Table 18 Serious Adverse Events – Seasonale Treatment Group (Study SEA 301)

Site #	Subject #	Serious AE	Relationship to drug	Subject discontinued
3	21	Appendectomy	None	No
12	01	Disc surgery	None	No
18	03	Worsening goiter	None	No
18	10	Gunshot wound	None	No
20	23	Mild concussion	None	No
26	18	Cholecystectomy	None	No
29	25	Food poisoning	None	Yes
38	02	Intermittent syncope	Remote	Yes
38	34	Pulmonary embolus	Likely	Yes
39	26	Meningoencephalitis	None	Yes
50	01	Motor vehicle accident	None	Yes

Source: Original NDA submission

Medical officer's comments:

Subject 26/18

Although subject 26/18 had been on oral contraceptives prior to her participation in Study SEA 301, her cholecystitis and cholecystectomy occurred on study day 160 and could be related to Seasonale use.

Subject 38/02

Subject 38/02 had two syncopal episodes reported while she was driving. A hospitalization work up revealed no evidence of seizures. Her hypertension medication was increased. She was not discontinued from study drug due to the syncopal episodes but discontinued two months later due to unacceptable bleeding. It is unlikely that combination oral contraceptives are playing a role in these syncopal episodes.

Subject 38/34

Subject 38/34 was a 39-year-old Caucasian woman (202 pounds, 68 inches); non-smoker. She had used oral contraceptives previously for a short time period (Ortho Novum for 2 months in 1985-discontinued due to headaches) and had one pregnancy that ended in an abortion. She had used condoms during her previous menstrual cycle. She had a history of headaches, mild acid reflux, broken left arm, and right breast lumpectomy. Elevated LDL (131 mg/dL) was noted at screening; all other evaluations were normal. The patient began receiving Seasonale on 8 October 2000. On — (cycle 3 day 47), she presented to the emergency room with a one-day history of sudden onset of left-sided chest pain, worse with inspiration. A CT scan was positive for pulmonary embolus (serious, severe, likely related to study drug per the study investigator). The CT scan showed multiple bilateral lower lobe segmental and subsegmental pulmonary arterial emboli. The patient was admitted on — She reported recent travel history, noting one or two airline flights that were 1.5 hours each in duration. Her last airline flight was 3 days prior to her admission. She gave no history of

hypercoagulable disorder in the family. There was no apparent history of recent surgery or immobilization.

She was admitted to telemetry and was treated with Lovenox, heparin, coumadin and percocet. She remained symptom-free throughout her entire hospitalization. Protein S and protein C levels were ordered, but the patient was discharged before blood samples were obtained. Lower extremity dopplers were negative for deep vein thrombosis. The patient was discharged home the following day (——— *) on Lovenox and Coumadin with instructions to follow up regularly for titer checks. The patient had discontinued study medication the day before hospital admission and she was instructed at the time of discharge to use an alternative birth control method outside of oral contraceptive agents. Other AEs experienced by this subject during the course of the study were acne, headache, nausea, acid reflux, and upper respiratory infection. The patient had received aspirin and ibuprofen for occasional headache and headache with nausea (11/00), Hytussin for pharyngitis (5/01), Alka Seltzer and NyQuil for URI (10/02), and Percocet for chest pain (5/25 – 5/29/01).*

After discussions with the sponsor regarding this subject, additional blood testing was performed to assess for an underlying thrombophilia or coagulation disorder. Comprehensive coagulation studies were performed (lupus anticoagulant, protein S panel, protein C, Factor II, DNA analysis, anticardiolipin, antithrombin III, Factor V Leiden, and Factor VIII activity) The results of these studies were normal.

Although the possibility of recent travel contributing to the pulmonary embolus cannot be discounted, the hormonal usage has to be considered in the etiology of this adverse event. Although subjects in the Seasonale treatment arm received more estrogen and progestin per year than the Nordette treatment arm, a single case of thromboembolic disease in this clinical study does not signal that this extended oral contraceptive therapy provides greater risk for this complication than conventional 28-day cycle therapy when comparing the same dosage formulation.

Nordette Treatment Group (Serious Adverse Events). Serious adverse events reported for the Nordette-treated subjects are listed in Table 19 by subject. Also listed is the likely relationship of the adverse events to study drug as assessed by the Investigator and whether the subject discontinued participation in the trial because of the adverse event. Serious adverse events were reported for 3 Nordette treated subjects.

Table 19 Serious Adverse Events – Nordette Treatment Group (Study SEA 301)

Site #	Subject #	Serious AE	Relationship to drug	Subject discontinued
13	02	Menorrhagia	None (attributed to fibroids)	Yes
19	35	Cholecystitis	Possible	Yes
24	26	Depression	Possible	No

Source: Original NDA submission

Seasonale Ultra-Lo Treatment Group (Serious Adverse Events). Serious adverse events reported for the Seasonale Ultra-Lo-treated subjects are listed in Table 20 by subject. Serious adverse events were seen in 13 Seasonale Ultra-Lo subjects.

Table 20 Serious Adverse Events - Seasonale Ultra-Lo Treatment Group (Study SEA 301)

Site #	Subject #	Serious AE	Relationship to drug	Subject discontinued
01	77	Viral meningitis	None	No
03	26	Chronic pelvic pain/adhesions	None	No
05	13	Kidney stones	None	No
19	08	Lumbar surgery	None	No
19	15	Cholecystectomy	Possible	No
20	08	Gallbladder surgery	Remote	No
21	21	Foot surgery	None	No
28	26	Pneumonia	None	No
30	40	Bipolar disorder	None	No
34	43	Postoperative bleeding	None	No
35	12	Automobile accident	None	No
40	16	ACL repair/infection	None	Yes
45	05	Ovarian cyst	Remote	No

Source: Original NDA submission

Medical officer's comments:
There are no new signals of unexpected serious adverse events related to extended use of Seasonale Ultra-Lo that would translate to extended use of Seasonale.

Levlite Treatment Group (Serious Adverse Events). Serious adverse events reported for the Levlite-treated subjects are listed in Table 21 by subject. Serious adverse events were seen in 4 Levlite subjects.

Table 21 Serious Adverse Events – Levlite Treatment Group (Study SEA 301)

Site #	Subject #	Serious AE	Relationship to drug	Subject discontinued
19	37	Gunshot wound	None	Yes
32	48	Ectopic pregnancy	Definite	Yes
37	24	Appendicitis	None	No
42	25	Concussion	None	Yes

Source: Original NDA submission

(3) Adverse Events Leading to Discontinuation from Study

Table 22 was derived by this reviewer from the sponsor's section on adverse events leading to discontinuation from the study. Some categories were combined into one row such as irritability, emotion, and mood.

Table 22 Adverse Events Leading to Discontinuation from Study (Study SEA 301)

	Seasonale (N=456)		Nordette (N=226)		Seasonale Ultra-Lo (N=463)		Levlite (N=231)	
Discontinuation Reason [A]	N	%	N	%	N	%	N	%
Anemia			1	0.44	1	0.22		
Gastrointestinal	6	1.32	10	4.42	17	3.67	3	1.30
Chest pain	1	0.22			1	0.22		
Fatigue	2	0.44			3	0.65	1	0.43
Blood pressure increase					1	0.22		
Weight/appetite increased	7	1.54	3	1.33	3	0.65	3	1.30
Musculoskeletal	2	0.44	2	0.88	4	0.86		
Breast lump	1	0.22						
Breast tenderness/ pain	4	0.88	1	0.44	3	0.65	1	0.43
Headache NOS	2	0.44	4	1.77	3	0.65	1	0.43
Migraine NOS	1	0.22					2	0.87
Libido disorder	3	0.66			4	0.86		
Depression NOS	1	0.22	1	0.44	1	0.22	1	0.43
Mood, emotions, irritability	9	1.9	3	1.33	10	2.15	3	1.30
Dysmenorrhea			1	0.44				
Menorrhagia	26	5.70	4	1.77	42	9.07	1	0.43
Premenstrual syndrome	1	0.22						
Dyspnea	1	0.22						
Acne	6	1.31	4	1.77	1	0.22	3	1.30

A. In some instances, 2 reasons for discontinuation were reported for a patient. Thus the total number of events in a treatment group may exceed the total number of patients in that group who discontinued.
Source: Original NDA submission

Medical officer's comments:
The menorrhagia category constitutes the largest category of adverse events. However, this is a misnomer. For the most part, menorrhagia reflects breakthrough bleeding and spotting rather than heavy withdrawal bleeding. Both extended dose regimens show far greater amounts of "menorrhagia" than the 28-day regimens.

Table 23 lists by month all women who reported bleeding problems as a reason for discontinuing treatment.

Table 23 Subject Discontinuation by Month Due to "Bleeding Problems" (ITT Population, SEA 301)

	Seasonale (N=456)		Nordette (N=266)		Seasonale Ultra-Lo (N=463)		Levlite (N=231)	
Patient-month	N	%	N	%	N	%	N	%
1	1	0.22	1	0.44	1	0.22	0	0
2	5	1.10	0	0	13	2.81	0	0
3	4	0.88	0	0	7	1.51	0	0
4	4	0.88	0	0	13	2.81	1	0.43
5	6	1.32	1	0.44	8	1.73	0	0
6	3	0.66	0	0	6	1.30	0	0
7	7	1.54	0	0	7	1.51	1	0.43
8	0	0	0	0	1	0.22	0	0
9	1	0.22	2	0.88	2	0.43	0	0
10	3	0.66	0	0	4	0.86	0	0
11	1	0.22	0	0	2	0.43	0	0
12	0	0	0	0	0	0	0	0
Total Discontinued	35	7.7	4	1.8	64	13.8	2	0.9

Source: Original NDA submission

Medical officer's comments:
There is a fourfold greater discontinuation in the Seasonale group compared to Nordette. By 91-day treatment cycle, the number of subjects in the Seasonale group discontinuing for unacceptable bleeding are 1st cycle: 10 subjects, 2nd cycle: 13 subjects, 3rd cycle: 8 subjects, and 4th cycle: 4 subjects.

Of the 35 subjects with unacceptable bleeding, 26 had hematocrit and hemoglobin determinations at screening and at end of treatment. Although a small number of subjects in the Seasonale arm developed anemia (described in laboratory adverse events section), none of these particular 26 discontinuing subjects developed anemia (Hct < 35, Hgb < 11.6). Ten of the 26 showed a drop (but not anemia) in their hematology lab parameters, thirteen showed an increase, and three remained the same.

(4) Most Frequently Reported Adverse Events

The most frequently reported adverse events (5% or greater in at least one treatment group) are listed in Table 24. Also listed in the Table are the incidence rates for migraines and breast tenderness.

