

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-241

MEDICAL REVIEW(S)

NDA 21-241 - Ortho Tri-Cyclen® Lo

Medical Officer's Review (Original NDA)

Date submitted: 8/25/00

Review completed: 6/12/01

Reviewer: Gerald D. Willett MD

Applicant:

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Established name: norgestimate/ethinyl estradiol

Proprietary name: Ortho Tri-Cyclen® Lo

Chemical names:

Norgestimate (18,19-Dinor-17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17 α)-(+)-)

Ethinyl Estradiol (19-nor-17 α -pregna,1,3,5(10)-trien-20-yne-3,17-diol)

Dosage form: tablets

Strengths:

180 mcg norgestimate/25 mcg ethinyl estradiol x 7days, followed by
215 mcg norgestimate/25 mcg ethinyl estradiol x 7days, followed by
250 mcg norgestimate/25 mcg ethinyl estradiol x 7days, followed by
Placebo x 7 days

Route of administration: Oral

Proposed indication: _____

Related INDs: Norgestimate & Ethinyl Estradiol (IND 11,391); 17-deacetylnorgestimate/ethinyl estradiol transdermal system (IND 50,488)

Related NDAs: Ortho Tri-Cyclen (NDA 19-697); Ortho-Cyclen (NDA 19-653)

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Table of Contents

Medical Officer's Review (Original NDA)	1
<i>Table of Contents</i>	2
<i>Executive Summary</i>	2
I. Recommendations.....	2
A. Recommendation on Approvability:	2
B. Recommendation on phase 4 studies and risk management steps.....	2
II. Summary of Clinical Findings.....	2
A. Brief Overview of Clinical Program	2
B. Efficacy.....	3
C. Safety	5
D. Dosing	6
E. Special Population	6
<i>Clinical Review</i>	6
I. Introduction and Background	6
A. Drug name, class, indication, dosage, regimens, age groups, relevant facts.....	7
B. State of Armamentarium for Indication.....	7
C. Important milestones in product development.	9
D. Other relevant information	10
E. Important issues with other pharmacologically related agents.....	10
II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and /or Other Consultant Reviews	11
III. Human Pharmacokinetics and Pharmacodynamics.....	11
A. Pharmacokinetics.....	11
IV. Description of Clinical Data and Sources	11
V. Clinical Review Methods	12
VI. Integrated Review of Efficacy	13
A. Conclusions and Label Claim differences.....	13
B. General Approach to Review of the Efficacy of the Drug	14
C. Detailed Review of Trials.....	14
D. Efficacy Conclusions.....	32
VII. Integrated Review of Safety	40
A. Conclusions	40
B. Patient Exposure	40
C. Methods and Specific Findings	42
D. Adequacy of Safety Testing	52
E. Summary of Critical Safety Findings	52
VIII. Dosing Regimen, and Administration Issues	52
IX. Use in Special Populations.....	52
X. Conclusions and Recommendations.....	53
XI. Appendix.....	53
Abbreviations:	53
Definitions:.....	54

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Executive Summary

I. Recommendations

A. Recommendation on Approvability:

Ortho Tri-Cyclen® Lo can be approved if the labeling reflects the pregnancy rates observed in the pivotal clinical trial.

B. Recommendation on phase 4 studies and risk management steps

There are no recommendations for phase 4 study or additional risk management steps.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Ortho Tri-Cyclen® Lo is a combination oral contraceptive containing norgestimate and ethinyl estradiol.

The overall clinical development program consisted of seven studies, including one pivotal Phase 3 efficacy and safety study, two dose-ranging/supportive efficacy studies, and four pharmacokinetic and bioavailability studies. The to-be-marketed product was studied in one of the phase I studies, one of the phase II studies and in the pivotal phase 3 study. Overall, a total of 1,785 women received Ortho Tri-Cyclen® Lo in the trials. In the phase III pivotal trial 1,723 women received Ortho Tri-Cyclen® Lo for up to 13 cycles. The number of subjects evaluable for efficacy was 1673. The difference in the preceding numbers was accounted for by the exclusion of site 11 and exclusions of subjects who became pregnant prior to taking study medication.

In the Ortho Tri-Cyclen® Lo treatment arm there were 1351 subjects less than 35 years of age accounting for 8773 cycles of use. There were 321 subjects 35 years and older accounting for 2224 cycles of use. Two hundred twenty-one subjects \leq 35 years of age completed 13 cycles of Ortho Tri-Cyclen® Lo. Eight hundred twenty subjects \leq 35 years of age completed 6 cycles of Ortho Tri-Cyclen® Lo.

In the Loestrin® arm there were 943 subjects less than 35 years of age accounting for 6160 cycles of use and 198 subjects 35 years and older accounting for 1337 cycles of use.

B. Efficacy

Cycle completion analysis reveals that there were 274 women who completed 13 cycles in the Ortho Tri-Cyclen® Lo treatment arm and 1361 completed 6 cycles. In the Loestrin® arm 185 women completed 13 cycles and 924 completed 6 cycles.

Ortho Tri-Cyclen® Lo showed comparable contraceptive efficacy when compared to the approved oral contraceptive Loestrin® Fe 1/20. The efficacy results are based on 1,673 evaluable women taking Ortho Tri-Cyclen® Lo in the pivotal phase III trial (NRGLOW-OC-001) compared to 1141 evaluable women taking Loestrin®

For these 1,673 women there were 11,003 cycles (846.3 women years). There were 14 pregnancies due to method failure and 6 pregnancies due to user failure for a total of 20 pregnancies in the Ortho Tri-Cyclen® Lo treatment arm. The method failure Pearl Index is 1.65 (0.79, 2.52). The overall Pearl Index is 2.36 (1.33, 3.40). For women less than 35 years of age, the method failure Pearl Index is 1.78 and the overall Pearl Index is 2.67.

For the comparator drug, Loestrin, there were 1,141 women, 7497 cycles, and 576.7 women-years. For women in the study taking Loestrin there were 17 pregnancies due to method failure and 2 pregnancies due to user failure for a total of 19 pregnancies. The method failure Pearl Index for Loestrin was 2.95 (1.55, 4.35) with an overall Pearl Index of 3.29 (1.81, 4.77). For women less than 35 years of age the method failure Pearl Index is 3.38 and the overall Pearl Index is 3.80.

This reviewer feels that the sponsor has not presented a strong argument that the lower estrogen in this product is providing a strong clinical benefit over products containing 35µg of ethinyl estradiol and norgestimate. The sponsor provided information in response to the agency's request to compare estrogen related side effects of Ortho Tri-Cyclen® Lo to their other norgestimate products Ortho Tri-Cyclen® and Ortho-Cyclen®. There was no clear reduction in the estrogen-related side effects of headache, breast tenderness, nausea, and vomiting.

The clinical benefit of good cycle control compared to Loestrin® in the pivotal phase III trial is questionable because historically and in this study Loestrin® has shown poor cycle control. Ortho Tri-Cyclen® Lo shows comparability on cycle control when it is compared to Ortho Tri-Cyclen® and Ortho-Cyclen®.

Shortly after the Ortho Tri-Cyclen® Lo clinical trials began, three oral contraceptives with 20µg of ethinyl estradiol were approved. All have lower Pearl Indices than Ortho Tri-Cyclen® Lo (Alesse® -overall Pearl Index = 0.84, Mircette® - overall Pearl Index = 1.11, and Levlite® - overall Pearl Index of 1.8 in U.S. study, 0.29 in European study)

Current product labeling of approved oral contraceptives is not consistent for contraceptive efficacy. Some labels include the results of clinical trial efficacy analysis and report the Pearl Index. Other sponsors, including those with somewhat higher Pearl Indices use class labeling and do not report their own product's actual performance in the clinical trials.

Current class labeling for oral contraceptives discusses pregnancy risk in two different areas. One is a comparative table of many contraceptive methods taken from Hatcher's book (*Contraceptive Technology*). The other area that discusses pregnancy risk is in the Brief Summary Patient Package Insert section.

The comparative table in Hatcher's *Contraceptive Technology* is derived from work by Trussell et al. and contains an extremely low pregnancy rate for perfect use of oral combination contraceptives (0.1% of women experiencing an unintended pregnancy within the first year of use). The selection of this low rate appears to be derived from the author's conviction that there should be little method failure if the pills are taken correctly. The author's report of a 0.0% pregnancy rate listed in one of the book's tables is derived from studies of combination oral contraceptives containing 80µg of estrogen. These pills are no longer clinically used due to the high estrogen content.

The FDA experience with a number of clinical trials of lower dose pills raises concerns about the 0.1% pregnancy rate reported in the Trussell table and contained in oral contraceptive labeling. Certainly the clinical trials that have been reviewed in the past 5-10 years have shown that the "perfect use" failure rate to be higher than the 0.1% rate. Ortho Tri-Cyclen® Lo trials showed "perfect use" in 14 of the 20 subjects who became pregnant. There was no indication that they had missed any pills. The overall method failure Pearl Index was 1.65 (1.78 for women less than 35 years of age).

Recent "class" labels under Brief Summary Patient Package Insert section have indicated that the failure rate of oral contraceptive when used without missing any pills is approximately 1%. A more accurate label in regard to Ortho Tri-Cyclen® Lo should be a statement indicating a 1-2 % failure rate.

With both of these sections of the typical class label not correlating with the sponsor's efficacy results for Ortho Tri-Cyclen® Lo, it is important that the label for Ortho Tri-Cyclen® Lo truly reflects the pregnancy rates observed. Because this sponsor already includes the contraceptive efficacy results from its other norgestimate products in their labels, it is reasonable to ask them to include the pregnancy rates from their pivotal trial in their label for this product

As discussed more fully in the integrated review of efficacy (Section VI) many of the sponsor's arguments concerning historical differences in study design appear valid in regard to explaining the higher Pearl Index for the Loestrin® comparator in the pivotal study for Ortho Tri-Cyclen® Lo compared to the lower Pearl Index found for Loestrin at the time of its approval.

Despite these aforementioned reservations, this product can be approved based on the following arguments:

- Historically the agency has approved products with equal or higher Pearl Indices (Estrostep® 2.4, Trinorinyl® 2.6, Brevicon® 5.18, and Norinyl® 2.51)
- Ortho Tri-Cyclen® Lo demonstrated a lower pregnancy rate than an approved oral contraceptive, Loestrin® Fe 1/20, in the pivotal phase III trial for efficacy and safety.
- Though no strong benefit was demonstrated in either cycle control or estrogenic side effects by the pivotal study or historical comparisons, there may be benefits for individual patients in taking a lower amount of estrogen.
- There are no safety concerns for this product over and above the risks known to be associated with low dose oral contraceptive products.

C. Safety

The number of subjects exposed and the cycle duration of exposure are listed in Table 1.

**Table 1: Subjects Exposed to Ortho Tri-Cyclen® Lo
(Subjects Evaluable for Safety in the ISS)**

	Subjects Treated with ≥1 Dose	Total Cycles Treated	Total Woman-Years
Phase 3			
NRGLOW-OC-001	1,723	11,062	850.9
Phase 2			
K90-023	46	124	9.5
Phase 1			
NRGLOW-PHI-001	16	47	3.6
TOTAL	1,785	—	—

There were no deaths in the Ortho Tri-Cyclen® Lo or the Loestrin treatment arms of the pivotal study. There was one death in the Cyclophasic 25/180,250 (25µg EE, 180,250 NGM)-treatment arm secondary to gastric adenocarcinoma. This death is unlikely to be related to study medication.

