SYNOPSIS

Issue Date: 26 March 2009
Document No.: EDMS-USRA-10985962

Name of Sponsor/Company	Ortho-McNeil Janssen Scientific Affairs, L.L.C.
Name of Finished Product	ORTHO TRI-CYCLEN® LO
Name of Active Ingredients	norgestimate/ethinyl estradiol

Protocol No.: NRGMONCON4002

Title of Study: An Open-Label Study to Evaluate Cycle Control with ORTHO TRI-CYCLEN® LO (norgestimate/ethinyl estradiol) and YAZ® (drospirenone/ethinyl estradiol) in Healthy, Sexually Active Females (Ortho Regimen Study [ORS])

Publication (Reference): None

Study Period: May 27, 2008 – October 27, 2008

Phase of Development: 4

Objectives: The primary objective of this study was to evaluate cycle control with ORTHO TRI-CYCLEN LO (norgestimate/ethinyl estradiol 25 mcg or NGM/EE25) versus YAZ (drospirenone and ethinyl estradiol 20 mcg [product of Bayer Healthcare Pharmaceuticals, Inc.]). Subject satisfaction was assessed as a secondary objective. Overall safety was also assessed.

Methods: This was a randomized open-label, active-controlled, multicenter study conducted in the United States in 20 centers that evaluated cycle control with ORTHO TRI-CYCLEN LO versus YAZ in healthy, sexually active females between the ages of 18–45 years, who chose oral hormonal contraceptive (HC) for the prevention of pregnancy. At Visit 1 (baseline), subjects gave informed consent, gave medical history, and had a physical examination including a breast examination, height, weight, vital signs, a Chlamydia test, a urine pregnancy test (UPT), and a vaginal/cervical examination. Subjects also had a Pap smear performed at this visit unless documentation was provided of a Pap smear within the preceding 12 months showing no evidence of moderate or severe dysplasia or any malignancy. Subjects who met all eligibility criteria were randomized in a 1:1 fashion to receive either ORTHO TRI-CYCLEN LO or YAZ according to a predetermined randomization schedule, stratified by center and recent HC exposure. The possible groupings for HC exposure were as "fresh starts" (no HC exposure in previous 60 days or more), and "switchers" (HC exposure within 60 days). Study drug (Day 1) was started on the first day of the subject's next menses following Visit 1. The open-label treatment phase lasted for three 28-day cycles. The final study visit occurred after subjects completed 3 cycles of study medication (Days 85-91). At the final visit, subjects were weighed, had vital sign assessments performed, reported any adverse events (AEs) and changes in concomitant medications, and completed the satisfaction questionnaire. Bleeding information was collected through a daily diary using an interactive voice response system (IVRS).

Number of Subjects (planned and analyzed): Approximately 300 subjects were planned; 355 subjects were randomized in a 1:1 ratio to receive either ORTHO TRI-CYCLEN LO (178 subjects) or YAZ (177 subjects).

Diagnosis and Main Criteria for Inclusion: Healthy, sexually active females between the ages of 18 to 45 years choosing oral HC for the prevention of pregnancy were enrolled in the study. Subjects having a history of or presence of disorders commonly accepted as contraindications to steroid hormonal therapy were excluded from the study.

Test Product, Dose and Mode of Administration, Batch No.: Subjects on commercially obtained ORTHO TRI-CYCLEN LO received 3 cycles of a standard regimen as given below:

ORTHO TRI-CYCLEN LO Dialpak Info[a]

	Active	Color
Days 1-7	180 mcg NGM/25 mcg EE	White Tablets
Days 8-14	215 mcg NGM/25 mcg EE	Light Blue Tablets
Days 15-21	250 mcg NGM/25 mcg EE	Dark Blue Tablets
Days 22-28	Inert ingredients	Green Tablets

NGM = norgestimate; EE = ethinyl estradiol

[a] Each Dialpak contained a 28-day regimen.

Reference Therapy, Dose and Mode of Administration, Batch No.: Subjects on commercially obtained YAZ received 3 cycles of a standard regimen as given below:

YAZ Blister Pack Info[a]

	Active	Color
Days 1-24	3 mg DRSP/20 mcg EE	Pink Tablets
Days 25-28	Inert ingredients	White Tablets

DRSP = drospirenone; EE = ethinyl estradiol

[a] Each blister pack contained a 28-day regimen.

Duration of Treatment: Subjects received ORTHO TRI-CYCLEN LO or YAZ in an open-label manner for three 28-day cycles.

Criteria for Evaluation: The primary efficacy variable was the subject's total number of unscheduled bleeding days during Cycles 1 to 3 as recorded using the IVRS diary on a daily basis. Other bleeding endpoints, subject satisfaction, and weight change were secondary endpoints. The secondary efficacy variable, satisfaction, was assessed using the subject satisfaction questionnaire.

Safety was assessed by physical examinations, AEs, body weight and vital signs. As detailed in the Package Insert, subjects randomized to YAZ and taking any medication that could increase serum potassium levels had their potassium level checked during their first cycle of treatment (Days 15 to 28 of treatment).