Table 24 Most Frequently Reported Adverse Events (SEA 301)

MedDRA term	Seasonale (N=456)		Nordette (N=226)		Seasonale Ultra-Lo (N=463)		Levlite (N=231)	
	N	%	N	%	N	%	N	%
Acne	21	4.6	10	4.4	13	2.8	13	5.6
Back Pain	29	6.3	19	8.4	25	5.4	25	10.8
Breast tenderness	16	3.5	3	1.33	9	1.94	7	3.0
Depression Nos	10	2.1	13	5.7	11	2.3	2	0.8
Dysmenorrhea	26	5.7	9	3.9	14	3.0	6	2.6
Fungal infection	27	5.9	11	4.8	34	7.3	14	6.0
Headache Nos	94	20.6	64	28.3	103	22.2	49	21.2
Influenza	32	7.0	15	6.6	25	5.4	16	6.9
Influenza-like illness	19	4.1	11	4.8	20	4.3	12	5.1
Menorrhagia	53	11.6	6	2.6	69	14.9	6	2.6
Migraine Nos	20	4.4	7	3.1	16	3.5	6	2.6
Nasopharyngitis	100	21.9	67	29.6	97	20.9	53	22.9
Nausea	34	7.4	20	8.8	32	6.9	18	7.7
Sinusitis Nos	45	9.8	25	11.0	53	11.4	19	8.2
Sore throat	37	8.11	12	5.3	29	6.2	18	7.7
URI	25	5.4	22	9.7	33	7.1	13	5.6
UTI	20	4.3	14	6.1	23	4.9	19	8.2

Source: Original NDA submission

Medical officer's comments:

A higher percentage of Seasonale-treated patients reported breast tenderness than Nordette-treated patients. The percentages of subjects reporting headaches, and specifically migraines, appeared similar in the extended groups compared to those in the traditional treatment groups. Of the subjects that reported headaches at the first available visit, 44.8% of these receiving Seasonale and 40.5% of these receiving Nordette reported headaches at the last reported visit.

The sponsor mentioned that there was a lower incidence of urinary tract infection in the extended treatment groups. The etiology for this was not postulated. It also is unclear why a higher percentage of subjects receiving Nordette reported depression compared to the other three treatment arms. Depression was reported in 1.1% of subjects in the original NDA for Nordette 1981.

Menorrhagia is the MedDRA term that incorporates a number of adverse events related to vaginal bleeding (intermittent, unexpected, breakthrough, etc.). MedDRA also utilizes the

terms "menstruation irregular" and "menstrual disorder Nos". As noted later in this review, the extended regimens show a higher level of unanticipated bleeding/spotting.

(5) Bleeding/Spotting During Treatment

Total Bleeding and/or Spotting

The total number of days of bleeding and/or spotting by cycle (ITT population) is presented in Table 25.

Table 25 Total Days of Bleeding and/or Spotting by Cycle (ITT Population, SEA 301)

Drug	Cycle	N (Subjects)	Mean	Median	Mean / Median per Patient-Month [A]
Seasonale	1	446	18.6	15.0	5.7 / 4.6
	2	368	14.8	10.0	4.6 / 3.1
	3	309	13.8	9.0	4.3 / 2.8
	4	282	12.3	8.0	3.9 / 2.5
Nordette	1	218	5.4	5.0	
	2	213	5.0	5.0	
	3	209	4.6	4.0	
	4	198	4.3	4.0	
	5	193	4.6	4.0	
	6	188	4.3	4.0	
	7	180	4.2	4.0	
	8	177	4.5	4.0	
	9	175	4.4	4.0	
	10	172	4.4	4.0	
	11	165	4.6	4.0	
	12	163	4.3	4.0	
	13	162	4.9	4.5	

[A] Obtained by multiplying the 91-day cycle by the factor (28/91) "to adjust" (per the Sponsor) for the difference in cycle length compared to a 28-day convention cycle.
Source: Original NDA submission and FDA reviewer's calculation of the means.

Medical officer's comments: The sponsor has utilized data from the preceding table to propose that total bleeding with Seasonale improves over time (decreased median number of total bleeding days in the later cycles of use). This improvement may be partially explained by the discontinuation of subjects for unacceptable bleeding. The mean number of days was added by this reviewer in the final column in addition to the medians listed by the sponsor

Unscheduled Bleeding

The total number of unscheduled bleeding/spotting days by cycle are listed in Table 26.

Table 26 Total Days of Unscheduled Bleeding and/or Spotting by Cycle (ITT Population, SEA 301)

Drug	Cycle	N	Mean	Median	Mean / Median per Patient-Month [A]
Seasonale	1	446	15.1	12.0	3.8 / 3.0
	2	368	11.6	6.0	2.9 / 1.5
	3	309	10.6	6.0	2.7 / 1.5
	4	282	8.8	4.0	2.2 / 1.0
Nordette	1	218	2.1	1.0	
	2	213	1.9	1.0	
	3	209	1.6	1.0	
	4	198	1.3	1.0	
	5	193	1.6	1.0	
	6	188	1.5	1.0	
	7	180	1.4	1.0	
	8	177	1.6	1.0	
	9	175	1.6	1.0	
	10	172	1.7	1.0	
	11	165	2.0	1.0	
	12	163	1.6	1.0	
	13	162	1.6	1.0	

[A] Obtained by multiplying the 91-day cycle result by the factor (21/84) "to adjust" for the difference in cycle length compared to a 28-day convention cycle.

Source: Original NDA submission and FDA reviewer's calculation of the means.

Medical officer's comments:
The sponsor used the data from this table to suggest that unscheduled bleeding and/or spotting for Seasonale improves over time and by the end of the study was the same as for Nordette. This interpretation again is based on utilizing the median over the mean value and may partially be a result of more Seasonale subjects discontinuing early in the Study for unacceptable bleeding. The derived mean number of 2.2 at cycle four of Seasonale is still higher than any of the mean numbers for Nordette.

Table 27 (prepared by this reviewer) presents the data for Seasonale on unanticipated bleeding/spotting from the sponsor's April 23, 2003 submission (SEA-301, dataset "Seasonale").

Table 27 Analysis of Unanticipated Bleeding/Spotting for Seasonale Subjects in SEA 301

Days of unanticipated bleeding and/or spotting recorded in the diary per cycle	Cycle 1 % of completers N=385	Cycle 2 % of completers N=331	Cycle 3 % of completers N=296	Cycle 4 % of completers N=261
≤ 6 days	133/385 = 35%	160/331 = 48%	149/296 = 50%	152/261 = 58%
≥ 7 days	252/385 = 65%	171/331 = 52%	147/296 = 50%	109/261 = 42%
≥ 20 days	136/385 = 35%	78/331 = 24%	59/296 = 20%	40/261 = 15%

Source: Prepared by FDA reviewer from sponsor data set "Seasonale" (April 23, 2003 submission)

This reviewer recommends that [redacted] a summary of the table) be incorporated into the product label. This table provides clinicians with a much clearer perspective of the unanticipated bleeding/spotting than a labeling comment about a decrease in the median number of days of unanticipated bleeding/spotting that occurs over time.

For comparison Table 28 (prepared by this reviewer) presents the data for Nordette on unanticipated bleeding/spotting from the sponsor's April 23, 2003 submission (SEA-301, dataset "Nordette").

Table 28 Analysis of Unanticipated Bleeding/Spotting for Nordette Subjects in SEA 301

Days of unanticipated bleeding and/or spotting recorded in the diary per time period	Months 1-3 % of completers N=204	Months 1-4 % of completers N=194	Months 11-13 % of completers N=158	Months 10-13 % of completers N=158
≤ 6 days	141/204 = 69%	120/194 = 62%	112/158 = 71%	96/158 = 61%
≥ 7 days	63/204 = 31%	74/194 = 38%	46/158 = 29%	62/158 = 39%
≥ 20 days	9/204 = 4 %	11/194 = 6%	3/158 = 2%	7/158 = 4%

Source: Prepared by FDA reviewer from sponsor data set "Nordette" (April 23, 2003 submission)

Both three and four month blocks at the beginning and end of the Nordette year trial are listed to adjust for the cycle differences from Seasonale. The percentage of women with bleeding/spotting ≥ 20 days is still clinically significantly higher for Seasonale compared to Nordette at both the beginning and the end of the year. The two previous tables (27 & 28) were sent to the sponsor for confirmation. They concurred with the data in the tables but correctly noted that the 70% listed after 141/204 should be 69%.

The sponsor also analyzed the unexpected bleeding and/or spotting by study week in addition to the daily diary. Table 29 lists the subjects' weekly responses to the question: "Have you experienced: Unexpected Bleeding and/or Spotting in the preceding week."

Table 29 Percent Subjects Reporting Unexpected Bleeding/Spotting in Preceding Week (SEA 301)

Study Week	Seasonale	Nordette
0	5.3	9.1
1	3.1	1.7
2	5.5	5.0
3	5.7	5.0
4	7.5	8.5
5	8.3	7.5
6	10.7	9.7
7	16.8	6.6
8	19.7	7.7
9	24.7	9.8
10	27.6	4.3
11	27.2	3.6
12	30.1	6.7
13	30.8	5.2
14	27.2	5.8
15	22.0	3.2
16	14.6	6.4
17	14.7	6.1
18	10.5	1.6
19	9.4	3.3
20	9.6	5.7
21	13.8	6.5
22	14.4	10.7
23	21.7	4.0
24	24.1	5.2
25	24.8	6.8
26	24.2	5.2
27	23.2	4.7
28	17.8	3.0
29	11.8	8.5
30	9.9	5.5
31	7.4	3.7
32	6.0	3.8
33	7.1	3.7
34	10.7	4.8
35	15.3	3.8
36	15.9	3.8
37	22.5	3.3
38	26.0	3.2
39	25.4	2.6
40	22.2	3.1
41	15.1	3.8
42	11.4	6.7
43	9.9	6.7
44	10.2	7.9
45	10.2	8.7
46	9.4	4.1
47	11.2	2.8
48	12.2	4.1
49	15.3	2.8
50	19.8	3.6
51	18.0	4.9
52	20.9	3.5

Source: Original NDA submission

Medical officer's comments:

This analysis of the weekly questionnaire data provides a different perspective of the subjects' assessment of unexpected bleeding/spotting than the adjusted analysis of the daily diary bleeding recordings. In the daily diary analyses, the converted median values (but not the mean values) for unexpected bleeding/spotting are similar in both the Seasonale and Nordette groups during the last three months of the study (Seasonale cycle 4 and Nordette months 9-12). The weekly questionnaire indicates that the percentage of subjects reporting unexpected spotting or bleeding is greater for Seasonale subjects compared to Nordette throughout the full year. During cycle 4 (weeks 40-52) the percentage of subjects in the Seasonale group reporting unexpected bleeding/spotting in a given week ranged from 9.4% to 22.2%. During the same period the weekly percentage of women in the Nordette group reporting unexpected bleeding/spotting ranged from 2.8% to 8.7%

Consultation Regarding Unanticipated Bleeding/Spotting

Dr. Lesley Furlong from the Division also reviewed the sponsor's data concerning the unanticipated bleeding/spotting. She noted the following:

"The reason for developing Seasonale was to decrease the frequency of menses and menses-related complaints. However, based on a 1-year comparative trial in which women kept electronic daily menstrual diaries, more women dropped out of the Seasonale group compared with the Nordette group. In addition, more women cited "unacceptable bleeding" as a reason for dropping out in the Seasonale group compared with the Nordette group (Table 1). Nonetheless, a small percentage (9-16% in each 91-day cycle) of Seasonale users had amenorrhea for the 84 days active therapy. For this group of women, Seasonale had the intended effect of decreasing the frequency of bleeding".