There were a total of 13 serious adverse events recorded for Ortho Tri-Cyclen® Lo (12 in the pivotal phase 3 trial and one in the phase 2 trial). Of these 13 cases, only one case of hypertension and one case of depression are felt by this reviewer to be related to study medication. There were no cases of deep vein thrombosis or pulmonary embolism reported in any of the clinical studies.

In the adverse events leading to discontinuation there were no significant findings other than events known to be related to oral contraceptive use or common for this age group.

The most common treatment-emergent adverse events for Ortho Tri-Cyclen® Lo were headache (29.4%); upper respiratory tract infection (16.8%); nausea (14.7%); abdominal pain (13.7%); breast pain (9.8%); dysmenorrhea (9.7%); and sinusitis (9.1%). Again there are no significant differences for Ortho Tri-Cyclen® Lo compared to Loestrin® or oral contraceptives in general.

The sponsor's four-month safety update (12-15-01) and final safety update (6-8-01) did not indicate any safety concerns.

D. Dosing

The dosing for contraceptive efficacy was established via a phase II protocol (K90-023) to assess ovulatory inhibition via progesterone monitoring ($\geq 3\text{ng/mL}$). Dosing information was also obtained in the phase III pivotal trial where Ortho Tri-Cyclen® Lo was compared to two other cyclophasic products containing ethinyl estradiol and norgestimate. Ortho Tri-Cyclen® Lo performed better than these cyclophasic products in regard to contraceptive efficacy.

E. Special Population

Increasing body weight and body surface area were each associated with slight decreases in C_{max} and AUC (0-24h) values for the primary active metabolite norelgestromin and ethinyl estradiol and slight increases in oral clearance for ethinyl estradiol. However, of the 14 method failure pregnancies in the pivotal trial, there were only two subjects with a BMI greater than 30. Race had no significant pharmacokinetic or pharmacodynamic effects.

Although the pivotal phase 3 trial reported a higher pregnancy rate among non-white subjects, further analysis did not reveal that this was related to method failure.

Clinical Review

I. Introduction and Background

A. Drug name, class, indication, dosage, regimens, age groups, relevant facts

Ortho Tri-Cyclen® Lo is a combination triphasic oral contraceptive composed of norgestimate and ethinyl estradiol. The indication is prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception. Through the pill cycle the norgestimate dose increases while the ethinyl estradiol remains the same. The product is to be marketed as a 28-tablet pack with 7 tables consisting of inert ingredients. Oral contraceptives are also commonly used off-label for management of dysfunctional and

heavy uterine bleeding. Some clinicians have prescribed oral contraceptives to reduce the risk for ovarian carcinoma.

B. State of Armamentarium for Indication

There are over thirty approved oral contraceptives already on the market. These include the following large groups.

- Combinations pills (estrogen and progestin)
 1. Monophasic type
 2. Multiphasic type
- Progestin Only pills

Oral contraceptive pills today have much lower hormone doses than the pills that were introduced in the 1960s. The lowering of the progestin and estrogen doses through the years has improved the safety profiles for severe adverse events. Reduction of the hormone dose levels may also reduce the side effects of nausea, breast tenderness, fluid retention, weight gain, headaches, and mood changes.

In a multiphasic combination oral contraceptive regimen, the dosages of one or both components (progestin and estrogen) varies through the pill-taking cycle. The aim of the multiphasic approach is to achieve lesser metabolic effects, reduce breakthrough bleeding and amenorrhea, but maintain efficacy. Some authors feel that the multiphasic preparations have shown either no difference or only slight improvements compared to low-dose monophasic products.

Estrogen and progestin variations in the multiphasic preparations are described in Table 2 and Table 3:

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Table 2. Comparison of multiphasic oral contraceptives by dose and progestin type.

Contraceptive	Estrogen	Estrogen dose	Progestin	Progestin dose
Estrostep®	EE	0.020mg x 7d 0.030mg x 7d 0.035mg x 7d	NETA	1mg x 21 days
Mircette®	EE	0.020mg x 21d no EE x 2d 0.010mg x 5d	DSG	0.15mg x 21 days no D for 7d
Ortho-Novum 7/7/7®	EE	0.035mg x 21 days	NET	0.5mg x 7d 0.75mg x 7d 1.0mg x 7d
Ortho-Novum 10/11®	EE	0.035mg x 21 days	NET	0.5mg x 10d 1.0mg x 11d
Ortho Tri-Cyclen®	EE	0.035mg x 21 days	NGM	0.180mg x 7d 0.215mg x 7d 0.250mg x 7d
Ortho Tri-Cyclen® Lo	EE	0.025mg x 21 days	NGM	0.180mg x 7d 0.215mg x 7d 0.250mg x 7d
Tri-Levlen®	EE	0.030mg x 6d 0.040mg x 5d 0.030mg x 10d	LNG	0.050mg x 6d 0.075mg x 5d 0.125mg x 10d
Tri-Norinyl®	EE	0.035mg x 21 days	NET	0.5mg x 7d 1.0mg x 9d 0.5mg x 5d
Triphasil®	EE	0.030mg x 6d 0.040mg x 5d 0.030mg x 10d	LNG	0.050mg x 6d 0.075mg x 5d 0.125mg x 10d
Trivora®	EE	0.030mg x 6d 0.040mg x 5d 0.030mg x 10d	LNG	0.050mg x 6d 0.075mg x 5d 0.125mg x 10d

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Table 3. Comparison of multiphasic oral contraceptives by hormonal alteration during the cycle

<i>Hormonal Alteration</i>	<i>Contraceptive product</i>
<i>Increasing estrogen dose</i>	<i>Estrostep®</i>
<i>Higher level of estrogen midcycle</i>	<i>Tri-Levlen®, Triphasil®, Trivora®</i>
<i>Small amount of estrogen in the off-week</i>	<i>Mircette®</i>
<i>Estrogen level constant throughout</i>	<i>Ortho-Novum 7/7/7®, Ortho-Novum 10/11®, Ortho Tri-Cyclen®, Ortho Tri-Cyclen® Lo, Tri-Norinyl®</i>
<i>Increasing progestin dose</i>	<i>Ortho-Novum 7/7/7®, Ortho-Novum 10/11®, Ortho Tri-Cyclen®, Ortho Tri-Cyclen® Lo, Tri-Levlen®, Triphasil®, Trivora®</i>
<i>Higher level of progestin midcycle</i>	<i>Tri-Norinyl®</i>
<i>Progestin level constant throughout</i>	<i>Estrostep®, Mircette®</i>
<i>Both estrogen and progestin are altered</i>	<i>Tri-Levlen®, Triphasil®, Trivora®</i>

As can be seen from the tables above, there are many oral contraceptives available to clinicians. The product offered by the sponsor in this NDA basically offers a triphasic norgestimate combination pill with a lower estrogen dose (25µg compared to 35µg) than contained in the sponsor's similar product Ortho Tri-Cyclen® Lo.

C. Important milestones in product development.

Telephone Conversation with FDA (August 5, 1996). Based on an August 5, 1996 agreement, conditions for the acceptability of one study included a requirement for 200 women completing 13 cycles of use, with a minimum of 10,000 cycles of exposure.

End-of-Phase 2 Meeting (January 8, 1997). At the End-of-Phase 2 meeting between RWJPRI and DRUDP, amendment 2 for Protocol NRGLOW-OC-001 was revised and submitted to the FDA for review and comment. Changes made to the protocol were related to the interim analysis, discontinuation of treatment groups, re-randomization of subjects after interim analysis, adjustment for multiple comparisons, and safety evaluations.

Pre-NDA meetings were held on June 22, 1999 and October 4, 1999 with members of the division of DRUDP and RWJPRI. The June 22, 1999 meeting addressed important clinical efficacy concerns in addition to pharmacokinetic and preclinical questions. The October 4, 1999 meeting addressed CMC issues related to the planned NDA submission.

The key clinical efficacy concerns discussed at the June 22, 1999 meeting are as follows:

1. The sponsor asked: Can comparative results from a randomized controlled trial, comparing an approved oral contraceptive to an investigational oral contraceptive, demonstrate the efficacy of the investigational regimen when the Pearl rate for the approved product is 3.29?

In response to this question, the agency asked the sponsor for information regarding possible differences between the Ortho Tri-Cyclen study design and the study design for this trial to see if this could clarify the higher pregnancy rates. The agency also acknowledged that Loestrin data from the past might not be comparable to current studies. The sponsor was also asked to provide pregnancy rates reported with perfect use and was informed that there would be no superiority claim for efficacy for this application.

2. The sponsored asked: If comparative data from a randomized controlled trial is accepted as proof of efficacy for an investigational regimen, even when the approved product comparator has a study Pearl of 3.29, would the labeled description of efficacy be the same for the investigational product as for the approved product?

The agency's response to question two was that it would be a review issue and that the label might need to reflect the actual results from the study.

D. Other relevant information

This product is not marketed in any country worldwide.

E. Important issues with other pharmacologically related agents

Important clinical and regulatory issues with this class of drugs includes the following:

- Though lower dose formulations have decreased the incidence of serious side effects, oral contraceptives have rare but significant known safety risks including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease.
- Data from case-control and cohort studies report that oral contraceptives containing desogestrel are associated with a two-fold increase in the risk of venous thromboembolic disease as compared to other low-dose (containing less than 50µg of estrogen) pills containing other progestins.
- An August 1999 draft guidance for combined oral contraceptive labeling discusses perfect use and typical pregnancy rates based on a table from Contraceptive Technology. Further discussion of this labeling is found in the efficacy summary and executive summary of this review.

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and /or Other Consultant Reviews

The chemistry review included a number of requests and requirements for the sponsor in regard to holding times, analytical testing, impurity acceptance, dissolution specifications, expiration dating, stability testing, and labeling. These requests and requirements were fulfilled.

There are no other significant findings from the other disciplines except for issues related to labeling additions of pharmacokinetic information. This information will be addressed in the Pharmacology review.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Following single oral administration of Ortho Tri-Cyclen® Lo, norgestimate and ethinyl estradiol are rapidly absorbed. Norgestimate is converted to two major metabolites, 17d-deacetylnorgestimate and norgestrel. Systemic concentrations of unchanged norgestimate are negligible. Peak concentrations of 17d-deacetylnorgestimate, norgestrel and ethinyl estradiol are obtained within 1 to 3 hours of administration.

Population analysis of pooled pharmacokinetic data following single administration of Ortho Tri-Cyclen® Lo showed that increasing body weight and body surface area were each associated with decreases in C_{max} and AUC_{0-24h} of 17d-deacetylnorgestimate, norgestrel and ethinyl estradiol. Increasing age was also associated with decrease in these parameters for 17d-deacetylnorgestimate and norgestrel. These effects were statistically significant. The clinical implications are not clear. Only two of the method failure pregnancies were noted to have a BMI greater than 30.

IV. Description of Clinical Data and Sources

A. Overall Data

The sources of data in this submission include both clinical study data and referenced material. The clinical study data though is the primary material on which a decision will be based.

