** Pearl Index based on using 12 "during treatment" pregnancies in protocol 303740 and 3 "during treatment" pregnancies in protocol 303860).

The overall exposure in terms of numbers of subjects and duration of exposure is acceptable. The three large studies for both the Yasmin 20 product (protocols 303740, 303860 and 14523) provide exposure of a total of 1763 separate subjects. These studies account for 24,425 28-day cycles of safety data or 1,878 women-years.

There were two deaths reported in the clinical studies of Yasmin 20. These deaths both occurred in protocol 303740 (Yasmin 20, 24-day regimen) at the single US Study site. Neither of these deaths was related to Study medication. One death, secondary to pesticide poisoning, occurred one month following discontinuation of Study drug. The other death, occurring three months after starting Study medication, was secondary to smoke inhalation in a fire.

The serious adverse events attributable to Study drug in the pivotal trial for the 24-day regimen (303740) included one case of migraine, one case of depression and one case of cholelithiasis. The serious adverse events attributable to Study drug in the pivotal trial for the 21-day regimen (303860) included two cases of pulmonary emboli, one case of migraine, one case of ovarian cyst and one case of cholecystitis. All of these adverse events have been previously associated with combination oral contraceptive use. There were no SAEs attributable to Study drug in any of the other submitted studies

With caveats regarding rate estimations of rare events derived from typical Phase 3 registry studies for oral contraceptives, the finding of two confirmed venous thromboembolic adverse events (2 cases of pulmonary emboli in Study 303860) translates to a rate of 10.6 per 10,000 women-years for the Yasmin 20 products. This rate is similar to the findings of the approved

product Yasmin in the first year of the EURAS Study (approximately 15 per 10,000) which is described in greater detail later in this summary.

In Yasmin 20, 24-day regimen (303740) the adverse event contributing to the greatest number of drug discontinuations was headache (14 incidents, 1.3%). Headache was also the most common adverse event at 13.3%. The most common reasons for Study discontinuation in the Yasmin 20, 21-day regimen (303860) were decreased libido and depression (5 subjects each, 1.0%). Vaginal moniliasis (17.2%) constituted the highest number of adverse events in the 21-day regimen with headache (13.6%) showing similar numbers as in the 24-day regimen.

Safety labs were performed only in the 24-day regimen protocol. The laboratory analysis from the 24-day regimen Study is sufficient for safety evaluation of the Yasmin 20 product overall. Increased mean levels of lipids were seen in women who used Yasmin 20 (24-day regimen). These findings are comparable to the well-characterized effects on lipids by combination oral contraceptives (COCs). Careful potassium monitoring was performed due to the potential potassium sparing effects of drospirenone. All of the elevated potassium levels identified in the 24-day regimen protocol appeared to represent "pseudohyperkalemia" resulting from hemolysis or transport problems. There was no evidence of true hyperkalemia or any hyperkalemic type symptomatology found at the time of these elevated values. Repeat testing in each case revealed normal values. Neither regimen showed any significant mean changes in vital signs or body weight.

Both the Yasmin 20, 24-day regimen and the Yasmin 20, 21-day regimen had acceptable menstrual cycle control data. The levels of pill-associated amenorrhea and intracyclic bleeding were low for both regimens.

The Applicant has provided data from two large ongoing postmarketing safety surveillance trials supporting the safety of the presently marketed DRSP product Yasmin:

The European Active Surveillance Study (EURAS) was initiated for Yasmin in March 2001. This surveillance Study is part of a European effort to perform postmarketing safety on contraceptive formulations with new progestins and/or estrogen. This Study was last updated on 9 June 2004. At that time 50,000 women were enrolled representing 64,000 women-years of observation. The comparative table (see Table B) shows the thrombotic/thromboembolic adverse event rates for Yasmin, levonorgestrel-based oral contraceptives and "other" oral contraceptives. The results demonstrate that Yasmin does not have a thrombotic/thromboembolic rate higher than other COCs that do not contain DRSP.

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

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.

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.

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/s/

Gerald Willett
1/20/2006 12:50:40 PM
MEDICAL OFFICER

Scott Monroe
1/23/2006 03:13:24 PM
MEDICAL OFFICER
I concur with Dr. Willett that this Application is approvable contingent upon the satisfactory resolution of all outstanding issues.