(6) **Vital sign safety findings**

There were no notable changes in vital signs (i.e. systolic and diastolic blood pressure, heart rate, weight, or temperature) over time, within or between treatment groups. The incidence and range of abnormal blood pressure reading (defined as systolic blood pressure >150 mmHg and diastolic blood pressure >90 mmHg are comparable between treatment groups and are not unexpected in this population.

Medical officer's comments:
The following table (Table 30) derived by the Medical Reviewer from the Sponsor's data using JMP shows the weight analysis for Seasonale and Nordette by visit. Weight gain was listed as one of the reasons for discontinuation by 7/185 (3.8%) of the subjects in the Seasonale arm. Weight gain does not appear to be a significant problem for Seasonale.

Table 30 Mean and Median Subject Weights (Pounds) in Study SEA 301

	Seasonale			Nordette		
Visit	N	Mean	Median	N	Mean	Median
Screening	461	156.4	148.0	229	156.9	149.0
Visit 1	462	157.1	147.5	225	157.5	148.0
Weeks 12/13	375	157.9	150.0	197	158.2	148.0
Weeks 24/26	317	157.0	151.0	183	158.7	148.0
Weeks 39/40	288	158.5	150.5	166	157.6	145.0
Final	383	158.1	149.0	193	158.8	150.0

Source: Original NDA submission

(7) Laboratory safety findings

The sponsor stated that the most notable laboratory changes from baseline to the end of study are those commonly associated with oral contraceptive use including elevations in both the mean and median for total cholesterol and LDL in all treatment groups. Triglycerides were also somewhat elevated.

Table 31 provides selected laboratory test values particularly pertinent to oral contraceptive users and compares the screening and endpoint mean values in the Seasonale and Nordette groups.

Table 31 Screening and Endpoint Lipid and Hematology Mean Values (SEA 301)[A]

Test/ Treatment arm	N	Screening mean	Endpoint mean
Total cholesterol			
Seasonale	264	182.8 mg/dl	191.9mg/dl
Nordette	155	181.1 mg/dl	192.3mg/dl
Triglycerides			
Seasonale	264	122.0 mg/dl	128.9 mg/dl
Nordette	155	110.0 mg/dl	117.2 mg/dl
LDL			
Seasonale	258	104.9 mg/dl	115.3 mg/dl
Nordette	154	104.7 mg/dl	115.4 mg/dl
HDL			
Seasonale	263	53.0 mg/dl	50.5 mg/dl
Nordette	155	54.5 mg/dl	53.8 mg/dl
Hemoglobin			
Seasonale	259	13.4 g/dl	13.7 g/dl
Nordette	154	13.6 g/dl	13.6 g/dl
Hematocrit			
Seasonale	251	40.2 %	40.8 %
Nordette	146	40.5 %	40.7 %

A. Mean values based on study completers only.
Source: Original NDA submission

Medical officer's comments: The means are similar for both Seasonale and Nordette.

Table 32 and Table 33 provide the shift analysis for total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, hemoglobin and hematocrit for Seasonale and Nordette

Table 32 Shift Analyses for Lipid and Hematology Values (Seasonale Group, SEA 301)

Lab	Baseline	L	%	N	%	H	%	Total
Hgb (11.6-16.2 G/DL)	L	2	25	6	75.0	0	0.0	8
	N	3	0.8	357	98.9	1	0.3	361
	H	0	0.0	0	0.0	0	0.0	0
	Total	5		363		1		
Hct (35-47%)	L	1	10.0	9	90.0	0	0.0	10
	N	3	0.8	351	98.3	3	0.8	357
	H	0	0.0	2	100.0	0	0.0	2
	Total	4		362		3		
Total Chol (130-200 mg/DL)	L	4	20.0	16	80.0	0	0	20
	N	4	1.6	196	78.1	51	20.3	251
	H	0	0	22	22.4	76	77.6	98
	Total	8		234		127		
Triglyc (24-250 mg/DL)	L	3	25.0	9	75.0	0	0	12
	N	6	1.8	317	93.0	18	5.3	341
	H	0	0	10	62.5	6	37.5	16
	Total	9		336		24		
HDL (30-150 mg/DL)	L	1	33.3	2	66.7	0	0.0	3
	N	3	0.8	363	99.2	0	0.0	366
	H	0	0.0	0	0.0	0	0.0	0
	Total	4		365		0		
LDL (0-130 mg/DL)	L	0	0.0	0	0.0	0	0.0	0
	N	0	0.0	251	82.8	52	17.2	303
	H	0	0.0	19	28.8	47	71.2	66
	Total	0		270		99		

Source: Sponsor submission May 9, 2003

Table 33 Shift Analyses for Lipid and Hematology Values (Nordette Group, SEA-301)

Lab	Baseline	L	%	N	%	H	%	Total
Hgb (11.6-16.2 G/DL)	L	1	50.0	1	50.0	0	0	2
	N	0	0	186	100.0	0	0	186
	H	0	0	2	100.0	0	0	2
	Total	1		189		0		
Hct (35-47%)	L	1	25.0	3	75.0	0	0	4
	N	3	1.6	180	98.4	0	0	183
	H	0	0	3	100.0	0	0	3
	Total	4		186				
Total Chol (130-200 mg/DL)	L	3	37.5	5	62.5	0	0	8
	N	3	2.3	100	75.2	30	22.6	133
	H	0	0	13	26.5	36	73.5	49
	Total	6		118		66		
Triglyc (24-250 mg/DL)	L	1	25.0	3	75.0	0	0	4
	N	2	1.1	180	97.3	3	1.6	185
	H	0	0	1	100.0	0	0	1
	Total	3		184		3		
HDL (30-150 mg/DL)	L	0	0.0	1	100.0	0	0.0	1
	N	1	0.5	188	99.5	0	0.0	189
	H	0	0.0	0	0.0	0	0.0	0
	Total	1		189		0		
LDL (0-130 mg/DL)	L	0	0.0	0	0.0	0	0.0	0
	N	0	0.0	132	85.7	22	14.3	154
	H	0	0.0	8	22.2	28	77.8	36
	Total	0		140		50		

Source: Sponsor submission May 9, 2003

Medical officer's comments: The previous two tables were derived from a separate sponsor submission (May 9, 2003-requested by the Division) where the laboratory shift tables use the last observed value as the endpoint and include data from both completers and patients who terminated prematurely. The percentages of patients who went from the normal range at baseline to above the normal range at final measurement was slightly numerically greater in the Seasonale group for triglycerides (5.3%) and LDL (17.2%) compared to those in the Nordette group (1.6% and 14.3%, respectively). This small difference is unlikely to be of clinical significance.

Of the three subjects who were listed as going from normal to anemic in the shift table analysis for Seasonale, two had a clinically significant decrease and are listed in Table 34.

Table 34 Seasonale Subjects with Anemia (SEA 301)

Site	Subject #	Collection dates	Hemoglobin	Hematocrit	Comment
2	1	07/27/2000	12.5	37.4	Subject began Seasonale on 9/17/00. Discontinued on 7/10/01 for reasons of decreased libido. Final lab done 2 months after discontinuation
2	1	09/06/2001	10.1	31.1	
30	33	08/23/2000	11.7	35	This subject had 33 days of unscheduled bleeding/spotting in cycle 4.
30	33	09/06/2001	10.2	30.7	

Source: Sponsor's original NDA submission

The sponsor's analysis of these two subjects suggests that the laboratory changes are either mild or not clinically significant and not related to study drug. This reviewer disagrees with the sponsor's analysis for these two cases. These subjects should have had additional assessments and monitored until the lab deficiencies resolved.

Subject 2/1 may have had heavy bleeding following her discontinuation of Seasonale, but there is no diary information to assess this.

More subjects actually move from the anemic to normal range on Seasonale. Therefore, despite these two particular patients, there does not appear to be a concern that the breakthrough bleeding and spotting that is common with Seasonale actually leads to clinically significant anemia in a large number of subjects.

Decreases in hematocrit were not just found in the Seasonale group. Three Nordette subjects showed changes also as noted below:

- *Patient 8/21: 36.7% to 33.7%*
- *Patient 24/21: 39.9% to 34.0%*
- *Patient 36.4% to 34.1%*

A full case listing analysis of anemia range values for both Seasonale and Nordette is included in Section 7 of the appendix.

Seasonale and Nordette showed small and comparable elevations in bilirubin, ALT and AST in the shift table analysis as shown in Table 35 and Table 36. These laboratory changes are also known effects of combined oral contraceptives. The four subjects who went from normal to high total bilirubin levels on Seasonale had elevated levels that ranged from 1.6 to 1.9 mg/dL (ULN ≤1.2 mg/dL).

Table 35 Shift Analysis for Liver Function Tests (Seasonale Group, Study SEA 301)

Lab	Baseline	L	%	N	%	H	%	Total
Total Bilirubin (0.2-1.2 mg/DL)	L	2	11.	16	88.9	0	0	18
	N	6	1.7	337	97.1	4	1.2	347
	H	0	0	2	50.0	2	50.0	4
	Total	8		355		6		
ALT (6-37 IU/L)	L	0	0	0	0	0	0	0
	N	0	0	337	96.0	14	4.0	351
	H	0	0	14	77.8	4	22.2	18
	Total	0		351		18		
AST (10-36 IU/L)	L	0	0	0	0	0	0	0
	N	1	0.3	346	96.6	11	3.1	358
	H	0	0	8	72.7	3	27.3	11
	Total	1		354		14		

Source: Sponsor submission May 9, 2003

Table 36 Shift Analysis for Liver function Tests (Nordette Group, Study SEA-301)

Lab	Baseline	L	%	N	%	H	%	Total
Total Bilirubin (0.2-1.2 mg/DL)	L	0	0	13	100.0	0	0	13
	N	2	1.1	169	96.6	4	2.3	175
	H	0	0	1	50.0	1	50.0	2
	Total	2		183		5		
ALT (6-37 IU/L)	L	0	0	1	100.0	0	0	1
	N	0	0	176	95.1	9	4.9	185
	H	0	0	4	100.0	0	0	4
	Total	0		181		9		
AST (10-36 IU/L)	L	0	0	0	0	0	0	0
	N	0	0	183	96.8	6	3.2	189
	H	0	0	1	100.0	0	0	1
	Total	0		184		6		

Source: Sponsor submission May 9, 2003

(8) Endometrial Biopsy Findings

The sponsor found that endometrial biopsy results from a subset of Seasonale and Seasonale Ultra-Lo subjects reflect the expected endometrial thinning without evidence of pathologic changes.

Medical officer's comments:
The data sets were evaluated by this Medical Reviewer using JMP from the SAS transport files provided by the Sponsor. Baseline and final biopsy results were obtained in 50 Seasonale subjects and 61 Seasonale Ultra-Lo subjects. The expected increase in inactive glands and stromal decidualization was identified. These histologic changes are well recognized for any woman on long-term combination estrogen/progestin regimens.