B. Clinical Trials

Phase 1 Studies (Number of Subjects Enrolled)

Bioavailability

NRGLOW-PHI-003 (total N = 24)

NRGLOW-PHI-004 (total N = 24)

Pharmacokinetics/Dose Proportionality

NRGLOW-PHI-001 (total N = 16)

NRGLOW-PHI-002 (total N = 16)

Phase 2 Safety and Efficacy Studies

Dose-Ranging and Dose-Response

N93-031 (total N = 210)

K90-023 (total N = 236)

Phase 3 Controlled Safety and Efficacy Study

Pivotal Phase 3 Safety and Efficacy Study

NRGLOW-OC-001 (total N = 6,022 - for all four treatment arms)

C. Postmarketing Experience

This product is not marketed yet in any country.

D. Literature Review

A general literature review via journals and texts was performed for oral contraceptives, ethinyl estradiol and norgestimate.

V. Clinical Review Methods

All the clinical trials were reviewed for safety, efficacy, and pharmacokinetics-bioavailability. Primary attention was directed at the pivotal phase III trial. Additional INDs and NDAs were reviewed for pregnancy rate information of other oral contraceptives. Electronically submitted data was used, especially individual case report forms to establish pregnancy results.

VI. Integrated Review of Efficacy

A. Conclusions and Label Claim differences

The sponsor's conclusions from the integrated summary of efficacy are as follows:

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- Ortho Tri-Cyclen® Lo, a 25 µg EE formulation of Ortho Tri-Cyclen, has contraceptive efficacy at least as good as Loestrin based on a comparative randomized controlled trial.
- Ortho Tri-Cyclen® Lo has an upper limit of the 95% CI for the probability of pregnancy in the first year of use that is well below the 5% typical use pregnancy rate in the class label.

The principal differences in these conclusions versus the proposed labeling claims are as follows:

- The sponsor seeks oral contraceptive class labeling. Class labeling for oral contraceptives utilizes a table from Hatcher's *Contraceptive Technology*, which for combined oral contraceptives, uses 0.1 as the percentage of woman experiencing an unintended pregnancy within the first year of perfect use. Ortho Tri-Cyclen® Lo was found to have a method failure Pearl Index of 1.65 which is well above the Hatcher table results for "perfect use".
- The method failure Pearl Index of 1.65 is also inconsistent with the "as directed use" information from the Brief Summary Patient Package Insert taken from either the Ortho Tri-Cyclen® or the Mircette® labels which state:
 1. Ortho Tri-Cyclen® = The incidence of pill failure resulting in pregnancy is approximately one percent (i.e., one pregnancy per 100 women per year) if taken every day as directed, but more typical failure rates are about 3%.
 2. Mircette® = The incidence of pill failure resulting in pregnancy is approximately one percent (i.e., one pregnancy per 100 women per year) if taken every day as directed, but more typical failure rates are about 5%. If failure does occur, the risk to the fetus is minimal. (currently accepted class labeling)

Medical officer's comments: This reviewer feels that a statement stating "approximately one to two percent" would be a more accurate portrayal of perfect use pregnancy rate in this section.

- The present label for Ortho Tri-Cyclen and Ortho-Cyclen contains the following contraceptive efficacy information:

"In clinical trials with ORTHO-CYCLEN, 1,651 subjects completed 24,272 cycles and a total of 18 pregnancies were reported. This represents an overall use-efficacy (typical user efficacy) pregnancy rate of 0.96 per 100 women-years. This rate includes patients who did not take the drug correctly.

In four clinical trials with ORTHO TRI-CYCLEN, the use-efficacy pregnancy rate ranged from 0.68 to 1.47 per 100 women-years. In total, 4,756 subjects completed

45,244 cycles and a total of 42 pregnancies were reported. This represents an overall use-efficacy rate of 1.21 per 100 women-years. One of these 4 studies was a randomized comparative clinical trial in which 4,633 subjects completed 22,312 cycles. Of the 2,312 patients on ORTHO TRI-CYCLEN, 8 pregnancies were reported. This represents an overall use-efficacy pregnancy rate of 0.94 per 100 women-years.”

Similar information reflecting the method failure rates from the clinical trials should be included in the Ortho Tri-Cyclen® Lo label so that prescribers and patients will know how its pregnancy rate compares to the two other norgestimate products.

B. General Approach to Review of the Efficacy of the Drug

The efficacy database reviewed in detail comes from the pivotal phase III trial (NRGLOW-OC-001) and the phase II (K90-023) comparative trial.

C. Detailed Review of Trials

Pivotal phase III trial of Ortho Tri-Cyclen® Lo for safety and efficacy

Protocol No.: NRGLOW-OC-001

Title of Study: A Randomized, Comparative, Multicenter, Safety and Contraceptive Efficacy Study of Two Cyclophasic Norgestimate/Ethinyl Estradiol Regimens, and One Triphasic Norgestimate/Ethinyl Estradiol Regimen and Loestrin ® Fe 1/20

Investigators/Centers: Multicenter (221 in U.S. and Canada)

Study Period: April 1997 to July 1998

Objectives: The objective of this study was to compare one triphasic low estrogen regimen and two Cyclophasic low estrogen regimens against Loestrin ® Fe 1/20 with regard to contraceptive efficacy, safety, and cycle control. Additionally, subject satisfaction indices were to be evaluated.

Sponsor's Background Information: Since the introduction of oral contraceptives more than three decades ago, an attempt has been made in many subsequent development programs to reduce both the estrogen and the progestin levels, while maintaining efficacy and tolerability. Following reports associating venous thromboembolic events with the estrogen component in combination oral contraceptives, development focused on the reduction of the estrogen dose. In addition, the introduction of newer progestational agents such as levonorgestrel and norgestimate lead to reductions in the progestin dose of combination monophasic oral contraceptives.

Multiphasic regimens were introduced which also allowed a decrease in the overall progestin dose. This was achieved by designing regimens with an incremental increase in the dose of the progestin during consecutive phases of the 28-day contraceptive cycle. The purpose was to minimize the negative metabolic impact of the progestin. Ortho Tri-Cyclen® is a triphasic regimen of norgestimate (NGM) and ethinyl estradiol (EE). The current study has continued the development of the triphasic norgestimate regimens by further reducing the EE level from 35 µg to 25 µg.

Prior to the present study, a Phase 2 clinical trial (Protocol K90-023) with Ortho Tri-Cyclen® as a comparator indicated that Ortho Tri-Cyclen® Lo produced ovulation suppression similar to Ortho Tri-Cyclen. Cycle control was also acceptable with Ortho Tri-Cyclen® Lo. Of 41 subjects evaluable for ovulation suppression in the Ortho Tri-Cyclen® Lo group, 3 (7.3%) experienced ovulation (defined as progesterone level \geq 3ng/mL) or luteal activity (defined as progesterone level \geq 1 ng/mL but $<$ 3ng/mL during Days 19-21 of Cycle 3 [or 4]) as compared to 3 (7.0%) of 43 subjects in the Ortho Tri-Cyclen group. During Cycles 1-3, the mean incidence of subjects by cycle with breakthrough bleeding or spotting was 17.2% in the Ortho Tri-Cyclen® Lo group and 14.4% in the Ortho Tri-Cyclen group.

The active comparator chosen for the phase III pivotal study was Loestrin. This comparator was chosen because at the start of the study it was the only oral contraceptive available in the US with less than 30 µg EE. It was important to select an oral contraceptive containing less than 30 µg EE as the comparator because the bleeding profile of oral contraceptives containing less than 30 µg EE was known to be different from that of oral contraceptives with a higher EE content.

Methodology: This study was a randomized, multicenter study to evaluate three blinded regimens of norgestimate and ethinyl estradiol (NGM/EE) oral contraceptives and an open-label control regimen of Loestrin®. A planned, blinded, interim analysis was performed to evaluate the cycle control of the three NGM/EE treatment groups in comparison to Loestrin. The interim analysis focused on Cycles 1-3 of 1100 subjects: approximately the first 300 subjects enrolled in each of the three NGM/EE regimens and the first 200 subjects enrolled in the Loestrin regimen. At the conclusion of the interim analysis, one NGM/EE treatment group, Cyc 20/60,180, was discontinued. Contraceptive efficacy was determined by pregnancy rates during therapy. Cycle control was recorded from bleeding information recorded on subjects' diary cards. Safety was assessed using adverse events (AEs), vital signs, laboratory tests, physical and gynecologic examinations, and Papanicolaou smears.

Number of Subjects: The sample size for this study was determined to meet FDA requirements for the evaluation of the safety and efficacy of oral contraceptives. A sample was selected to provide at least 10,000 cycles of exposure in NGM/EE treatment groups not discontinued after the interim analyses. Additionally, the study was designed so that a minimum of 200 subjects completed 13 cycles in these NGM/EE treatment groups. Up to 6,300 subjects were to be enrolled in the study. The ratio of subjects

assigned to each of the NGM/EE treatment groups and the Loestrin treatment group was to be 3:2. The first 500 subjects in each of the NGM/EE regimens and 330 subjects in the Loestrin regimen were enrolled to complete 13 cycles of medication. All subsequent subjects were enrolled to complete six cycles.

Subject Recruitment:

Subjects were recruited among women who had not used hormonal contraceptives in the two-month period immediately preceding the study (starters) as well as among women who had used a progestin/estrogen combination oral contraceptive in the two-month period immediately preceding the study (switchers). Switchers were further differentiated as:

- Direct Switchers - subjects who took oral contraceptives until they started taking study medication
- Indirect Switchers - subjects who were not taking oral contraceptives immediately prior to the start of study medication, but had been taking oral contraceptives within the two months prior to start of study medication

Protocol Amendments:

There were two amendments to the original protocol. Before any subjects were enrolled in the study, the first amendment (issued 21 January 97) added the requirement for a routine urine dipstick test at the early termination and Cycle 6 evaluations. Amendment 1 also included an update of the statistical section after FDA discussions. The second amendment was based on comment and negotiation with the reviewing division of the FDA and was implemented shortly after enrollment started. This amendment (issued 22 August 97) specified that subjects from the discontinued treatment group would not be randomized to the other regimens as planned. The second amendment also decreased the number of subjects to be enrolled from 6,400 to 6,300 subjects. This decrease in the number of subjects to be enrolled was based on a reassessment of the sample size for the lack of re-randomization and a lower predicted dropout rate (25% instead of 35%).

Inclusion Criteria:

Women who met all of the following criteria were eligible for admission into the study:

- were 18 to 45 years of age. Women between the ages of 35 and 45 must have been nonsmokers
- were sexually active with regular coitus

- had regular menses occurring every 25-35 days
- were within the acceptable body mass index (within 35%)
- had at least two normal menstrual periods (typical in duration and amount of flow for that subject) which occurred since their last pregnancy
- had at least one normal menstrual period (typical in duration and amount of flow for that subject) since removal of an intrauterine device (IUD)
- had terminated their last pregnancy at least 42 days before admission to the study
- were not lactating
- were in good health as confirmed by the investigator after review of the women's:
 - medical history
 - physical examination (including vital signs)
 - gynecologic examination (including breast examination)
 - laboratory test results;
- had a sitting systolic blood pressure <140 mmHg and a sitting diastolic blood pressure <90 mmHg
- were not pregnant as demonstrated by a negative serum β -subunit human chorionic gonadotropin (β -subunit HCG) radio-immunoassay (RIA) pregnancy test within seven days prior to taking study medication
- had no current evidence of cervical dysplasia
- agreed to use only the assigned study medication as contraception during the study for up to 13 cycles except when back-up contraception or STD protection was required
- agreed not to use any other steroid hormonal therapy other than topical corticosteroids during the course of the study
- read and signed the informed consent form after the nature of the study had been fully explained.