Statistical Methods: Safety analyses included all subjects who took at least 1 dose of study medication and for whom there was post-baseline safety information. Efficacy analyses were conducted on a Full Analysis Set, defined as all randomized subjects who took at least 1 week of study drug and for whom there was post-baseline efficacy data after Day 7.

The primary efficacy variable was the total number of days of unscheduled bleeding during Cycles 1 to 3. For the purposes of this study, unscheduled bleeding was defined as any bleeding that occurred while taking active hormones, regardless of the duration of regimen. In this context, spotting was categorized as bleeding. Furthermore, bleeding that began during a hormone-free interval and continued through Days 1-4 of the subsequent active cycle was considered scheduled. The 2 treatment groups were compared using the Wilcoxon-Mann-Whitney test.

Other bleeding endpoints, subject satisfaction, and weight change were secondary variables. The bleeding endpoints of total number of days of scheduled bleeding and total bleeding and number of episodes of unscheduled bleeding were analyzed using the Wilcoxon-Mann-Whitney test to compare the two treatment groups. The bleeding endpoints of incidence of unscheduled blood loss were analyzed with Fisher's exact test to compare the two treatment groups. The responses on the subject satisfaction questionnaire on overall satisfaction, physical well-being, emotional well-being, and premenstrual symptoms for the 2 treatment groups were compared using the Wilcoxon-Mann-Whitney test. The changes in weight and blood pressure from baseline to last visit for the 2 treatment groups were compared using the two-sample t-test. Subjects in each treatment group who became pregnant were summarized.

RESULTS:

A total of 355 subjects were randomized in a 1:1 ratio to receive either ORTHO TRI-CYCLEN LO (178 subjects) or YAZ (177 subjects). A total of 24 (13.5%) subjects in the ORTHO TRI-CYCLEN LO group and 21 (11.9%) subjects in the YAZ group discontinued from the study prematurely. The most common reasons for discontinuation from efficacy population was lost to follow-up (6 [3.4%] in the ORTHO TRI-CYCLEN LO group and 4 [2.3%] in the YAZ group).

The treatment groups were comparable with regard to most of the demographics and baseline clinical characteristics. The majority of subjects were white. Subjects ranged in age from 18 to 45 years with a median age of 26 years. The obstetric and gynecological histories were also similar in both treatment groups.

EFFICACY RESULTS: The overall number of days with unscheduled blood loss was significantly lower ($p=0.0031$) in the ORTHO TRI-CYCLEN LO group (mean, 4.6 days; median, 2 days) compared to the YAZ group (mean, 6.1 days; median, 4 days). Overall, 55 (33.3%) subjects in the ORTHO TRI-CYCLEN LO group and 29 (17.4%) subjects in the YAZ group did not experience any episode of unscheduled blood loss, and 46 (27.9%) subjects in the ORTHO TRI-CYCLEN LO group and 41 (24.6%) subjects in the YAZ group experienced 1 episode of unscheduled blood loss. Conversely, 55 (66.7%) in the ORTHO TRI-CYCLEN LO group and 138 (82.6%) in the YAZ group experienced unscheduled bleeding ($p=0.0010$).

The overall number of days with scheduled blood loss was significantly ($p<0.0001$) higher in the ORTHO TRI-CYCLEN LO group (mean, 11.2 days; median, 12 days) compared to the YAZ group (mean, 7.0 days; median, 8 days). However, data collection using the efficacy criteria was truncated at day 28 in cycle 3; hence, these data should be interpreted with caution. The incidence of scheduled blood loss was significantly higher in the ORTHO TRI-CYCLEN LO group (89.1% at Cycle 1, 85.0% at Cycle 2, 79.0% for Cycle 3) compared to the YAZ group (73.1% at Cycle 1, 61.8% at Cycle 2, 58.5% for Cycle 3) for each cycle ($p\leq0.0002$) and overall ($p\leq0.0002$); this analysis was not affected by data truncation at Cycle 3.

ORTHO TRI-CYCLEN LO subjects reported a lower incidence of "absence of withdrawal bleeding" than YAZ subjects at each cycle, and this finding was also not affected by data truncation at cycle 3 (10.9% vs. 26.9% cycle 1; 15% vs. 38.2% cycle 2; 21% vs. 41.5% cycle 3; $p\leq0.0002$ at each cycle).

The overall number of days with total blood loss (sum of unscheduled plus scheduled blood loss) was significantly ($p<0.0001$) higher in the ORTHO TRI-CYCLEN LO group (mean, 15.8 days; median, 14 days) compared to the YAZ group (mean, 13.2 days; median, 11 days). Total days of blood loss is affected by the data truncation in Cycle 3.

For subjects in the stratum of fresh starts, the overall number of days with unscheduled blood loss was similar between the ORTHO TRI-CYCLEN LO group (mean, 6.4 days; median 5 days) and the YAZ (mean, 6.8 days; median, 4 days) treatment groups. The overall difference between the groups was not statistically significant ($p=0.6155$).