Reader number 2 (sponsor's analysis) appeared to differ slightly in the pathology readings from reader 1 and reader 3. Reader 2 listed one simple hyperplasia without atypia in the Seasonale Ultra-Lo arm, but this was not confirmed by the other two readers who felt the pattern was proliferative. Reader 2 also utilized a diagnosis of "atrophy" more than the other readers, who utilized the term "inactive".

It could be argued that the endometrial biopsies were not necessary. The endometrial histologic findings related to continuous combination therapy of different strengths have been well characterized over the last thirty years. Use of more combination oral contraceptive tablets per year does not translate into a theoretical endometrial risk because the estrogen/progestin ratio remains the same in this regimen.

In summary, there are no safety concerns from the endometrial biopsy evaluations.

3. Safety information from the BA/BE studies

The following table (Table 37) lists the submitted BA/BE studies and summarizes the most significant safety findings. There were no deaths in the BA/BE studies. Three (3) subjects

discontinued from the BA/BE studies due to adverse events (ectopic pregnancy, pneumonia, and abdominal pain)

Table 37 Safety Findings from Pharmacology (BA/BE) Studies

Protocol #	Study design	# Entered/ completed	Safety
99027	Randomized; 2-way crossover: Seasonale Ultra-Lo Levlite	35/30	One SAE = ectopic pregnancy (subject # 22) Subject #19 withdrew due to pneumonia Minor adverse events include bleeding irregularities, headaches, nausea, etc.
99028	Randomized; 3-way crossover: Seasonale TBM [A] Nordette Min-Ovral	30/29	Subject #3 is listed with loss of consciousness and convulsion during the Min-Ovral phase of the study (not related to drug) Minor adverse events include bleeding irregularities, headaches, nausea, etc.
10216205	Randomized; 2-way crossover: Seasonale CT [B] Seasonale White II	30/30	Minor adverse events include bleeding irregularities, nausea, dizziness, etc.
10216206	Randomized; 2-way crossover: Seasonale TBM Seasonale CT	30/30	No serious adverse events. Minor adverse events include bleeding irregularities, headaches, etc.
10216208	Randomized; 2-way crossover: Seasonale CT Seasonale White I	30/29	Subject # 20 withdrew due to abdominal pain Minor adverse events include headaches, nausea, etc.

A: TBM = to be marketed formulation
B. CT = clinical trial formulation
Source: Original NDA submission

Medical officer's comments:
There are no safety concerns related to the findings from the BA/BE studies.

4. Safety information from the original Nordette application

The following information is derived from the medical officer review of Nordette (NDA-18-668) submitted in 1981.

The overall discontinuation rate for Nordette was 11.8%. The most frequent reason for discontinuation was breakthrough bleeding. The mean length of menses in the Nordette clinical trial was 4.3 ± 1.2 days. Table 38 highlights breakthrough bleeding and/or spotting by cycle for Nordette.

Table 38 Percent of Subjects with Breakthrough Bleeding/Spotting on Nordette (NDA 18-668)

Cycle	BTB %	Spotting %	BTB/Spotting %
Pre-treatment	9.3	5.7	13.5
1	10.1	16.2	21.3
3	7.6	8.4	14.0
6	5.6	7.5	11.7
9	6.2	8.0	Not provided
12	4.6	5.3	9.2

BTB = Breakthrough bleeding (required sanitary protection)
Spotting = sanitary protection not needed

The percentages of adverse events in cycle 1(from the Nordette pivotal trial) are listed in Table 39.

Table 39 Frequent Adverse Events in Nordette Subjects (Original NDA 18-668)

Side effect	Cycle 1 (%)
Simple headache	9.6
Migraine headache	1.2
Dysmenorrhea	6.3
GI symptoms	5.6
Acne	5.5
Nausea	6.9
Breast discomfort	4.0
Vaginal discharge	1.8
Appetite increase	2.1
Depression	2.0
Backache	2.1
Fatigue	2.0

Twelve endometrial biopsies were obtained from 11 patients by one investigator in the original Nordette NDA application. All showed a healthy but suppressed endometrium.

There were no reports of thrombotic adverse events in the Nordette application. Eighteen subjects had pressures recorded at greater than 140/90 during therapy after giving negative histories of blood pressure elevations on entry.

5. Safety information from the AERS database on Nordette

This information was provided in Section II of this review (Clinically Relevant Findings/ Other Consultative Reviews)

6. Safety information from SEA-301A Extension Study

a. Regulatory Overview

The sponsor submitted on February 14, 2003 the 4-Month Safety Update that was based on data that had not undergone full quality assurance review. A revised 4-Month Safety Update, based on data that had undergone quality assurance checks in accordance with he Sponsor's SOPs was submitted on May 7, 2003. There were additional questions concerning this data and some discrepancies. The Division requested that a final complete interim safety report be filed with summary information and data files similar to SEA-301. Because the amount of new data submitted with the final interim study report of SEA-301A was voluminous, a 3-month extension was required to review this material.

The only Seasonale study conducted since the submission of NDA 21-544 is the currently ongoing Study SEA-301A (2 year extension study) which began on December 9, 2001. The last patient was enrolled on May 19, 2002. A total of 351 subjects have been treated in this study which includes both Seasonale and Seasonale Ultra-Lo. Very few subjects transitioned immediately with no delay from SEA-301 into SEA-301A . There was a significant gap (delay) between participation in the two studies for most subjects due to lack of study drug. All the subjects who experienced a gap in treatment either received no treatment or received treatment with an alternative oral contraceptive between studies. As of the cutoff date for this safety submission (January 24, 2003), Study SEA-301A has 277 patients currently participating.

b. Safety Assessments and Data Collection Methods

(1) Protocol

The extension study is identical to the pivotal phase 3 Study SEA-301 except for the following:

- This is an open-label non-randomized study lasting two years
- There is no subset endometrial biopsy component
- The extension study has two arms instead of four (Seasonale or Seasonale Ultra-Lo)
- Patients who received either Nordette or Seasonale during study SEA-301 were to initially receive Seasonale in study SEA-301A. Those randomized to Seasonale Ultra-Lo or Levlite in study SEA-301 were to receive Seasonale Ultra-Lo in study SEA-301A. Investigators have the option, at their discretion, to change the treatment assignment at the start of each new 91-day cycle.
- A pharmacokinetic (PK) sub-study was conducted at three of the SEA-301A investigative sites to evaluate drug levels past 21 days of use.

The Schedule of Events for the extension study is listed in Table 40.

Table 40 Schedule of Events Study SEA-301A (extension study)

Parameter	Enrollment	Initiation (Month 0)[d]	Visits 1-3[e] (Months 3, 6, 9)	Visit 4[g] (Month 12)	Visits 5-7[e] (Months 15, 18, 21)	End of Study
Informed consent for study extension	X					
Physical exam including pelvic exam	X[f]			X		X
Weight, vital signs	X		X	X	X	X
Pap smear	X[f]			X		X
Clinical laboratory tests[a]	X[f]			X		X
Urine pregnancy test	X[b]	X	X	X	X	X
Study drug distribution	X	X	X	X	X	
Study diaries distribution[c]	X	X	X	X	X	
Electronic diary download			X	X	X	X
Study drug compliance measurement			X	X	X	X
Adverse event recording	X	X	X	X	X	X

a Clinical laboratory tests include CBC, serum chemistry, lipid profile, urinalysis.
b Urine pregnancy test required if two or more weeks have passed since final study visit for SEA-301.
c Electronic Diary with training manual and paper diary.
d Initiation visit may take place at the same time as enrollment.
e Study visits will take place within 7 days prior to completion of study medication for that cycle.
f Required only if enrollment occurs ≥ 6 months after completion of SEA-301 end of study procedures.
g Visit 4 will take place during the last week of active pills (i.e., prior to the expected onset of menses).
Source: Appendix 16.1.1., Protocol and Protocol Amendments

Patients were evaluated every three months in the extension study for adverse events, change in smoking history, concomitant medications, study drug compliance, vital signs, and a urine pregnancy test. Patients also continued to complete daily electronic diary recordings whether they had taken their pills and providing information about bleeding and spotting. On an annual basis, patients also were to undergo a physical examination, CBC, clinical chemistry measurements, UA, and pap smear.

(2) Responsibilities for Conduct of Clinical Trial

Freedolph D. Anderson, MD, Jones Institute for Reproductive Medicine, Norfolk VA served as the Principal Investigator for this multicenter study being conducted at 27 study sites in the U.S. Responsibility for data collection was transferred to [redacted] (since acquired by [redacted], responsibility for central laboratory activities was transferred to [redacted], responsibility for clinical supplies was transferred to [redacted] formerly [redacted] All other responsibilities (study management, monitoring, database closure, database auditing, analysis) have been retained by Barr Research.

c. Safety Findings

(1) Treatment Assignments, Interval ("Gap") between Pivotal and Extension Study, and Subject Disposition

Treatment Assignments

Table 41 shows the distribution of treatment assignments in the pivotal study SEA-301A versus the initial treatment assignments in the extension study SEA-301A. The SEA-301A protocol specified that patients should continue to receive Seasonale or Seasonale Ultra-Lo or the comparable dosage combination if they had received Nordette or Levlite in SEA-301 when they entered SEA-301A. However, Table 41 shows that a small percentage of patients were switched to either the higher or lower dose combination for their initial SEA-301A treatment assignment. After the initial treatment cycle in Study SEA 301A, patients also could be switched, at the investigator's discretion, to either the higher or lower dose formulation at the beginning of a new 91-day treatment cycle

Table 41 SEA-301 Study Drug Assignments vs. Initial SEA-301A Study Drug Assignments

	SEA-301A Initial Study Drug		
SEA-301 Study Drug	Seasonale	Seasonale Ultra-Lo	Total
Seasonale	105	9	114
Nordette	59	8	67
Seasonale Ultra-Lo	11	96	107
Levlite	16	47	63
Total	191	160	351

Source: May 13, 2003 Study Report, page 46

Interval ("Gap") between Pivotal and Extension Studies

Most patients completed study SEA-301 before study SEA-301A was implemented. The mean duration of the gap between patient's participation in study SEA-301 and study SEA-301A was 107 days for those initially taking Seasonale in study SEA-301A and 105 days for those initially taking Seasonale Ultra-Lo. The majority of patients had a gap of greater than 84 days (Table 42). Two patients had no gap between study SEA-301 and SEA-301A. Nearly two-thirds of treated patients were reportedly taking OCs throughout the gap from the end of their participation in pivotal study SEA-301 until their enrollment in study SEA-301A. The majority of patients who were initially assigned to Seasonale in study SEA-301A who used other OC therapy throughout the gap used Nordette (67%). Similarly, the majority of patients who were initially assigned to Seasonale Ultra-Lo in study SEA-301A who used other OC therapy throughout the gap used Levlite (63%).