Exclusion criteria:

Subjects who met any of the following exclusion criteria were not eligible for admission into the study:

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- had a history of or had present disorders commonly accepted as contraindications to combined oral contraceptives, including but not limited to the following:
 - deep vein thrombophlebitis or thromboembolic disorders
 - cerebral vascular or coronary artery disease, hypertension or severe migraines
 - a benign or malignant liver tumor which developed during the use of oral contraceptives or other estrogen containing products
 - known or suspected carcinoma of any body system, including the breast or genital tract
 - insulin-dependent diabetes
 - known or suspected estrogen-dependent neoplasia
 - cholestatic jaundice;
- had present disorders commonly accepted as contraindications to oral contraceptives, including but not limited to the following:
 - undiagnosed abnormal vaginal bleeding
 - any neurovascular lesion of the eye or serious visual disturbance
 - any impairment of liver function or liver disease, or renal disease;
- were recent (within 12 months prior to the Screening Visit) abusers of alcohol or other substances;
- had received any experimental drug and/or used any experimental device within 30 days prior to the Screening Visit;
- had received a _____ injection (or any other depot hormone injection) within the six months prior to the Screening Visit;
- had used barbiturates, antiepileptics, rifampin, griseofulvin or other hepatic enzyme-inducing drugs within the 30 days prior to the Screening Visit;
- had an uncontrolled thyroid disorder;
- had been exposed to etretinate (_____);
- had concomitant use of isotretinoin (_____), tretinoin (_____) or _____) or had taken them within the 30-day period immediately prior to the Screening Visit.

Any subject, as deemed by the investigator, who had questionable reliability in her ability to comply with the protocol and provide accurate information, should have been disqualified from entry into the study.

Dose and Mode of Administration: Subjects were to be randomized to receive one of the following four oral contraceptive regimens:

NGM 180, 215, 250/EE 25 (Triphasic-25)

180 µg NGM/25 µg EE (Days 1-7)
215 µg NGM/25 µg EE (Days 8-14)
250 µg NGM/25 µg EE (Days 15-21)
Placebo (Days 22-28)

NGM 180, 250/EE 25 (Cyclophasic-25)

180 µg NGM/25 µg EE (Days 1, 2, 5, 6, 9, 10, 13, 14, 17, 18, 21)
250 µg NGM/25 µg EE (Days 3, 4, 7, 8, 11, 12, 15, 16, 19, 20)
Placebo (Days 22-28)

NGM 60, 180/EE 20 (Cyclophasic-20)

60 µg NGM/20 µg EE (Days 3, 4, 7, 8, 11, 12, 15, 16, 19, 20)
180 µg NGM/20 µg EE (Days 1, 2, 5, 6, 9, 10, 13, 14, 17, 18, 21, 22)
Placebo (Days 23-28)

Loestrin

1000 µg NETA/20 µg EE (Days 1-21)
Placebo - 75 mg ferrous fumarate (Days 22-28)

The sponsor's definitions of cyclophasic and triphasic are as follows:

Cyclophasic = Investigational method of administering combined estrogen and progestin in which the estrogen dose is held constant and two doses of progestin are alternated for short periods, e.g., one or two days.

Triphasic = Investigational method of administering combined estrogen and progestin in which the estrogen dose is held constant and three doses of progestin are administered, each for one week.

Study Evaluations:

Prestudy

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During the first (Prestudy) visit, eligible potential subjects were to be given complete information describing their role in the study and were to be encouraged to ask any questions regarding the study. The risks, benefits, and requirements of the study, as well as the potential hazard to the fetus if pregnancy occurred during the study, was to be explained to each potential subject. Those potential subjects eligible to participate in the study were to read and sign the approved informed consent.

All subjects must have had the following procedures completed within 60 days prior to study medication administration:

- complete medical history with emphasis on menstrual history and use of hormonal contraceptives;
- complete physical and gynecologic examinations, including vital signs, breast and pelvic exams. Any pre-existing conditions should have been documented;
- Papanicolaou (Pap) smear (smear done within two months with report available prior to the Prestudy Visit was also acceptable); and
- assessment of body mass index (BMI)

Admission

Subjects were to return for a hematology profile, clinical chemistries, and urine dipstick tests after having fasted overnight (10-12 hours). A serum β -subunit HCG RIA pregnancy test must have been performed within seven days prior to anticipated initiation of study medication administration. If the subject had fasted as required, the prestudy and admission visits may have been combined provided the visit was within seven days prior to the anticipated start of study medication.

Subjects enrolled into the study were to be categorized, based on their hormonal status as follows:

Direct Switchers - any subject who was presently on oral contraceptives could start study medication at the completion of her current oral contraceptive cycle without interruption of therapy.

Indirect Switchers - any subject who had used hormonal contraceptives within the last two months prior to the start of study medication, but was not presently using hormonal contraceptives.

Fresh Starters - any subject who had not used hormonal contraceptives within the last two months prior to the start of study medication.

It should be noted that Direct Switchers randomized to the Loestrin regimen were to begin taking study medication on the Sunday after the last active pill from the prior pill pack (any unused nonsteroidal tablets from the prior pill pack were discarded).

Direct Switchers randomized to a regimen other than Loestrin were to be instructed to start taking study medication the day after the last tablet was taken from the prior pill

pack if the subject was switching from a 28-day oral contraceptive regimen or eight days after the last tablet was taken from the prior pill pack if the subject was switching from a 21-day oral contraceptive regimen.

Once a review of all screening examinations and laboratory results indicated that the subject was qualified for enrollment, one cycle of study medication was to be dispensed to each subject.

Return Visits Cycles 1,3,6,9, and 13

The first 500 subjects randomized into each of the three NGM/EE regimens and the first 330 subjects randomized into the Loestrin regimen were enrolled into the study for 13 cycles. Once the goal had been reached, the project manager and lead clinical monitor at ~~the~~ notified the study sites to stop enrolling subjects for 13 cycles. Because subject numbers were assigned chronologically within a study site and more than one subject could have been randomized on one date, each study site was notified of the last subject number from their site that was included in the 13-cycle enrollment. All remaining subjects were enrolled into the study for six cycles.

Subjects who were to be involved in the study for up to 13 cycles were to be given specific instructions to return to the study site for a scheduled visit during the inactive tablet-taking interval (cycle Days 26-28) of Cycles 1, 3, 6, and 9.

Subjects who were to be involved in the study for up to six cycles were to return to the study site for a scheduled visit during the inactive tablet-taking interval (cycle Days 26-28) of Cycles 1 and 3.

Vital signs were to be obtained from all subjects at all visits. At the Cycle 6 and 13 post-therapy visits (scheduled 7 to 14 days after the last active tablet), blood was to be drawn for a hematology profile and clinical chemistries. Physical and gynecologic examinations including vital signs, breast and pelvic examination, β -subunit HCG RIA pregnancy test, and Pap smear were to be repeated at Cycles 6 and 13.

Subjects were to return their completed diary cards and used study medication packs for examination at each visit. The study coordinator was to evaluate compliance as well as the subjects' understanding of tablet-taking instructions. Any questions concerning the diary cards as well as the occurrence of any adverse events and concomitant medication usage were to be addressed and reported.

The amount of study medication and diary cards dispensed at each visit was supposed to be sufficient to keep the subject supplied until the next scheduled visit.

Absence of Withdrawal Flow:

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If a subject did not have onset of menses at some time during the six or seven inactive tablet-taking days of any cycle, she was to immediately contact the investigator and have a β -subunit HCG RIA pregnancy test performed. If the test result was negative, the subject could start the next cycle of tablets and continue in the study. If the subject did not return for the pregnancy test during the inactive tablet-taking days, she should have begun her next cycle of tablets but must have had the pregnancy test performed as soon as possible to rule out pregnancy. If the test result was positive, the subject was to discontinue taking study medication.

If pregnancy was confirmed for any subject, the investigator was to have attempted to determine whether the pregnancy resulted from poor subject compliance (failure of the subject to comply with the treatment regimen) or product failure. This information was to be recorded on the source document for inclusion in the pregnancy narrative.

Duration of Treatment: The first 500 subjects in each of the NGM/EE regimens and 330 subjects in the Loestrin regimen were enrolled to complete 13 28-day cycles of study medication. All subsequent subjects were to complete six 28-day cycles of study medication. Each eligible subject was to begin study medication on the first day of menses if randomized to a NGM/EE regimen or they were to start according to labeling (Sunday start) if randomized to Loestrin. All subjects were to take one tablet orally each day for 28 consecutive days for each cycle for up to 13 cycles.

Treatment Compliance:

Subjects were to be given detailed instructions for the administration of study medication and how to handle missed tablets. Subjects were also to be instructed to record tablet usage, bleeding information, adverse events (AEs), and concomitant medications on diary cards. Study site personnel were to instruct the subjects on the importance of compliance and the procedures to be followed in the event any tablets were missed or in the absence of menses. Subjects who had minor but consistent problems with compliance (missing one or two tablets with use of back-up contraception more than once a cycle) were to receive additional counseling. Subjects who had a major compliance problem (missing two or more tablets without using back-up in a cycle) received additional counseling as to whether an oral contraceptive was the appropriate method of contraception for them. Sites were to question each subject during their visits in Cycles 1, 3, 6, and 9, and Posttherapy/Early Withdrawal regarding compliance with dosing instructions.

Subjects Lost to Follow-Up:

If after having been dispensed study medication, a subject missed a scheduled visit, the subject was to be contacted by telephone to reschedule the visit. A postcard or letter was to be sent if telephone contact was unsuccessful. After waiting one month for the subject

to respond, a return-receipt certified letter containing instructions to call for an appointment was to be mailed to the subject. If no response was obtained within two weeks after sending the return-receipt letter, the subject was then considered as lost to follow-up as of the date the letter was mailed.

Efficacy Criteria for Contraceptive efficacy:

Contraceptive efficacy was assessed by the evaluation of pregnancy rates using the Pearl Index (number of pregnancies per 100 women-years) and life table analysis (cumulative probability of pregnancy). For contraceptive efficacy, the primary endpoint was completion of the study without pregnancy. Based on diary cards and on documentation by the investigator, each "on-therapy" pregnancy was classified as either a "method failure" or a "user failure". Pregnancy rates were to be determined for an ITT evaluation and a method failure evaluation. The ITT evaluation of pregnancy rates was to be considered primary. All subjects who took study medication and all on-therapy cycles during which study medication was taken were to be included in the ITT evaluation of efficacy. On-therapy cycles during which the subject was not compliant, or the subject used back-up contraception were to be excluded for the method failure evaluation. For the method failure evaluation of efficacy, the following subsets of on-therapy cycles were to be examined separately:

- cycles with perfect compliance and no use of back-up contraception; and
- cycles with perfect compliance, or imperfect compliance with correct procedures followed for missed tablets, and no use of back-up contraception for other reasons.