For subjects in the stratum of switchers, the overall number of days with unscheduled blood loss was significantly ($p=0.0005$) lower in the ORTHO TRI-CYCLEN LO group (mean, 3.3 days; median, 1 day) compared to the switchers in the YAZ group (mean, 5.6 days; median, 4 days).

During the unscheduled blood loss, 42 (38.2%) subjects in the ORTHO TRI-CYCLEN LO group and 66 (47.8%) subjects in the YAZ group had a maximum flow intensity of light and 24 (21.8%) subjects in the ORTHO TRI-CYCLEN LO group and 19 (13.8%) subjects in the YAZ group had heavy flow intensity. During the scheduled blood loss, 9 (6.0%) subjects in the ORTHO TRI-CYCLEN LO group and 22 (15.7%) subjects in the YAZ group had a maximum flow intensity of light, and 76 (50.3%) subjects in the ORTHO TRI-CYCLEN LO group and 48 (34.3%) subjects in the YAZ group had heavy flow intensity.

In overall satisfaction, 99 (62.3%) subjects in the ORTHO TRI-CYCLEN LO group and 115 (71.0%) subjects in the YAZ group were very satisfied ($p=0.0715$).

SAFETY RESULTS: Overall, the number of subjects reporting treatment-emergent adverse events (TEAEs) was comparable in both groups, each with 34 (20.4%) subjects reporting TEAEs. The most commonly reported TEAE was nausea (N=4) in the ORTHO TRI-CYCLEN LO group; and mood swings (N=5) and irritability (N=4) in the YAZ group.

Two subjects in each group experienced severe TEAEs during the study. In the ORTHO TRI-CYCLEN LO group, Subject 15006 reported severe bronchitis considered to be not related to study medication, and did not lead to discontinuation. Subject 15045 severe reported uterine leiomyoma, pelvic hemorrhage, and ruptured ovarian cyst. All of the events were considered SAEs and led to discontinuation of study drug. In the YAZ group, Subject 19014 reported a severe migraine on Day 2 considered very likely related to the study drug. Subject 17029 reported a severe pulmonary embolism. The event was considered to be an SAE and led to discontinuation of study drug.

No deaths were reported in this study. Two (1.2%) subjects in the ORTHO TRI-CYCLEN LO group reported 4 SAEs and 1 (0.6%) subject in the YAZ group reported 1 SAE. In the ORTHO TRI-CYCLEN LO group, Subject 15045 reported uterine leiomyoma, pelvic hemorrhage, and ruptured ovarian cyst and Subject 15006 reported intervertebral disc protrusion. These events were considered to be not related to the study drug. In the YAZ group, Subject 17029 reported severe pulmonary embolism that was considered possibly related to the study drug.

Seven subjects discontinued the study drug due to TEAEs: 3 in the ORTHO TRI-CYCLEN LO group and 4 in the YAZ group. One subject in each treatment group discontinued due to SAEs. Of the 3 subjects in the ORTHO TRI-CYCLEN LO group, only 1 subject reported TEAEs (nausea and vomiting) that led to discontinuation to be probably related to study mediation; the other two subjects reported TEAEs that led to discontinuation to be not related to study medication. All 4 subjects in the YAZ group reported adverse events that led to discontinuation to be either possibly or very likely related to study medication.

Seven pregnancies occurred during the screening period, after the subjects had signed informed consent, but before receiving study drug. One occurred during the treatment period. The positive urine pregnancy test occurred on Day 87; the subject was randomized to the ORTHO TRI-CYCLEN LO group and completed the study. The pregnancy was determined after the subject's last dose.

Serum potassium tests were performed for the YAZ-treated subjects, as indicated in the label (N=11). Results during the study were not clinically significant. In general, the changes in weight and vital signs (systolic and diastolic blood pressure) from baseline to last visit in both groups were small and neither clinically nor statistically significant.

CONCLUSIONS:

Overall, in the study's 3-cycles

- ORTHO TRI-CYCLEN LO subjects reported significantly fewer days of unscheduled bleeding than YAZ subjects (mean, 4.6 days vs. 6.1 days, respectively; p=0.0031).
- ORTHO TRI-CYCLEN LO subjects reported a significantly lower incidence of unscheduled bleeding than YAZ subjects (66.7% vs. 82.6%; p=0.0010).
- ORTHO TRI-CYCLEN LO subjects reported significantly fewer episodes of unscheduled bleeding than YAZ subjects (mean, 1.47 vs. 2.01; p=0.0013).
- ORTHO TRI-CYCLEN LO subjects reported more scheduled bleeding than YAZ subjects (mean, 11.2 days vs. 7.0 days; p<0.001); however, the date collection was truncated in Cycle 3.
- ORTHO TRI-CYCLEN LO subjects reported a lower incidence of "absence of withdrawal bleeding" than YAZ subjects at each cycle; this finding was not affected by data truncation at Cycle 3.
- Both groups reported a high degree of overall satisfaction.

- Both groups experienced comparable weight change from baseline to end of study (mean, 0.7 lbs vs. 0.4 lbs; p=0.6319).

- Both regimens were well tolerated and no deaths were reported in either group.

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.