Table 42 Distribution of "Gap" Duration

Gap Duration	Seasonale (N=191)	Seasonale Ultra-Lo (N=160)
# of Days	N (%)	N (%)
0-3	2 (1.1)	1 (0.6)
4-7	0 (0)	2 (1.3)
8-14	0 (0)	0 (0)
15-28	14 (7.3)	10 (6.3)
29-56	15 (7.9)	20 (12.5)
57-84	28 (14.7)	23 (14.4)
>84	132 (69.1)	104 (65.0)

Source: May 13, 2003 Study report summary, page 39

Medical officer's comments: Although the gap in the use of extended therapy does not lead to a significant safety concern it does limit the utility of the data in regard to breakthrough bleeding and spotting. Instead of three-year continuous treatment data, the sponsor will be able to provide only two-year data when the extension study is fully completed.

Subject Disposition

Table 43 shows the disposition of the subjects in the extension study as of the January 24, 2003 cut-off date.

Table 43 Disposition of Subjects in Study SEA 301A (Cutoff of January 24, 2003)

Status Reason for discontinuation	Seasonale (N=191)		Seasonale Ultra-Lo (N=160)		Total (N=351)	
	N	%	N	%	N	%
On-Treatment	150	78.5	127	79.4	277	78.9
Discontinued Treatment	41	21.5	33	20.6	74	21.1
Non-compliance	1	0.5	2	1.3	3	0.9
Lost to follow-up	1	0.5	2	1.3	3	0.9
Pregnancy	1	0.5	3	1.9	4	1.1
Unacceptable bleeding [A]	3	1.6	2	1.3	5	1.4
Investigator discretion	1	0.5	0	0.0	1	0.3
Subject request	15	7.9	12	7.5	27	7.7
Adverse event	14	7.3	7	4.4	21	6.0
Other	5	2.6	5	3.1	10	2.8

A. Does not include all patients who discontinued because of bleeding related issues (See Table 48 for a complete listing).
Source: May 13, 2003 Study Report, page 34

Medical officer's comments: The sponsor reported one on-treatment pregnancy (Subject 30/5) during Seasonale use in the extension study. It is difficult to assess the Pearl Index because the study is still ongoing, but a single additional pregnancy for this study population does not raise any additional efficacy concerns at this point. Not all the bleeding problems are reflected

in the "unacceptable bleeding" row. A full listing of the ten subjects (5.2%) who discontinued for bleeding related issues is found in Table 48.

(2) Deaths

One patient receiving Seasonale Ultra-Lo (Patient 17/21) died as a result of a motorcycle accident.

Medical officer's comments: Patient 17/21 was a 41 year-old Caucasian woman (144 pounds, 67 inches); nonsmoker. She had a history of three pregnancies, two of which resulted in term, live births, and one of which ended in either a miscarriage or an abortion. Her medical history included tension headaches, sinusitis, acne, and blindness in the right eye since age three. She began taking Seasonale Ultra-Lo on 30 December 2001. She completed study visit 1 on 28 March 2002 and was due to return for study visit 2 on 6 June 2002. However, on 13 May 2002, (cycle 2 day 44) the patient was a passenger on a motorcycle, which hit a curb and flipped over. The patient sustained numerous severe head and facial injuries (serious, severe, unrelated to study drug) and was pronounced dead at the scene of the accident.

(3) Serious Adverse Events

Table 44 lists the SAEs reported through the data cutoff date of this report. SAEs were reported for 6 patients, two on Seasonale and four on Seasonale Ultra-Lo (including Seasonale Ultra-Lo patient 017/021 who died from a motorcycle accident). Two of the SAEs resulted in the patient's discontinuation from the study (Patients 40/24 and 17/21).

Table 44 Serious Adverse Events in Study SEA 301A

Treatment	Site/Pt.#	Serious AE	Relationship to Drug	Patient Discontinued
Seasonale	24/30	Vulvar cancer	None	No
Seasonale	40/24	Uterine fibroids	Remote	Yes
Seasonale Ultra-Lo	8/19	Motorcycle accident	None	No
Seasonale Ultra-Lo	17/21	Death due to motorcycle accident	None	Yes
Seasonale Ultra-Lo	32/69	Gallbladder disease	Possible	No
Seasonale Ultra-Lo	34/62	Cholecystitis	None	No

Source: May 13, 2003 Study Report, page 58

Medical officer's comments: This reviewer feels after reviewing the case reports that the relationship of study drug to fibroids (Subject 40/24) and cholecystitis (Subject 34/62) should both be considered possible.

(4) Adverse Events Leading to Study Discontinuation

The adverse events leading to study discontinuation are shown in Table 45.

Table 45 Adverse Events Leading to Study Discontinuation in SEA-301A

Site/ Patient	Adverse Event	Severity	Days to AE Onset	Duration (Days)	Relation	Ongoing	SEA 301 Rx
Seasonale Group (SEA 301A extension)							
1/12	Elevated blood pressure	Mild	-5		Remote	Yes	Seasonale
1/53	Hypertension	Mild	354		Possible	Yes	Seasonale
1/57	Unexpected vaginal bleeding	Mild	52	8	Probably	No	Seasonale
4/27	Uterine fibroids	Mild	60		Remote	Yes	Seasonale Ultra-Lo
4/35	Hepatic mass x 2	Moderate	342		Possible	Yes	Seasonale
18/23	Excessive bleeding and spotting	Mild	63	39	Possible	No	Seasonale
19/47	Metrorrhagia	Moderate	166	28	Definite	No	Seasonale
37/24	Unacceptable bleeding	Moderate	251	18	Definite	No	Levlite
38/14	Intermittent right side pain	Moderate	95	58	Remote	No	Nordette
39/22	Decreased libido	Moderate	214	22	Possible	No	Seasonale
39/29	Depression	Moderate	72	130	Possible	No	Nordette
40/24	Uterine Fibroid Tumors	Moderate	168		None	Yes	Nordette
41/15	Irregular vaginal bleeding	Moderate	41	54	Probably	No	Nordette
Seasonale Ultra-Lo Group (SEA 301A extension)							
1/11	Weight gain	Mild	84		Remote	Yes	Seasonale Ultra-Lo
1/35	Intermittent vaginal bleeding	Mild	8	81	Possible	No	Levlite
4/3	Migraine headaches	Moderate	17	2	Remote	No	Seasonale Ultra-Lo
	Anxiety	Moderate	18	78	Remote	No	
18/19	Weight gain	Mild	77	66	Possible	No	Seasonale Ultra-Lo
	Irritability	Mild	46	58	Possible	No	
30/28	Endometriosis	Mild	17		None	Yes	Seasonale Ultra-Lo
41/11	Moodiness	Moderate	13		Probably	Yes	Levlite
	Irritability	Moderate	13		Probably	Yes	

Source: May 13, 2003 Study Report, page 59

Medical officer's comments: Some of the subjects who were taking Seasonale in the SEA-301 study eventually discontinued in the extension study for bleeding problems. The subject with the hepatic mass was diagnosed with focal nodular hyperplasia, which has a known association with oral contraceptives.

(5) Adverse Events

Table 46 lists the adverse events occurring at ≥ 5 % in study SEA 301A.

Table 46 Reported Adverse Events (≥ 5%) in Study SEA 301A

	Seasonale (N=191)		Seasonale Ultra-Lo (N=159)	
Adverse Event :	N	%	N	%
Back Pain	9	4.7	14	8.8
Headache NOS	19	10.0	23	14.4
Menorrhagia	17	8.9	28	17.5
Nasopharyngitis	21	11	19	11.9
Sinus Headache	4	2.1	9	5.6
Sinusitis	21	11	17	10.6
URI	11	5.8	14	8.8
Urinary Tract Infection	15	7.9	8	5.0

Source: May 13, 2003 study report page 48-56

(6) Laboratory Safety Findings

Only patients who completed study SEA-301 six months before entering SEA-301A were required to have clinical laboratory measurements, Pap and physical examination done before enrollment into SEA-301A. Consequently, only 22 patients had laboratory evaluations done before treatment in SEA-301A. Therefore, shift tables prepared from data within SEA-301A would have limited value. To partially compensate for the limited number of baseline laboratory values in SEA-301A, shift tables were prepared using the final laboratory results from study SEA-301 as the study SEA 301A baseline values. Pertinent laboratory shift data is presented in Table 47.

Table 47 Laboratory Shift Table – Pre-Study SEA-301A Value (If Available) OR Last SEA-301 Value (If No Pre-Study SEA-301A Value Was Available) to Last SEA-301A Value

Seasonale Group								
Lab	Baseline	L	%	N	%	H	%	Total
Hgb	L	1	50	1	50	0	0	2
	N	**4**	**2.6**	152	97.4	0	0	156
	H	0	0	0	0	0	0	0
	Total	5		153		0		
Hct	L	2	66.7	1	33.3	0	0	3
	N	**5**	**3.3**	148	96.7	0	0	153
	H	0	0	2	100.0	0	0	2
	Total	7		151		0		
Total Cholesterol	L	1	33.3	2	66.7	0	0	3
	N	3	3.0	89	89.0	**8**	**8.0**	100
	H	0	0	13	23.6	42	76.4	55
	Total	4		104		50		
Triglyceride	L	1	33.3	2	66.7	0	0	3
	N	1	0.7	146	97.3	**3**	**2.0**	150
	H	0	0	3	60.0	2	40.0	5
	Total	2		151		5		
Total Bilirubin	L	0	0	1	100.0	0	0	1
	N	4	2.6	148	96.1	**2**	**1.3**	154
	H	0	0	3	100.0	0	0	3
	Total	4		152		2		
ALT	L	0	0	0	0	0	0	0
	N	0	0	143	93.5	**10**	**6.5**	153
	H	0	0	4	80.0	1	20.0	5
	Total	0		147		11		
AST	L	0	0	0	0	0	0	0
	N	0	0	143	94.1	**9**	**5.9**	152
	H	0	0	5	83.3	1	16.7	6
	Total	0		148		10		

Source: May 13, 2003 study report page 62-66

Medical officer's comments: The laboratory findings are similar to those seen in study SEA 301. As in SEA-301, there were a few individual subjects who had a drop in their hematocrit of 3-5 points, but there was no evidence of an increasing trend with continued extended use. Undiagnosed leiomyomata could also be an etiology for the bleeding in some individuals. The other laboratory changes are known effects of oral combination contraceptives.

The sponsor was contacted concerning subject 29/61 who had marked liver enzyme elevation. The sponsor's follow-up information revealed that this patient was found to have a large common bile duct stone.

(7) Analysis of Bleeding/Spotting in the Extension Study

Bleeding and Study Discontinuation

Subject bleeding which contributed to study discontinuation is shown in Table 48. This table was derived from the study discontinuation data set.

Table 48 Subjects on Seasonale with Bleeding Problems who Discontinued in SEA-301A

Site No.	Subject No.	Bleeding categorization	SEA-301 RX	Gap contraceptive used and days of use	SEA-301A extension RX
1	57	Unexpected vaginal bleeding; (also DCed to become pregnant)	Seasonale	Levlite/56 days	Seasonale
4	27	Unacceptable bleeding due to fibroids	Seasonale Ultra-Lo	Nordette/140 days	Seasonale
6	29	Unacceptable bleeding	Nordette	Levora/126 days	Seasonale
18	23	Unacceptable bleeding	Seasonale	Loestrin/126 days	Seasonale
19	47	Metrorrhagia	Nordette	Nordette/28 days	Seasonale
29	16	Unacceptable bleeding	Nordette	Desogen/140 days	Seasonale
37	24	Unacceptable bleeding	Levlite	Alesse/56 days Yasmin/56 days	Seasonale
41	15	Irregular vaginal bleeding	Nordette	Nordette/112 days	Seasonale
42	40	Unacceptable bleeding	Nordette	Nordette/56 days	Seasonale
46	22	Unacceptable bleeding	Nordette	Ortho Tri-Cyclen/ 119 days	Seasonale

Source: Final Interim Report and datasets (SEA-301A)

Medical officer's comments: This table illustrates again the bleeding issues with "new" use of the extended method since 7 of the 10 discontinuations were in subjects who were taking a 28 day cycle medication in the SEA-301 study.