Pregnancy rates were to be analyzed by the Pearl Index, the Odds Ratio method, and life table analysis. The Overall Pearl Index for an ITT evaluation was to be the primary endpoint for the assessment of contraceptive efficacy. Odds ratios were to be used to contrast the efficacy results between each NGM/EE treatment group and the Loestrin treatment group.

Efficacy Criteria for Cycle Control:

Seven cycle control parameters {breakthrough bleeding and spotting (BBS), breakthrough bleeding, breakthrough spotting, early withdrawal flow (EWF), intermenstrual bleeding, duration of menses, and duration of latent period} were defined using data recorded on the subject diary cards. (See appendix for definitions)

All subjects who took study medication and provided on-therapy diary cards with bleeding information were to be included in the evaluation of cycle control. Cycle control data were to be summarized and analyzed for an ITT evaluation and an evaluation of a subset of valid on-therapy cycles.

The ITT evaluation was to be based on all on-therapy cycles except those where:

- the cycle had no inactive tablet-taking interval; that is, the first day of active tablet-taking of the next cycle was the day after the last day of active tablet-taking of the cycle under consideration, or the cycle was immediately subsequent to a cycle with no inactive tablet-taking interval; and
- the cycle had missing bleeding information.

The assessment of cycle control based on the ITT evaluation was to be considered primary.

The evaluation of cycle control for valid cycles excluded cycles for the above two reasons plus the following three reasons:

- there were three or more missed active tablets and/or days with no active tablet-taking information, or at least two consecutive days with missed active tablets and/or days with no active tablet-taking information during the cycle, and the immediately subsequent cycle;
- the cycle length was greater than 31 days, or the cycle was immediately subsequent to a cycle whose length was greater than 31 days. (Cycle length is defined as the number of days from the first active tablet taken to the first active tablet taken of the next cycle);
- the cycle was immediately subsequent to a cycle with a shortened (less than five days) inactive tablet-taking interval;

Descriptive statistics were to be calculated for each bleeding parameter. Two-sided 95% CIs were to be computed to make comparisons between each NGM/EE treatment group and the Loestrin treatment group at each on-therapy cycle. The protocol identified the proportion of subjects who experienced intermenstrual bleeding at Cycle 3 as the primary endpoint for the summary and analysis of cycle control.

Bleeding graphs for Cycles 1 through 13 were to be presented for each of the three characteristics: (1) BBS, (2) breakthrough bleeding and (3) break-through spotting. These graphs were to be plots of the percentage of subjects who exhibited the characteristic on each day of the pill cycle. The set of graphs was to be presented separately for each treatment group.

The incidence of cycles with no withdrawal flow, cycles with no breakthrough bleeding or spotting, and amenorrhea was to be given by treatment group. Other bleeding variables, such as the length of the menstrual cycle, the number and length of breakthrough bleeding and/or breakthrough spotting episodes and segments⁵ were to be summarized and analyzed as needed.

**Table 4: Enrollment and Disposition of Study Subjects
(Study NRGLOW-OC-001)**

	Loestrin	Ortho Tri- Cyclen® Lo	Cyc 25/180,250	Cyc 20/60,180
Number randomized	1233	1826	1828	1474
Number safety evaluable	1171	1723	1740	1388
Number discontinued	300 (25.6%)	461 (26.8%)	520 (29.9%)	1318 (95.0%)
Number completed at:				
Cycle 6	677 (57.8%)	978 (56.8%)	944 (54.3%)	63 (4.5%)
Cycle 13	187 (16.0%)	277 ^b (16.1%)	265 (15.2%)	1 (0.1%)
Other	5 (0.4%)	6 (0.3%)	11 (0.6%)	4 (0.3%)

Treatment Compliance:

Perfect compliance by cycle ran from 73-88% in the Ortho Tri-Cyclen® Lo and Loestrin® Fe 1/20-treatment arms.

Protocol Deviations at Study Entry:

Ten subjects across groups had cervical dysplasia at baseline, but were inadvertently enrolled in the study. No greater than 2.8% of the subjects in each treatment group had any specific protocol deviation. The most common deviations of entry criteria were BMI outside of specified range, systolic and/or diastolic blood pressure outside of specified range, and investigator-specified protocol violation.

Contraceptive efficacy results:

There were 34,507 cycles from 5,851 subjects included in the evaluation of pregnancy rates. All 38 subjects enrolled at Site 011 were excluded from the efficacy population. The sponsor described the data from this site as unevaluable.

Medical officer's comments: A teleconference was held on April 2, 1998 between RWJPRI and the FDA in regard to the termination of this site. None of the pregnancies that occurred at this site were in subjects who took either Ortho Tri-Cyclen® Lo or Loestrin® Fe 1/20.

There were 85 on-therapy pregnancies included in the contraceptive efficacy analyses: 19 in the Loestrin treatment group; 20 in the Ortho Tri-Cyclen® Lo treatment group; 30 in the Cyclophasic 25/180,250 treatment group; and 16 in the discontinued Cyclophasic 20/60,180 treatment group. Sixty-eight of these pregnancies were classified as on-therapy method failures: 17 of 19 in the Loestrin treatment group; 14 of 20 in the Ortho Tri-Cyclen® Lo treatment group; 22 of 30 in the Cyclophasic 25/180,250 treatment group; and 15 of 16 in the discontinued Cyclophasic 20/60,180 treatment group.

There were eight pretreatment pregnancies among subjects who took study medication: three in the Loestrin treatment group; two in the Ortho Tri-Cyclen® Lo treatment group;

Statistical Methods: The on-therapy pregnancy rates were evaluated by the Pearl Index and life table analysis. The relative risks of pregnancy and the cumulative probability of pregnancy through Cycle 13 were determined for each of the NGM/EE treatment groups that were not discontinued after the interim analysis. The relative risks were computed to contrast the NGM/EE treatment groups with the Loestrin treatment group. The number of pregnancies and Pearl Index are summarized for the discontinued NGM/EE arm; the relative risk and life table analyses were not performed for the dropped treatment arm because of the difference in the duration of exposure. The incidence of bleeding for five derived, cycle control bleeding variables (breakthrough bleeding and/or spotting, breakthrough bleeding, breakthrough spotting, early withdrawal flow, and intermenstrual bleeding) and the mean duration of menses and mean duration of the latent period were compared between each of the three NGM/EE treatment regimen and the Loestrin treatment regimen using confidence intervals. The subject satisfaction measures were summarized descriptively by visit for each of the four treatment regimens.

Efficacy Results:

Interim analysis:

The interim analysis included Cycle 3 data for 984 subjects. At the conclusion of the interim analysis the Cyc 20/60,180-treatment group was discontinued.

Demographics:

The four treatment groups were similar with respect to age, racial distribution, and body mass index. The treatment groups were also similar with respect to percentage of smokers, prior hormonal contraceptive status (direct switcher, indirect switcher, or starter), and length of menses.

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Study Completion/Withdrawal

Table 4 illustrates the number randomized, safety evaluable, and discontinuations for NRGLOW-OC-001.

Interim Analysis:

The objective of the interim analysis was to evaluate the cycle control of the three NGM/EE treatment groups in comparison to the Loestrin treatment group. It was planned that after the interim analysis, at least one of the three NGM/EE treatment groups would be discontinued.

The interim analysis was to be focused on the bleeding data from Cycles 1-3. It was to be based primarily on the first 300 subjects enrolled in each of the three NGM/EE treatment groups and on the first 200 subjects enrolled in the Loestrin treatment group. The analysis was planned to begin after the last of these subjects were enrolled and their diary cards for Cycles 1-3 were obtained and entered into the database. The database could also have included data for additional subjects who were enrolled and had provided diary cards for at least one cycle; however, the primary interim analysis focus was to be for subjects who had completed three cycles.

Subject Satisfaction: Six questions designed to assess the extent to which satisfaction with the oral contraceptive regimen was affected by subjective product impressions and experiences were to be asked by study site staff during the clinic visits of all subjects at the completion of Cycles 1, 3, 6, and 13, (if applicable) or when a subject discontinued from the study. Subject satisfaction measures were based on the subject's assessment of: (1) her overall satisfaction with the oral contraceptive regimen, (2) whether or not she would be willing to continue the oral contraceptive regimen after study completion, (3) her emotional well-being while on the oral contraceptive regimen, as compared to her emotional well-being prior to taking the product, (4) her physical well-being while on the oral contraceptive regimen, as compared to her physical well-being prior to taking the product, (5) the severity of her bleeding side effects while on the oral contraceptive regimen, and (6) the amount of her menstrual flow while on the oral contraceptive regimen, as compared to the amount of her menstrual flow prior to taking the product.

Pregnancy Evaluation:

For all cases of a positive pregnancy test result, the determination of the estimated date of conception was to be made by the investigators based on the following hierarchy:

1. Ultrasound;
2. Gynecologic examination;
3. Last menstrual period (LMP) and bleeding information from subject;
4. Determination of gestational age at pregnancy outcome; or
5. Quantitative β -subunit HCG RIA pregnancy test.

If sources of information were not in agreement, the more accurate source (i.e., higher in the hierarchy) was to be used.

and four in the Cyclophasic 25/180,250-treatment group. There were also 34 pregnancies diagnosed during screening, following which, no study medication was taken.

There were 25 posttreatment pregnancies: eight in the Loestrin treatment group; eight in the Tri 25/180,215,250 treatment group; five in the Cyclophasic 25/180,250 treatment group; and four in the discontinued Cyclophasic 20/60,180 treatment group.

**Table 5: Sponsor's Pearl Index Analysis of Pregnancy
(Efficacy Evaluable Population in Study NRGLOW-OC-001)**

	Loestrin	Ortho Tri-Cyclen® Lo	Cyclophasic 25/180,250	Cyclophasic 20/60,180
Number of Subjects ^a	1141	1673	1700	1337
Number of Cycles ^b	7497	11003	10894	5113
Number of Women-Years	576.7	846.4	838.0	393.3
Number of Pregnancies				
Method Failure	17	14	22	15
All	19	20	30	16
Pearl Index [95% CI]				
Method Failure	2.95 [1.55, 4.35]	1.65 [0.79, 2.52]	2.63 [1.53, 3.72]	3.81 [1.89, 5.74]
All	3.29 [1.81, 4.77]	2.36 [1.33, 3.40]	3.58 [2.30, 4.86]	4.07 [2.08, 6.06]

^a Data for subjects from Site 011 and for subjects who became pregnant before they started taking study drug (i.e., pretreatment pregnancy) are excluded.

^b Includes the cycle of conception. All cycles after the cycle of conception are excluded for subjects who became pregnant on-therapy

The Pearl Indices for all pregnancies were 3.29 in the Loestrin treatment group, 2.36 in the Ortho Tri-Cyclen® Lo-treatment group, 3.58 in the Cyclophasic 25/180,250-treatment group, and 4.07 in the Discontinued Cyclophasic 20/60,180-treatment group. The Pearl Indices for method failure pregnancies were slightly lower: 2.95 in the Loestrin treatment group, 1.65 in the Ortho Tri-Cyclen® Lo treatment group, 2.63 in the Cyc 25/180,250 treatment group, and 3.81 in the Discontinued Cyc 20/60,180 treatment group. The 95% confidence intervals (CI) about the Pearl Indices for each NGM/EE treatment group overlapped with the 95% CI for the Loestrin treatment group.

The cumulative probability of an on-therapy pregnancy through 13 cycles of use was 2.6%, 1.9% and 3.2% for the Loestrin, Ortho Tri-Cyclen® Lo, and Cyc 25/180,250 treatment groups, respectively. The cumulative probabilities of an on-therapy method failure pregnancies through 13 cycles of use were 2.4% in the Loestrin treatment group, 1.5% in the Ortho Tri-Cyclen® Lo, and 2.2% in the Cyc 25/180,250 treatment group

Cycle control results:

The proportion of subjects who experienced intermenstrual bleeding during Cycle 3 was the primary endpoint for the analysis of cycle control data in this study. The incidence of intermenstrual bleeding during Cycle 3 was 23.6% in the Ortho Tri-Cyclen® Lo treatment group compared to the Loestrin, Cyclophasic 25/180,250, and Discontinued Cyclophasic 20/60,180 treatment groups (37.2%, 28.9%, and 61.5%, respectively). Table 6 illustrates the intermenstrual bleeding per cycle for Ortho Tri-Cyclen® Lo and Loestrin.

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Table 6. Comparison of Loestrin and Ortho Tri-Cyclen® Lo in regard to intermenstrual bleeding

Cycle	Loestrin® Fe 1/20 NRGLOW-OC- 001 (%)	Ortho Tri- Cyclen® Lo NRGLOW-OC- 001 (%)
1	45.5	31.9
3	37.2	23.6
6	33.4	20.8
9	27.1	19.2
13	27.2	19.7

A table comparing Ortho Tri-Cyclen® Lo to Loestrin® Fe 1/20 in regard to breakthrough bleeding or spotting is shown in table 7.

Table 7. Comparison of Loestrin and Ortho Tri-Cyclen® Lo in regard to breakthrough bleeding/spotting.

Cycle	Loestrin® Fe 1/20 NRGLOW-OC- 001 (%)	Ortho Tri- Cyclen® Lo NRGLOW-OC- 001 (%)
1	34.9	16.3
3	22.9	11.5
6	22.2	10.3
9	15.9	7.9
13	13.1	7.7

In the ITT population, the incidence of early withdrawal flow over all cycles was comparable between the Ortho Tri-Cyclen® Lo and Loestrin treatment groups (13.3% and 14.0%, respectively). The incidence of EWF was more frequent in the Cyc 25/180,250 treatment group (18.0%), and was most frequent in the discontinued Cyc 20/60,180 treatment group (36.0%)

The duration of menses was shorter in the Loestrin treatment group than in the Ortho Tri-Cyclen® Lo, Cyclophasic 25/180,250 or the discontinued Cyclophasic 20/60,180 treatment groups (4.4, 5.4, 5.7, 6.5, mean number of days, respectively). The results from the analysis based on the 95% CIs were statistically significant and demonstrated that the Loestrin group had a shorter duration of menses than the other three groups.

The incidence of cycles with no withdrawal flow for all cycles in the ITT evaluation was 1430 (19.6%) in the Loestrin treatment group, 464 (4.3%) in the Ortho Tri-Cyclen® Lo treatment group, 520 (4.9%) in the Cyclophasic 25/180,250 treatment group, and 581 (11.9%) in the discontinued Cyclophasic 20/60,180 treatment group. For each cycle, the percentage of subjects who experienced no withdrawal flow was lower in the NGM/EE treatment groups than in the Loestrin treatment group.

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Subject Satisfaction:

With regard to subject satisfaction measures, the results were similar across treatment groups for direct switchers, indirect switchers, and starters. Approximately 55-65% of subjects in both the Ortho Tri-Cyclen® Lo and Loestrin® treatment arms were very satisfied with their oral contraceptive regimen and indicated they would like to continue their oral contraceptive regimen after study completion.

Sponsor's Conclusions: Ortho Tri-Cyclen® Lo, a 25 µg formulation of Ortho Tri-Cyclen, is an effective oral contraceptive that is at least as effective as Loestrin in contraceptive efficacy. Ortho Tri-Cyclen® Lo has superior cycle control to Loestrin. The adverse events reported by subjects treated for up to 13 cycles with Ortho Tri-Cyclen® Lo were similar to the control group and typical of adverse events reported by women taking combination oral contraceptives. There were no notable changes in laboratory values, vital signs, or physical or gynecologic examination findings.

Medical officer's comments: See reviewer's comments on page 33

Protocol No.: K90-023

Title of Study: Comparative, randomized, trial of five regimens of norgestimate and ethinyl estradiol-containing oral contraceptives.

Investigators: Nine investigators

Study Centers: Nine study centers in the United States.

Studied Period: February 19, 1991 to June 30, 1992

Phase of development: 2

Objectives: To determine an optimum oral contraceptive regimen of norgestimate (NGM) and ethinyl estradiol (EE) with respect to efficacy (ovulation suppression), safety, and cycle control.

Methodology: 250 subjects were randomized in equal numbers to five groups for treatment with a study oral contraceptive for 3 cycles (or 4 cycles if they could not return at cycle 3). The four investigational treatments (three cyclophasic, one triphasic) were blinded, while the control treatment (Ortho Tri-Cyclen) was not. Efficacy (ovulation inhibition) was determined from a serum progesterone measurement taken during pill days 19-21 of cycle 3 (or 4). Ovulation was defined as a progesterone level of $\geq 3\text{ng/mL}$. Cycle control was determined from bleeding information recorded on subjects' diary cards.

Number of Subjects: 250 subjects were enrolled; 236 were evaluable for safety.

Diagnosis and Main Criteria for Inclusion: Subjects were to be healthy women between 18 and 40 years of age, with regular menstrual cycles and no disorders that would preclude oral contraceptive use. Subjects had to agree to use an acceptable method of backup contraception during the study unless they had had a prior tubal ligation or had a vasectomized partner.

Test Product, Dose and Mode of Administration:

NGM/EE 180/250/35 1-Day

NGM 180 μg and EE 35 μg every odd day, Days 1-21

NGM 250 μg and EE 35 μg every even day, Days 1-21

NGM/EE 180-250/35 2-Day

NGM 180 μg and EE 35 μg Days 1,2, 5,6, 9,10, 13,14, 17,18, 21

NGM 250 μg and EE 35 μg Days 3,4, 7,8, 11,12, 15,16, 19,20

NGM/EE 180/250/25 2-Day

NGM 180 μg and EE 25 μg Days 1,2, 5,6, 9,10, 13,14, 17,18, 21

NGM 250 μg and EE 25 μg Days 3,4, 7,8, 11,12, 15,16, 19,20

NGM Triphasic/25 (Ortho Tri-Cyclen® Lo)

NGM 180 μg and EE 25 μg Days 1-7

NGM 215 μg and EE 25 μg Days 8-14

NGM 250 μg and EE 25 μg Days 15-21

Duration of Treatment: Three 28-day cycles (four cycles were allowed if subject could not return at cycle 3).

Efficacy Criteria for Evaluation: Contraceptive efficacy was assessed by calculating the incidence of ovulation occurring with each of the study regimens during cycle 3 and by statistical comparisons between pairs of selected regimens. The cycle control characteristics were summarized for the five regimens, and statistical comparisons made between selected regimens for individual cycles of treatment. Cycle control calculations and comparisons were made using valid cycles for all subjects as well as valid cycles for the subset of fresh subjects.

Statistical Methods: The incidence of ovulation at cycle 3 was compared between regimens using Fisher's exact two-sided test. The incidence of bleeding for five derived bleeding variables was compared between regimens at each cycle using a Chi-square or Fisher's exact test. Mean duration of menses and mean duration of the latent period were compared between regimens using the two-sample t-test.

Study Results:

Ovulation was identified in 3 of 43 control subjects taking Ortho Tri-Cyclen and in none of 41 subjects taking Ortho Tri-Cyclen® Lo. Ovulation was defined by a progesterone level ≥ 3 ng/mL. "Luteal activity", characterized as progesterone values of ≥ 1 ng/mL and < 3 ng/mL, showed a different pattern of occurrence than that of ovulation. None of the Ortho Tri-Cyclen subjects showed progesterone levels in this range. Three of 41 subjects taking Ortho Tri-Cyclen® Lo showed progesterone values in this range.

Cycle control, overall, was somewhat better with Ortho Tri-Cyclen than with the four investigational regimens although, for the majority of bleeding parameters, no statistically significant differences were found in comparisons made between selected pairs of regimens.

D. Efficacy Conclusions

The sponsor's main conclusions from the phase 3 pivotal study (NGLOW-OC-001) are as follows:

- Ortho Tri-Cyclen® Lo is as effective as Loestrin® Fe 1/20 in contraceptive efficacy.
- Ortho Tri-Cyclen® Lo provides superior cycle control compared to Loestrin® Fe 1/20.
- Ortho Tri-Cyclen® Lo has an upper limit of the 95% CI for the probability of pregnancy in the first year of use that is well below the 5% typical use pregnancy rate in the class label.

The sponsor's main conclusion from the phase 2 ovulatory study (K90-023) is as follows:

- Ortho Tri-Cyclen® Lo appeared to be as effective as the Ortho Tri-Cyclen in inhibiting ovulation, based on single progesterone measurements performed during the third treatment cycle.

Medical officer's comments:

Review of the submitted data confirms the pregnancy rates reported by the sponsor for this product. The primary concern related to approval is whether the pregnancy rate is unacceptably high with use of this product, especially in light of the relative lack of benefits of this product compared to the other norgestimate products (Ortho Tri-Cyclen and Ortho-Cyclen) and the presence of a number of more effective low dose pills already on the market.

The pivotal study was not powered a priori for efficacy equivalency or superiority with regard to cycle control.

The use of a comparative study design that demonstrates poorer clinical performance of an approved product raises not only the approval issues of Ortho Tri-Cyclen® Lo but raises questions on how the division will proceed in the future in regard to clinical study design, acceptance of comparators, and appropriate labeling for oral contraceptives. I will present my analysis and conclusions via the following question and answer approach:

1. Should randomized controlled clinical trials comparing approved products to investigation products provide the basis for approval for new applications?

Medical officer's comments: Consideration should be given to defining an upper limit for a Pearl Index in a guidance document. Though comparative studies were advocated by the World Health Organization at one time for contraceptive products, I believe that a comparator is not necessary for contraceptive efficacy studies and can be handled entirely by Pearl Index and life table analysis. Comparators would serve a better role comparing side effects or cycle control.

The pivotal phase III study for this product began in April 1997. The "approved" comparator chosen by the sponsor based on an estrogen dose less than 30µg/day was Loestrin. At the time the clinical study started, Loestrin was essentially the only product with an estrogen dose that low to offer comparison. Alesse® received approval three days before the start of their clinical trial (March 27, 1997). Levlite received approval July 13, 1998 and Mircette received approval April 22, 1998.

The impact of present day study design on the performance of some of the older approved products remains uncertain to a large degree. The difference however in Loestrin's performance from 1972-3 and the present study is quite large in regard to the Pearl Index. The therapeutic effectiveness from 1972 was listed as 0.29 compared to a method failure Pearl Index of 2.95 in this study. This comparative study

concerning Loestrin does raise issues about its true performance, but until we have additional confirmatory data we cannot tell whether the 2.95 value is an unusually high level by chance alone.