Bleeding Data from Extension Study

The total number of days of bleeding (anticipated and unanticipated) per cycle from the ITT population of the extension study is shown in Table 49.

Table 49 Observed Total Number of Days of Bleeding and/or Spotting by Treatment Cycle (All Treated Patients - ITT)

Cycle	N	Mean	SD	Min	Q1	Median	Q3	Max	Median Per Monthly Cycle	*Study SEA-301 Median Per Monthly Cycle**
Seasonale										
1	187	12.3	11.7	0.0	4.0	8.0	17.0	58.0	2.5	*4.6*
2	166	8.6	9.4	0.0	3.0	5.0	11.0	54.0	1.5	*3.1*
3	134	7.4	9.0	0.0	2.0	5.0	9.0	50.0	1.5	*2.8*
4	118	5.2	5.9	0.0	1.0	3.0	7.0	32.0	0.9	*2.5*
5	60	1.0	1.3	0.0	0.0	1.0	2.0	5.0	0.3	
Seasonale Ultra-Lo										
1	154	14.4	13.9	0.0	5.0	10.0	21.0	79.0	3.1	*5.8*
2	136	12.2	10.4	0.0	4.0	10.0	17.0	55.0	3.1	*4.0*
3	113	10.5	10.1	0.0	3.0	7.0	14.0	49.0	2.2	*3.1*
4	104	8.1	9.1	0.0	2.0	6.0	10.0	53.0	1.8	*3.4*
5	62	2.3	4.2	0.0	0.0	0.0	3.0	21.0	0.0	

Source: Appendices 16.4.5-16.4.6: Daily Diary, 16.4.17: *SEA-301 CSR Table 25.1.2.

***Medical officer's comments:** In this table the sponsor again focuses on the median number of days and converts the median to monthly cycle equivalents. The lower numbers for days of bleeding in study SEA 301A compared to the SEA-301 study are probably a result, at least in part, by the fact that the extension study is composed of women who have less unanticipated bleeding/spotting in SEA 301 or who tolerate the bleeding/spotting better. The improvement in the median number of days in this study could also be a reflection of patient discontinuations. Because this table reflects an interim analysis, the focus on the results should center on the first three cycles. These bleeding results are also difficult to interpret due to the fact that most subjects had a gap during which they were taking 28-day regimen tablets and these data are not obtained from women continuously taking an extended regimen for two straight years.*

Table 50 **lists the number of days of an unanticipated bleeding/spotting per cycle. The same reviewer comments apply to this table as those stated above in reference to the previous table.**

Table 50 Observed Number of Days of Unscheduled Bleeding and/or Spotting by Cycle (ITT)

Cycle	N	Mean	SD	Min	Q1	Median	Q3	Max	Median Per Monthly Cycle	*Study SEA-301 Median Per Monthly Cycle**
Seasonale										
1	187	9.4	10.8	0.0	2.0	5.0	13.0	53.0	1.3	*3.0*
2	166	6.1	8.7	0.0	1.0	3.0	7.0	47.0	0.8	*1.5*
3	134	4.9	8.0	0.0	0.0	2.0	5.0	43.0	0.5	*1.5*
4	118	3.5	5.3	0.0	0.0	1.0	4.0	30.0	0.3	*1.0*
5	60	1.0	1.3	0.0	0.0	1.0	2.0	5.0	0.3	
Seasonale Ultra-Lo										
1	154	11.9	12.9	0.0	2.0	8.0	17.0	72.0	2.0	*4.0*
2	136	9.8	9.6	0.0	2.0	7.0	15.0	48.0	1.8	*2.8*
3	113	8.2	9.0	0.0	1.0	6.0	12.0	44.0	1.5	*2.0*
4	104	6.2	8.3	0.0	1.0	3.0	8.0	47.0	0.8	*2.0*
5	62	2.3	4.2	0.0	0.0	0.0	3.0	21.0	0.0	

Source: Appendices 16.4.5-16.4.6: Daily Diary, 16.4.17: *SEA-301 CSR Table 26.1.2.

Amenorrhea

The proportion of patients within each treatment group with no reported bleeding and/or spotting during each complete cycle for both treatment groups is displayed in Table 51. Included in the table are complete cycles as well as partial cycles of at least 56 days duration for those patients with ongoing treatment as of 24 January, 2003. The percentage of patients with amenorrhea ranged between 1.32% to 3.13% of those using Seasonale and between 0.59% and 2.35% for those on Seasonale Ultra-Lo. For both treatment groups, the highest proportion of amenorrhea occurred during cycle 4.

Table 51 Proportion of Patients With No Reported Bleeding and/or Spotting by Cycle

Treatment	Cycle	N	Patients with Amenorrhea	
			N	Percentage
Seasonale	1	179	8	1.32
	2	158	11	1.81
	3	130	9	1.48
	4	110	19	3.13
Seasonale Ultra-Lo	1	140	3	0.59
	2	130	8	1.56
	3	110	7	1.37
	4	102	12	2.35

References: Appendices 16.4.5-16.4.6: Daily Diary, 16.4.17:

Medical officer's comments: The previous table indicates that only a small number of women on extended use OC therapy will have no bleeding whatsoever. The sponsor's data for median number of days of scheduled bleeding in the extension study is in the 2-3 day range. Scheduled bleeding in the SEA-301 study showed a 3-4 day median.

D. Adequacy of Safety Testing

Since the sponsor's original submission did not contain 5,000 28-day cycle-months of safety exposure, the sponsor was asked to provide additional safety data from the SEA-301A extension study. The sponsor was initially asked to complete their auditing procedures so that the initial data from the February 14, 2003 submission could be reviewed. An abbreviated study report, based on audited data, was sent on May 7, 2003. The report summarized the key safety elements but was not a complete report. It was noted that the abbreviated report contained a significant number of changes compared to the February 14 document in regard to study exposure, adverse events, and adverse events leading to study discontinuation. There were no changes in the serious adverse events reported. The sponsor was asked to submit all of the safety data as a complete final interim report based on the January 24, 2003 cut-off date. The sponsor sent their complete final interim safety report for the SEA-301A and data files on May 15, 2003 and May 16, 2003.

Medical Officer's Comments. A preliminary review of this material indicated some data deficiencies. The sponsor stated that conversion from Word to Adobe Acrobat created some of the problems. Corrected documents were filed on May 29, 2003. The combination of the pivotal study SEA-301 and the SEA-301A extension study interim safety report provides enough 28-day cycle equivalents (5,946) to assess safety for Seasonale.

E. Summary of Critical Safety Findings and Limitations of Data

The following points summarize the safety findings and limitations of data:

- The combination of the pivotal study SEA-301 and the SEA-301A extension study interim safety report provides enough 28-day cycle equivalents (5,946) to assess safety for Seasonale.

- The primary adverse event related to Seasonale is unanticipated bleeding and spotting. This event caused more discontinuations in the Seasonale arm compared to the Nordette arm in the pivotal study SEA-301. Although this side effect diminishes somewhat with use, 15% of the subjects still had over 20 days of unanticipated bleeding/spotting in the fourth 91-day cycle of use and approximately 40% had greater than 7 days of unanticipated bleeding/spotting in the fourth cycle.

- Despite the prolonged number of days of unanticipated bleeding/spotting it appears that the quantity of blood loss with this bleeding is usually minimal. There was no evidence in the hematology laboratory dataset from the pivotal SEA-301 trial that there are significant problems with anemia (hematocrits < 35.0%) in those subjects taking Seasonale. The number of Seasonale subjects with anemia at the end of the study was comparable to that found in the Nordette arm. There was no problem with anemia in the subjects who prematurely discontinued in the Seasonale arm for reasons of unacceptable bleeding.

- The identification of one subject developing a pulmonary embolus while taking Seasonale does not provide a signal that the 91-day regimen duration compared to the 28-day regimen duration increases the risk for thromboembolic events. Due to the rarity of these events, standard postmarketing surveillance (AERS) is recommended to further monitor for these events.

- Seasonale showed similar blood pressure changes and laboratory alterations when compared to Nordette and oral contraceptives in general.

VIII. Dosing, Regimen, and Administration Issues

Dosing duration is the key difference in this combination oral contraceptive application. The combination oral contraceptive is being given for 84 days instead of 21 days before the seven-day hormonal withdrawal period. Because of the increased duration of the active treatment phase, patients are exposed to 9 more weeks of hormones for a year's dosing compared to a 28-day regimen. The following table (Table 52) demonstrates the dosing implications for Seasonale compared to other approved oral contraceptive products.

Table 52 Exposure to Ethinyl Estradiol (EE) and Levonorgestrel (LNG) (Seasonale vs. Other Approved Combination Oral Contraceptives

	Levlite	Nordette	Lo/Ovral	Seasonale	Ovral
EE dose/tablet	20 mcg	30 mcg	30 mcg	30 mcg	50 mcg
LNG dose/tablet	100 mcg	150 mcg	150 mcg	150 mcg	250 mcg
# active tablets/cycle	21	21	21	84	21
# cycles/yr	13	13	13	4	13
# active tablets/yr	273	273	273	336	273
Total EE/yr	5.46 mg	8.19 mg	8.19 mg	10.08 mg	13.65 mg
Total LNG/yr	27.3 mg	40.95 mg	40.95 mg	50.4 mg	68.25 mg

Key Labeling Issues

Since Seasonale has a different dose administration schedule, different bleeding pattern and a higher yearly hormonal exposure, specific labeling was written to address the differences from conventional 28-day combination oral contraceptives. The key labeling sections include the following:

- A statement which indicates that although studies to date have not shown an increased risk for thrombotic and thromboembolic disease, there may be an additional risk due to added exposure.

- A statement and table demonstrating that Seasonale has more intermenstrual bleeding and spotting than the 28-day comparator.

- Statements that direct women to strongly assess their pregnancy risk if they miss any of their expected withdrawal bleeds while taking Seasonale.

- Revised patient directions that are required to accommodate the administration differences.

Additionally, like other recent labeling for combination oral contraceptives, the Pearl Index for Seasonale was specifically stated.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The product is only intended for use in women.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

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

C. Evaluation of Pediatric Program

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

D. Comments on Data Available or Needed in Other Populations

No additional data is required in other populations.

X. Conclusions and Recommendations

Seasonale is efficacious for prevention of pregnancy. The Pearl Index of 1.98 is acceptable. No new serious safety concerns were demonstrated in the clinical studies. The use of Seasonale is associated with more unanticipated bleeding and spotting than a 28-day cycle regimen utilizing the same dose of hormones (Nordette). This bleeding and spotting does not present safety concerns of anemia but will likely present quality of life issues for some patients leading to discontinuation.

Approval of Seasonale for prevention of pregnancy is recommended. Agreements with the sponsor concerning product labeling were reached on September 4, 2003.

XI. Appendix

Section 1: Abbreviations

AE = Adverse event
AERS = Adverse Events Reporting System
ALT = Alanine aminotransferase
AST = Aspartate aminotransferase
BMI = body mass index
BP = Blood pressure
BRI = Barr Research, Inc.
CBC = Complete blood count
CI = Confidence interval
C_{max} = Maximum plasma concentration
COT = Completion of therapy
CRF = Case report form
CRO = Contract research organization
dL = Deciliter
ED = Electronic Diary
EDC = Electronic data capture
EE = Ethinyl estradiol
EMB = Endometrial biopsy
HRQOL = Health-related quality of life
IRB = Institutional review board
ITT = Intent-to-treat
IUD = intrauterine device
LNG = Levonorgestrel
µg = microgram
mg = milligram
NDA = New drug application
OC = Oral contraceptive
OTC = Over-the counter
PE = Pulmonary embolism
PITT = Pregnancy intent-to-treat
Pk = Pharmacokinetics
PPA = Per-protocol analysis
PPI = Patient package insert
PMS = Premenstrual syndrome
RSM = Remote study monitoring
SAE = Serious adverse event
SD = Standard deviation
SE = Standard error
SOPs = Standard operating procedures
T_{half} = Terminal elimination half-life
T_{max} = Time of maximum concentration
UA = Urinalysis
VTE = Venous thromboembolism
WNL = Within normal limits

Section 2: Paper Submission Listings for Original NDA

Volume	Description
1 (1.01)	Table of Contents Labeling Patent Information Financial Disclosure
2 (1.02)	Annotated label Pharmacologic Class, Rationale, Intended Use, Potential Benefits Foreign Marketing History CMC Summary Pharmacokinetic and Bioavailability Summary Clinical Data Summary Benefit/Risk Relationship
3 (1.56)	Investigator List Overview of Clinical Investigations Final Study Report
4 (1.57)	Summary Tables, SAE Narratives, Summary Statistics for Bleeding
5 (1.58)	Protocol, Diary, Sample CRF, QOL, IRB
6 (1.59)	Investigator List and Curriculum Vitae
7 (1.60)	Curriculum Vitae
8 (1.61)	Curriculum Vitae
9 (1.62)	Package Lot Information, Randomization and Start Dates
10 (1.63)	Randomization, Statistical Analysis Plan, Lab Certification, Contraceptive references, Data Listings for Subject Discontinuation
11 (1.64)	Data Listings (Protocol Deviations, Pearl Index)
12 (1.65)	Data Listings (Pearl Index, Demographics, Compliance)
13 (1.66)	Data Listings (Compliance and Cycle Completion)
14 (1.67)	Data Listings (Pregnancy Testing Information)
15 (1.68)	Data Listings (Site Pregnancy Information)
16 (1.69)	Data Listings (Adverse Events)
17 (1.70)	Data Listings (Adverse Events and Laboratory)
18 (1.71)	Laboratory Data Listings
19 (1.72)	Quality of Life Summary and Analysis
20 (1.73)	Medical Officer Review of Nordette (NDA 18-668) Medical Literature Reports of >28 Day OCP Regimens Safety information from Ongoing Phase III/IV extension SEA-301A
21 (1.74)	Integrated Summary of Efficacy Integrated Summary of Safety
22 (1.75)	Drug Abuse and Overdose Information Integrated Summary of Benefits and Risks References (including journal articles, Levlite Package Insert, Agency draft guidance for OCP labeling, Depo-Provera Pt. Brochure)

Section 3: Electronic Submission Listings for Original NDA

Included Items	Specifics
Case Report Forms for studies SEA-301, 99027-19 and 10116208 as PDF	Subjects who discontinued due to adverse events Subjects with serious adverse events Subjects who became pregnant on study
Datasets SEA-301 as SAS transport	Includes data for adverse events, demographics, bleeding, laboratory findings, pregnancy testing, diary information, QOL, endometrial biopsy
Datasets 10216205	EE and LNG PK endpoints
Datasets 10216206	EE and LNG PK endpoints
Datasets 10116208	EE and LNG PK endpoints
Cover letter from sponsor	
NDA table of contents	Not linked
Form 365	
Tabulations SEA-301 individual subject line listings and tables as PDF	

Section 4: Combined levonorgestrel and ethinyl estradiol contraceptive products

NDA #	Proprietary Name/ Applicant	Approval Date	EE strength (mg)	LNG strength (mg)	Generic/ #/Applicant/year
016672/ 016806	**Ovral/ Ovral-28** Wyeth Ayerst	1968	0.05	0.25*	**Ogestrel** 075406 SCS/1999
017612/ 017802	**Lo/Ovral Lo/Ovral-28** Wyeth Ayerst	1976	0.03	0.15**	**Low-Ogestrel-21/28** 075288 Watson/1999 **Cryselle** 075480 Duramed Pharm Barr/2001
018668/ 018782	**Nordette-21 Nordette-28** Wyeth Ayerst	5/10/82	0.03	0.15	**Portia-21** 075866 Barr Labs/2002 **Levora –21/28** 073592/ 073594 Watson/1993
019192/ 019190	**Triphasil 21/28** Wyeth Ayerst	11/01/84	0.03 0.04 0.03	0.05 0.125 0.075	**Trivora-21/28** 074538 Watson/1997 **Enpresse-21/28** 075809 Duramed Pharm Barr/2001
020683	**Alesse 21/28** Wyeth Ayerst	3/27/97	0.02	0.1	**Lessina-21/28** 075803 Barr/2002 **Aviane-21/28** 075796 Duramed Pharm Barr/2001
020860	**Levlite** Berlex	7/13/98	0.02	0.1	
020946	**Preven** Gynetics	9/01/98	0.05	0.25	

(*) Ovral (and its generic equivalent, Ogestrel 0.5/50) contains 0.5 mg d,l-norgestrel of which 0.25 mg is the active progestin levonorgestrel.
(**) Lo/Ovral (and its generic equivalents, Low-Ogestrel and Cryselle) contains 0.3 mg d,l- norgestrel, of which 0.15 mg is the active progestin levonorgestrel.

Section 5: Study Centers -SEA 301 (ITT)

Site	Principle Investigator	Site Location	No. Subjects
1	Freedolph D. Anderson MD	Norfolk, VA	81
2	Davis Baldwin MD	Palo Alto, CA	14
3	Irwin Kerber MD	Dallas, TX	34
4	Alfred Moffett MD	Leesburg, FL	59
5	James Simon MD	Laurel, MD	27
6	Karen Kreutner	Charleston, SC	36
7	John Angelo, DO	New Orleans, LA	26
8	Suzanne Barbier MD	Seattle, WA	23
9	Paul Blumenthal MD	Baltimore, MD	18
10	Anthony Chavez MD	Houston, TX	6
12	Nancy Cooley MD	Chaska, MN	23
13	Jay Cooper MD	Phoenix, AZ	41
14	Vivien D'Andrea MD	Sunnyvale, CA	6
15	Thomas Davies MD	Houston, TX	11
17	Edward Durbin MD, PhD	Granger, IN	21
18	Donald Edger MD	Lexington KY	57
19	Robert Feldman MD	Key Largo, FL	44
20	Frederick Fingerhut MD	Phoenix, AZ	25
21	Frances Fisk	Albuquerque, NM	33
22	Saul Berg, MD (formerly Samuel Flannagan MD	Pittsburgh, PA	14
23	Bill Griffin MD	Corpus Christi, TX	12
24	Charles Herring MD	Wilmington, NC	24
25	Andrew Kaunitz MD	Jacksonville, FL	12
26	Rebecca Knight MD	Peoria, IL	31
28	James Lackey MD	Oklahoma City, OK	42
29	Sooji Lee-Rugh MD	Arlington, VA	71
30	Thomas Littlejohn MD	Winston Salem, NC	38
31	James Maly MD	Lincoln, NE	42
32	Phyllis Marx MD	Chicago, IL	54
33	Marjorie Merod MD	Raleigh, NC	22
34	David Morin MD	Bristol, TN	51
35	David Rayl MD	Newport News, VA	27
36	Anjuli Nayak MD	Peoria, IL	20
37	Robert Nett MD	San Antonio, TX	46
38	David Portman MD	Columbus, OH	30
39	Paul Miller, MD	Greenville, SC	24
40	George Raad MD	Charlotte, NC	31
41	Sidney Rosenblatt, MD	Irvine, CA	20
42	Mark Shepard MD	Washington DC	52
43	John Stoukides MD	East Providence, RI	16
44	Michael Swor MD	Sarasota, FL	18
45	Timothy Truitt MD	Melbourne FL	12
46	Wulf Utian MD	Cleveland OH	44
47	Cheryl Walker MD Lynn Westphal MD	Stanford CA	6
48	Arthur Pitterman MD	Las Vegas, NV	20
49	John Willems MD	La Jolla, CA	6
50	Robert Prout MD	South Yarmouth, MA	6
Total			1376

Medical officer's comments: None of the above names and none of the names of the subinvestigators in this study were found on the ORA debarment list. The sponsor stated that sites 11, 16, and 27 never randomized any subjects in this study

Section 5: Study Centers -SEA 301A (ITT)

Site	Principle Investigator	Site Location	No. Subjects
1	William Gibbons, MD	Norfolk, VA	50
4	Alfred Moffett MD	Leesburg, FL	29
5	James Simon MD	Laurel, MD	7
6	Karen Kreutner	Charleston, SC	12
8	Suzanne Barbier MD	Seattle, WA	10
9	Paul Blumenthal MD	Baltimore, MD	3
12	Nancy Cooley MD	Chaska, MN	7
17	Edward Durbin MD, PhD	Granger, IN	10
18	Donald Edger MD	Lexington KY	5
19	Robert Feldman MD	Key Largo, FL	17
21	Frances Fisk	Albuquerque, NM	9
22	Saul Berg, MD (formerly Samuel Flannagan MD	Pittsburgh, PA	7
24	Charles Herring MD	Wilmington, NC	7
28	James Lackey MD	Oklahoma City, OK	22
29	Sooji Lee-Rugh MD	Arlington, VA	32
30	Thomas Littlejohn MD	Winston Salem, NC	12
31	James Maly MD	Lincoln, NE	13
32	Phyllis Marx MD	Chicago, IL	11
34	David Morin MD	Bristol, TN	9
37	Robert Nett MD	San Antonio, TX	13
38	David Portman MD	Columbus, OH	7
39	Paul Miller, MD	Greenville, SC	9
40	George Raad MD	Charlotte, NC	12
41	Sidney Rosenblatt, MD	Irvine, CA	7
42	Mark Shepard MD	Washington DC	17
44	Michael Swor MD	Sarasota, FL	4
46	Wulf Utian MD	Cleveland OH	10
Total			351

APPEARS THIS WAY
ON ORIGINAL

Section 6: Health-Related Quality of Life

Medical officer's comments: The following are abbreviated categories from the HRQoL.