If comparative efficacy to approved products makes up the bulk of the efficacy argument in the future, there will be a strong temptation for sponsors to always pick the weakest of the approved contraceptives and we may "creep" towards less and less effective pills.

2. What approved products should be compared to Ortho Tri-Cyclen® Lo in regard to contraceptive efficacy and what are their pregnancy rates?

Oral contraceptives containing less than 30µg of ethinyl estradiol should constitute the primary comparison. The method failure and user failure Pearl Index for oral contraceptives in this group are listed in Table 8. Estrostep® is included in the table because 20µg is used for one week and Estrostep® was also mentioned by the sponsor in their efficacy arguments.. The norgestimate products with 35µg of estrogen are also included to provide comparison to products with the same progestin.

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ON ORIGINAL**

Table 8. Comparison of 20µg ethinyl estradiol and norgestimate oral combination contraceptives for dosage, method failure Pearl Index, and overall Pearl Index.

Oral Contraceptive	Estrogen dose (ethinyl estradiol)	Progestin	Progestin dose	Method failure Pearl Index	Overall Pearl Index
Alesse®	0.020mg x 21d	LNG	0.10mg x 21	0.84	0.84
Estrostep®	0.020mg x 7d 0.030mg x 7d 0.035mg x 7d	NETA	1mg x 21 days	Not listed	2.4 (2.1 at best)
Levlite™ US study	0.020mg x 21	LNG	0.10mg x 21d	1.08	1.8
Levlite™ European	0.020mg x 21	LNG	0.10mg x 21d	0.29	0.29
Loestrin 1/20 Original submission	0.020mg x 21d	NETA	1mg x 21 days	0.29	0.75
Loestrin 1/20 as comparator in this NDA	0.020mg x 21d	NETA	1mg x 21 days	2.95	3.29
Mircette®	0.020mg x 21d no EE x 2d 0.010mg x 5d	DSG	0.15mg x 21 days no D for 7d	0.74	1.11
Ortho Tri-Cyclen® Lo	0.025mg x 21 days	NGM	0.180mg x 7d 0.215mg x 7d 0.250mg x 7d	1.65	2.36
Ortho Tri-Cyclen	0.035mg x 21 days	NGM	0.180mg x 7d 0.215mg x 7d 0.250mg x 7d	0.42-0.78	0.68-1.47 in 4 trials
Ortho-Cyclen	0.035mg x 21 days	NGM	0.250mg x 21d	Not listed	0.96

3. What were the sponsor's arguments in favor of historical study differences as explanation for higher Pearl Index figures for Loestrin®?

The sponsor proposed the following points in addressing historical differences in oral contraceptive study design that might account for higher Pearl index figures.

- *Shorter duration of subject participation*
- *Follow-up of Discontinued Subjects*
- *Planned pregnancy testing*

- *Acceptance of chemical pregnancies*
- *Non-removal of Subjects from Study/Analyses*
- *Classification of Method Failures*

1. Acceptance of Initial Diary Data

2. More Conservative Definition of User Failure

4. Is there any objective data to support the sponsor's historical differences in study design?

Yes, the Loestrin studies (from the early 1970s) did have extended study periods that extended up to 21 cycles with one chart recording no pregnancies occurring between the 10th to 21st cycle.

Pregnancy assessment was different in the early 1970s. Sophisticated hCG evaluation and transvaginal sonography were not available. The Loestrin protocol from the 1970s for pregnancy evaluation is as follows:

“Occurrences of pregnancy were recorded along with the physician's evaluation as to whether they were considered to be due to drug failure or to the subject's failure to take the medication properly. Subjects having two consecutive months of amenorrhea while on treatment were required to have pregnancy ruled out before continuing in a study. All pregnancies occurring while on treatment were to be followed and the outcome and the condition of the baby, where available, recorded.”

It is uncertain to what degree the researcher attempted to contact subjects lost to follow-up. The description of Loestrin subjects dropped from study is as follows:

“If a subject was dropped from a study, the reason for the drop was noted. Subjects who went for 1 cycle without medication were considered as dropped. Dropped subjects who re-entered at a later date were assigned the same study number but were restarted on Study Day 1. Any subject who missed 5 or more tablets in 2 consecutive cycles was to be dropped from the study as unreliable.”

In the 1972 NDA report from Loestrin 242/525 (46.7%) subjects dropped. Loss of contact accounted for 79 subjects (15%) and approximately one fourth of the subjects who dropped due to loss of contact failed to return.

The sponsor has suggested that planned pregnancy testing at termination may raise the reported pregnancy rate. There were two pregnancies in the Loestrin arm and one pregnancy in the Ortho Tri-Cyclen® Lo arm of this study that were picked up by hCG analysis at mandatory end of study testing and no other clinical suspicion. It is possible that studies in the 1970s might have missed some of these types of pregnancies.

With better hCG measurements, chemical pregnancies may also add to the number of pregnancies detected in modern day clinical trials.

The sponsor also presented data to indicate that a Triphasil® comparator used by RWJPRI for comparison to Ortho Tri-Cyclen and a contraceptive patch also had an increase in the Pearl Index with the more modern study (1997-99 compared to the earlier 1987-90) The overall Pearl Index in the 1987-90 study was 0.8 (CI 0.2,1.4) . The Pearl Index in the 1997-99 study was 2.18 (CI 0.57,3.8). The sponsor felt that the lack of a poststudy pregnancy test in the earlier trial might have contributed to the lower Pearl Index.

5. Is the sponsor's statement about improved cycle control for Ortho Tri-Cyclen® Lo versus Loestrin indicative of additional clinical benefit for Ortho Tri-Cyclen® Lo? How does Ortho Tri-Cyclen® Lo compare to other 20µg level ethinyl estradiol products for cycle control?

Cycle control data on Loestrin 1/20 (NDA 17-354) from the 1970s submission labeled as "2-1-72 update" is shown in Table 9.

Table 9. Percentage rate of irregular bleeding for Loestrin® 1/20 by cycle.

Cycle	Rate %
1	38.37
3	32.17
9	29.55
12	30.12

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ON ORIGINAL**

A comparative table (Table 10) of different oral contraceptives and cycle control was constructed as part of the medical review of Mircette® (information from NDA 20-713). This table includes two other 20µg level ethinyl estradiol pills and also Estrostep which has 20ug of ethinyl estradiol for the first week.

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ON ORIGINAL**

Table 10. Comparative Percentages of Breakthrough bleeding/spotting using Mircette as comparator.

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Cycle	Estrostep®	Loestrin® 1.5/30	Mircette® using same definition as Estrostep® & Loestrin®	Alesse®	Mircette® using same definition as Alesse	Desogen®	Mircette® using same definition as Desogen®
1	58	46	28.9	30.5	28.9	15.4	19.1
3	22	17	26.6	26.6	22.2	9.9	13.9
6	17	13	21.6	25.4	21.2	7.6	14.1
9			17.4	25.2	17.1	5.9	11.5
12			18.8	18.2	18.2		13.3
18			11.3	27.3	11.6		9.5

Medical officer's comments: Comparisons across various studies are difficult to interpret.

A comparison of cycle control from the pivotal phase 3 study for Ortho Tri-Cyclen® Lo and Loestrin is compared to historical data for Ortho Tri-Cyclen and Ortho-Cyclen in Table 11.

Table 11. Cycle control comparisons (Breakthrough bleeding/spotting) of Loestrin® Fe 1/20, Ortho Tri-Cyclen® Lo, Ortho Tri-Cyclen and Ortho-Cyclen.

Cycle	Loestrin® Fe 1/20 NRGLOW-OC-001	Ortho Tri-Cyclen® Lo NRGLOW-OC-001	Ortho Tri-Cyclen® (historical comparison)	Ortho-Cyclen® (historical comparison)
1	34.9	16.3	16.9	17.9
3	22.9	11.5	12.6	10.1
6	22.2	10.3	9.4	7.9
9	15.9	7.9		
13	13.1	7.7		

Although these cycle comparisons are difficult to evaluate because they come from different time periods and different protocols, it certainly appears that the sponsor did not put Ortho Tri-Cyclen® Lo up against a very strong comparator in regard to cycle control. Loestrin® was found to have a high irregular bleeding rate in the 1970s and continues to show about twice the bleeding-related problems of the norgestimate medications. This reviewer's conclusions about cycle control are the following:

- **Loestrin® is a poor comparator to choose to properly evaluate cycle control (especially in regard to breakthrough bleeding/spotting)**
- **Although cross study comparisons are difficult to interpret, Ortho Tri-Cyclen® Lo appears to provide about the same cycle control as Ortho Tri-Cyclen and Ortho-Cyclen products based on historical data.**
- **The cycle control for Ortho Tri-Cyclen® Lo is certainly acceptable but it does not represent a marked improvement over many of the approved oral contraceptives. There are no labeling claims being made in regard to cycle control for this product.**

Aside from cycle control, is Ortho Tri-Cyclen® Lo different from Ortho Tri-Cyclen in regard to estrogenic side effects?

The sponsor was requested to send in historical comparisons of Ortho Tri-Cyclen and Ortho-Cyclen to address this question. Table 12 represents an historical comparison by adverse event percentage experience. Table 13 lists the historical comparisons by discontinuations.

Table 12. Percentage of subjects reporting common estrogen-related adverse events - historical comparison of norgestimate products

	Ortho Tri-Cyclen® Lo	Ortho Tri-Cyclen	Ortho-Cyclen
Headache	29.4	46.8	31.2
Breast tenderness	9.8	7.1	5.7
Nausea	14.7	3.8	<5
Vomiting	<5	<5	<5

Table 13. Percentage of subjects discontinuing due to common estrogen-related adverse events - historical comparison of norgestimate products

	Ortho Tri-Cyclen® Lo	Ortho Tri-Cyclen	Ortho-Cyclen
Headache	0.8	3.0	4.1
Breast tenderness	0.1	<0.2	<1.0
Nausea/vomiting	0.5/0.2	2.2	3.8

There is no clear indication from the previous two tables that Ortho Tri-Cyclen® Lo clearly surpasses its norgestimate predecessors that contain 35µg EE. However, an individual patient might find some individual benefit from a decrease of 10µg of ethinyl estradiol in one or more estrogenic side effects.

Does the sponsor have a valid argument in relation to the agency approving other oral contraceptives with high Pearl Indices?

The sponsor includes the following statement in the risk/benefit analysis.

“In the Summary Basis of Approval (SBA) for Estrostep, the FDA-calculated Pearl Index was 2.4; the Alesse Pearl Index was 1.65 if “user failures” were included, and the Levlite Pearl Index for a 3, 612 cycle study was 1.8, if “user failures” were included.”

The figure quoted for Estrostep is correct. Estrostep was initially not approved based on this Pearl Index but further analysis and the finding of prior approvals with even higher Pearl Indices resulted in an approval for Estrostep. The other high Pearl Indices were for short 4-cycle evaluations of Trinorinyl® (2.6), Brevicon® (5.18), and Norinyl® (2.51).

I could not confirm the sponsor quoted Pearl Index of 1.65 for Alesse. The medical review indicated a Pearl Index of 0.84. The biometrics review listed an index over 2.0 but included individuals who became pregnant before initiation of medication.

The comment on Levlite is somewhat misleading because the separate European study had an excellent Pearl Index of 0.29 so that when the studies are combined the overall number is not as high. This raises an issue that user failure differences in pregnancy testing or appropriate evaluation of dropouts may be significant when two different countries have such discrepant results.