Baseline Questions	Follow-Up Questions
Q1 General health question	Q1 General health question
Q2 General health question -comparison to a year ago	Q2 General health question -comparison to a year ago
Q3 Daily activities question – health limitations (10 activities)	Q3 Daily activities question – health limitations (10 activities)
Q4 Work and health question	Q4 Work and health question
Q5 Work and emotional problems	Q5 Work and emotional problems
Q6 Social activities and health	Q6 Social activities and health
Q7 Bodily pain last month	Q7 Bodily pain last month
Q8 Pain and work	Q8 Pain and work
Q9 Tiredness, happiness etc last month	Q9 Tiredness, happiness etc last month
Q10 Social activities and health and emotional problems	Q10 Social activities and health and emotional problems
Q11 Attitude toward individual health	Q11 Attitude toward individual health
Q12 Reasons for taking OCP other than prevention of pregnancy Reduce headaches Lighten flow of periods Improve acne Know the timing of periods Reduce moodiness Reduce the number of your periods Reduce the number of days of bleeding Reduce cramping/menstrual pain Other	Q12 Reasons for taking OCP other than prevention of pregnancy Reduce headaches Lighten flow of periods Improve acne Know the timing of periods Reduce moodiness Reduce the number of your periods Reduce the number of days of bleeding Reduce cramping/menstrual pain Other
Q13 Relationship of PMS and menstrual symptoms to activities, energy, sexual activity, mood etc.	Q13 Relationship of PMS and menstrual symptoms to activities, energy, sexual activity, mood etc.
Q14 During the last three menstrual cycles how much of the time and how bothered are you with these symptoms Pain and cramping Headaches Lightheadness Fatigue Acne Nausea Breast tenderness Bloating Mood changes/ irritability Unexpected bleeding or spotting Lower back pain Weight gain	Q14 During the last three menstrual cycles how much of the time and how bothered are you with these symptoms Pain and cramping Headaches Lightheadness Fatigue Acne Nausea Breast tenderness Bloating Mood changes/ irritability Unexpected bleeding or spotting Lower back pain Weight gain
Q15 Question related to pregnancy worry and preference for less periods	Q15 In general, how often do you have side effects from your birth control pills

Section 6: Health-Related Quality of Life (Continued)

Baseline Questions	Follow-Up Questions
Q16 Question related to displeasure with menstrual period frequency	Q16 In general, how bothered are you by any side effects from your birth control pills
Q17 How many times a year would you prefer to have a period	Q17 Nine part question related to satisfaction with OCP the subject is using now (issues related to pregnancy worry, period frequency, cycle regulation, pad/tampon expense, health benefits, amount of PMS and PMS medication use
Q18 Satisfaction with current OCP to reduce menstrual pain	Q18 same as Q16 baseline
Q19 Satisfaction with current OCP to lighten flow	Q19 same as Q17 baseline
Q20 Satisfaction with current OCP to reduce duration of your period	Q20 similar to Q18 baseline
Q21 Would you recommend your current pills to another woman	Q21 similar to Q19 baseline
Q22 Attitude to convenience of your current OCP	Q22 similar to Q20 baseline
Q23 Williness to continue current OCP	Q23 same as Q21 baseline
Q24 How often do you have side effects with current OCP	Q24 same as Q22 baseline
Q25 How bothered are you by side effects of current OCP	Q25 same as Q23 baseline
Q26 How do you rate current OCP	Q26 comparison of present pills to subject's old birth control pills
Q27 Question about remembering to take OCP	Q27 same as Q26 baseline
	Q28 same as Q27 baseline

Medical officer's comments: Questions 1-11 come from the SF-36 with permission of the Medical Outcomes Trust, © 1994. The rest of the questions relate to oral contraceptive use. Though this QOL will not support labeling claims, some of the sections are pertinent to review of the Seasonale regime especially in regard to bleeding frequency and other OCP side effects listed in question 14. Women who were not currently using birth control pills only answered through question 17 in the baseline questionnaire.

Section 7: Subjects with laboratory findings of anemia (Seasonale/Nordette-SEA 301)

Seasonale Subjects with Laboratory Findings of Anemia (Hg and/or Hct < LLN)

Site	Subject	Collection date	Hgb (a)	Hct (b)	Age	Race	Comment
1	50	09/14/2000	10.7 L	33.5 L	27	Afr/Amer	Increased to normal at final
1	50	09/05/2001	13.3	40	27	Afr/Amer	
2	1	07/27/2000	12.5	37.4	18	Caucasian	Decreased to anemia at final
2	1	09/06/2001	10.1 L	31.1 L	18	Caucasian	DC'd for libido
7	21	09/28/2000	10 L	31.3 L	29	Afr/Amer	Increased to just about normal at final
7	21	02/08/2001	11.5 L	35.3	29	Afr/Amer	
15	5	08/24/2000	11.5 L	34.9 L	36	Caucasian	Increased to normal at final
15	5	09/28/2001	12.9	37.6	36	Caucasian	
19	14	08/16/2000	11.5 L	34.8 L	34	Caucasian	Increased to normal at final
19	14	10/16/2001	12.3	37.6	34	Caucasian	
29	66	11/18/2000	11.1 L	33.5 L	27	Caucasian	Increased to normal at final
29	66	12/18/2001	12.7	37.9	27	Caucasian	
29	81	12/20/2000	11.8	35.9	31	Afr/Amer	Decreased to slightly anemic at final
29	81	02/08/2002	11.4 L	34.9 L	31	Afr/Amer	
30	33	08/23/2000	11.7	35	19	Caucasian	Decreased to anemia at final; Completed study
30	33	09/06/2001	10.2 L	30.7 L	19	Caucasian	
31	15	09/12/2000	11 L	34.9 L	29	Caucasian	Increased to normal at final
31	15	10/06/2001	14.2	43.2	29	Caucasian	
32	3	07/24/2000	11.6	34.3 L	26	Afr/Amer	Increased to normal at final
32	3	08/17/2001	13	39.7	26	Afr/Amer	
32	5	07/25/2000	10.5 L	34.5 L	19	Afr/Amer	Anemic at baseline no final determination
40	8	08/21/2000	11.3 L	34.8 L	30	Afr/Amer	Anemic at baseline no final determination
40	35	10/10/2000	10.4 L	32.3 L	19	Afr/Amer	Remained at same level of anemia
40	35	10/23/2001	10.8 L	33.8 L	19	Afr/Amer	
41	9	08/15/2000	11 L	33.2 L	25	Caucasian	Increased to normal at final
41	9	09/18/2001	12.9	37.1	25	Caucasian	
46	49	10/05/2000	11.9	34.9 L	35	Caucasian	Increased to normal at final
46	49	10/23/2001	12.7	38.2	35	Caucasian	

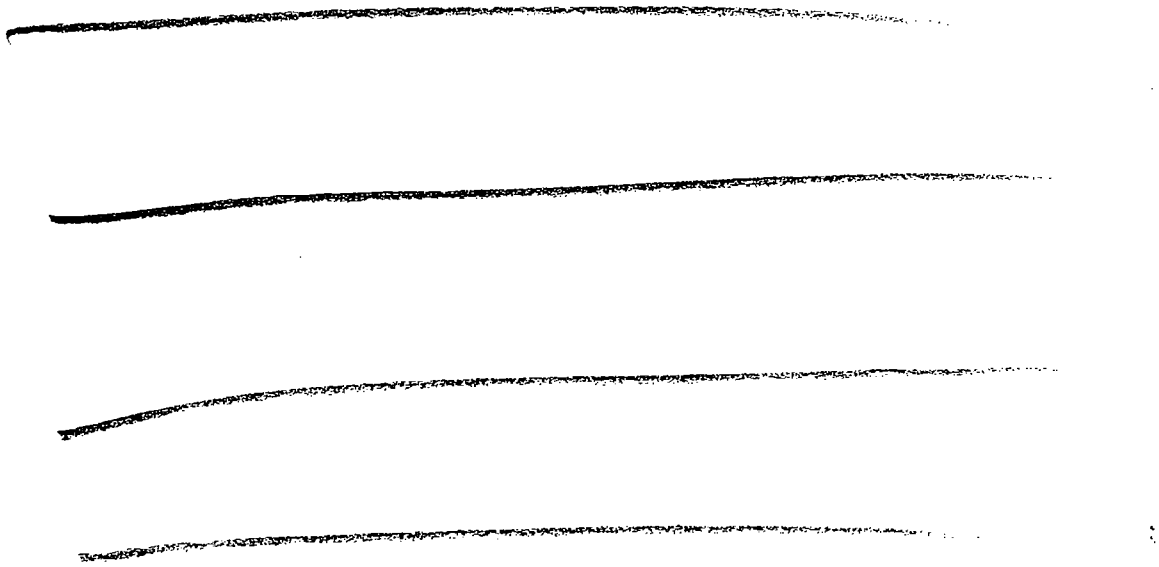
a: Hemoglobin (Normal = 11.6 to 16.2)
b: Hematocrit (Normal = 35 - 47)

Nordette Subjects with Laboratory Findings of Anemia (Hg and/or Hct < LLN)

Site	Subject	Collection date	Hgb (a)	Hct (b)	Age	Race	Comment
3	30	10/06/2000	12	34.9 L	34	Afr/Amer	Hgb down slightly Hct up slightly Essentially the same
3	30	04/04/2001	11.6	35	34	Afr/Amer	
6	36	10/05/2000	10.3 L	32.5 L	28	Afr/Amer	Increased but stayed anemic
6	36	11/06/2001	10.5 L	34.3 L	28	Afr/Amer	
8	21	10/04/2000	12.3	36.7	33	Caucasian	Hct decreased by 3 points to anemic range
8	21	10/18/2001	11.9	33.7 L	33	Caucasian	
8	22	10/04/2000	11.5 L	35.5	21	Asian	No final recording
13	2	07/21/2000	10.8 L	34.1 L	38	Caucasian	Increased to normal
13	2	10/05/2000	13.6	41.9	38	Caucasian	
24	21	09/21/2000	12.9	39.9	20	Caucasian	Hct decreased by 5.9 to anemic range
24	21	10/29/2001	11.9	34 L	20	Caucasian	
29	32	08/17/2000	12.4	36.4	35	Caucasian	Hct decreased by 2.3 to anemic range
29	32	08/22/2001	11.6	34.1 L	35	Caucasian	
42	6	07/18/2000	11.8	34.4 L	26	Caucasian	Increased to normal
42	6	08/23/2001	13.2	37.8	26	Caucasian	
48	22	10/18/2000	11.5 L	35.5	29	Afr/Amer	No final recording

a: Hemoglobin (Normal = 11.6 to 16.2)
b: Hematocrit (Normal = 35-47)

Section 8: DDMAC Labeling Recommendations



3 Page(s) Withheld

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

/s/

Gerald Willett
9/4/03 11:19:31 AM
MEDICAL OFFICER

Scott Monroe
9/5/03 02:43:30 PM
MEDICAL OFFICER
I concur.