VII. Integrated Review of Safety

A. Conclusions

In conclusion, the adverse events reported by subjects treated with Ortho Tri-Cyclen® Lo were similar to the control group and typical of events reported by women taking combination oral contraceptives. There were no notable changes in laboratory values, vital signs, or physical/gynecologic examination findings. A review of all available safety data indicates that Ortho Tri-Cyclen® Lo administered for up to 13 cycles is safe and well tolerated.

B. Patient Exposure

Three studies (Table 14) make up the database for safety analysis for Ortho Tri-Cyclen® Lo (K90-023, NRGLOW-PHI-001, and the pivotal NRGLOW-OC-001). Overall 1,785 subjects were treated with Ortho Tri-Cyclen® Lo. The primary safety analysis is the pivotal study, which evaluated 1,723 subjects taking the medication for contraception.

**Table 14: Subjects Exposed to Ortho Tri-Cyclen® Lo
(Subjects Evaluable for Safety in the ISS ^a)**

	Subjects Treated with ≥1 Dose	Total Cycles Treated	Total Woman-Years ^b
Phase 3			
NRGLOW-OC-001	1,723	11,062	850.9
Phase 2			
K90-023	46	124	9.5
Phase 1			
NRGLOW-PHI-001	16	47	3.6
TOTAL	1,785	--	--

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ON ORIGINAL**

Phase 3 demographics and exposure

In the Phase 3 study, safety results in the Ortho Tri-Cyclen® Lo group are compared to those in the control group, Loestrin®. Subjects ranged from 18 to 45 years of age with a mean of approximately 28 years. The Ortho Tri-Cyclen® Lo and Loestrin treatment groups were similar with respect to mean age (28.2 years and 28.1 years, respectively), racial distribution (White, 86.4% and 83.9%, respectively), Body Mass Index (23.7 kg/m² and 23.6 kg/m², respectively), and subjects who smoked (17.4% and 16.7%, respectively). Most women in each treatment group had menses lasting three to five days (81.8% and 82.5%, respectively).

Table 15 illustrates the exposure of Ortho Tri-Cyclen® Lo compared to Loestrin.

**Table 15: Enrollment and Disposition of Subjects in
(Study NRGLOW-OC-001)**

	Ortho Tri-Cyclen® Lo	Loestrin
Number randomized	1,826	1,233
Number evaluable for safety	1,723	1,171
Number completed at:	N (%)	N (%)
Cycle 6	978 (56.8)	677 (57.8)
Cycle 13	277 (16.1)	187 (16.0)
Other	6 (0.3)	5 (0.4)
Number discontinued	461 (26.8)	300 (25.6)

**APPEARS THIS WAY
ON ORIGINAL**

Phase 2 demographics and exposure

Subjects in the phase 2 study ranged in age from 18 to 40 years. The majority of subjects (89%) were White. Most subjects (over 80%) were non-smokers. Most women (over 96%) reported that they had experienced normal menses before taking OCs. The Ortho Tri-Cyclen® Lo and Ortho Tri-Cyclen® treatment groups were similar with respect to mean age (28.6 years and 29.2 years, respectively), and racial distribution (White, 87.0%

and 91.7%, respectively). The percentages of subjects with regular menses were similar among the treatment groups. However, there were more smokers in the Ortho Tri-Cyclen® Lo treatment group (23.9%) than in the Ortho Tri-Cyclen treatment group (14.6%). With this exception, there were no notable differences in demographic and baseline characteristics between the Ortho Tri-Cyclen® Lo and Ortho Tri-Cyclen® treatment groups.

The duration of treatment in the Phase 2 study was three, or in some cases, four cycles. (Table 16)

Table 16: Number of On-Therapy Cycles
(Study K90-023)

On-Therapy Cycle	Tri 25/180,215,250	Tri 35/180,215,250
	(N=50) N (%)	(N=50) N (%)
1	45 (90)	47 (94)
2	38 (76)	43 (86)
3	38 (76)	42 (84)
4	3 (6)	5 (10)
Total On-Therapy Cycles	124	137
Woman-Years*	9.5	10.5

Phase 1 demographics and exposure

In the phase 1 study, NRGLOW-PHI-001, subjects ranged in age from 20 to 43 years with a mean of 30.2 years. Approximately two-thirds (63%) of the subjects were white. The subjects were treated for three cycles.

C. Methods and Specific Findings

The Primary Safety Population (Study NRGLOW-OC-001)

The following safety assessment also includes the cyclophasic products in addition to Ortho Tri-Cyclen® Lo and Loestrin.

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Safety Assessment

Safety was assessed from summaries of data on treatment-emergent adverse events (TEAEs), changes from baseline in clinical laboratory test results, changes from baseline in vital sign measurements, and changes in physical and gynecologic examination findings (including Papanicolaou smear results) from pretreatment to the end of the study.

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Adverse Events

Deaths:

One subject died of stage IV gastric carcinoma after completing nine cycles of Cyclophasic 25/180,250. Subject 080005, a 27-year-old black woman, was enrolled in the study on 24 April 1997 and took her first dose of study medication on 29 April 1997. On 28 January 1998, the subject reported a four-month history of epigastric discomfort, heartburn, occasional nausea/vomiting, and dysphagia. The subject also reported having trouble swallowing solids, but reported that she had been able to swallow liquids. On 29 January 1998, she was admitted to the hospital. Upon admission, the subject also reported a 10 to 15 pound weight loss within the previous three to four months. A "barium swallow" revealed a possible esophageal stricture. Upper endoscopy revealed a pyloric area stricture. The results of a biopsy indicated gastric adenocarcinoma. Computed tomography scan revealed that the subject had ascites. The ascites were tapped and were shown to be malignant. The subject was diagnosed as having Stage IV gastric carcinoma and was given supportive treatment. On 17 February 1998, the subject was discharged from the hospital with hospice care. The subject died on 19 February 1998. The gastric carcinoma was not felt to be related to study medication.

Serious adverse events:

The definition of serious adverse events was similar in the Phase 3, Phase 2 and Phase 1 studies. Serious adverse events in all studies included any adverse events that were fatal, life-threatening, permanently disabling, required or prolonged in-patient hospitalization, resulted from an overdose, or were congenital anomalies or cancer. There were some small differences in the definitions of serious adverse events among the studies, such as the definition of an overdose and of an "unexpected" adverse event, which were specified in some, but not all, protocols.

Serious adverse events were reported for 11 subjects (0.6%) in the Ortho Tri-Cyclen® Lo treatment group, and seven subjects (0.6%) in the Loestrin® treatment group. In addition, serious adverse events were reported for 23 subjects (1.3%) in the cyclophasic 25/180,250-treatment group. One of these subjects (Subject 080005) had a fatal SAE and was described above. There were also five subjects (0.4%) in the discontinued cyclophasic 20/60,180 treatment group who experienced at least one serious adverse event.

Medical officer's comments: 12 SAE were identified in the case summaries for Ortho Tri-Cyclen® Lo as opposed to the 11 listed in the study report. They are as follows:

- *T12 burst fracture, paraplegia secondary to a fall from a ladder (URSM)*

- *Gall bladder symptoms predating medication start, prior history of gallstones (URSM)*
- *Pneumonia (URSM)*
- *Cervical dysplasia, high grade (URSM)*
- *Strep Throat, Campylobacter food poisoning (URSM)*
- *Asthmatic attack (URSM)*
- *Cervical dysplasia, CIS (PRSM)*
- *Major depression, personality disorder (URSM)*
- *Herniated disk (URSM)*
- *Pneumonia (URSM)*
- *Recurrent tongue carcinoma (URSM)*
- *Labrum tear, right shoulder (URSM)*

URSM = unlikely related to study medication

PRSM = possibly related to study medication

Depressive episodes can be triggered by progestins. The patient with the depression was on the medication for a few weeks when the episode occurred. The sponsor is showing some inconsistency by labeling one cervical dysplasia as possibly related to study medication and the other unlikely. The relationship of OCPs to cervical dysplasia has been controversial and this reviewer feels that the relational risk is low compared to sexual activity and human papillomavirus exposure.

Serious adverse events in the Ortho Tri-Cyclen® Lo and Loestrin® treatment groups are summarized in Table 17. Serious adverse events reported by more than one subject per treatment group were limited to carcinoma (two subjects in the Ortho Tri-Cyclen® Lo group), pneumonia (two subjects in the Ortho Tri-Cyclen® Lo group), and inflicted injury (two subjects in the Ortho Tri-Cyclen® Lo group and one subject in the Loestrin® treatment group).

**APPEARS THIS WAY
ON ORIGINAL**

Table 17: Occurrence of Serious Adverse Events
(The Safety Evaluable Population in Study NRGLOW-OC-001)

Body System Primary Term	Ortho Tri-Cyclen® Lo (N=1,723)	Loestrin (N=1,171)
Any serious adverse event	12	7
Body as a whole – general disorders	2	1
Allergic reaction	1	0
Back pain	0	1
Pain	1	0
Central and periph nervous system disorders	1	2
Leg cramps	0	1
Migraine	0	1
Paraplegia	1	0
Gastrointestinal system disorders	0	1
Gastroenteritis	0	1
Musculo-skeletal system disorders	1	0
Bone disorder	1	0
Neoplasms	2	0
Carcinoma	2	0
Psychiatric disorders	2	0
Depression	1	0
Personality disorder	1	0
Reproductive disorders	1	1
Cervical dysplasia	1	0
Ectopic pregnancy	0	1
Resistance mechanism disorders	1	0
Bacterial infection	1	0
Respiratory system disorders	3	2
Asthma	1	1
Bronchitis	0	1
Pneumonia	2	0
Secondary Terms	3	1
Food poisoning	1	0
Inflicted injury	2	1
Vascular (extracardiac) disorders	0	1
Superficial thrombitis	0	1

Brief narratives for the two subjects with serious adverse events categorized as related to study medication are presented below.

**APPEARS THIS WAY
ON ORIGINAL**

Subject 029/029054, a 37-year-old white woman in the Ortho Tri-Cyclen® Lo treatment group, had cervical carcinoma-in-situ (marked, possibly related to study medication) reported as a serious adverse event. The subject had no physical, gynecologic or breast abnormalities at admission. Eleven days after taking her last scheduled dose of study medication, the subject had her scheduled final study visit procedures performed. The Pap smear results from the subject's end of study visit revealed a squamous carcinoma in situ. The subject had a colposcopy but the results were unknown as of the date of this ISS.

Subject 019/019004, a 36-year-old White woman in the Loestrin treatment group, had superficial thrombophlebitis of the right leg (moderate, probably related to study medication) reported as a serious adverse event. The subject took her first dose of study medication on 13 April 1997. On 21 November 1997, the subject complained of a pain in her right popliteal area that had started on 15 November 1997. A superficial thrombus was confirmed by Doppler ultrasound, and treated with aspirin. The subject was discontinued from the study on 22 November 1997. An ultrasound exam on 31 December 1997 indicated that the blood clot had resolved.

Medical officer's comments: The above table was corrected to 12 instead of 11 based on the number of SAE related events reported in the case summaries.

Discontinuation

Reasons for discontinuation for subjects included in the safety population are presented in Table 18. Information concerning the reason for discontinuation was obtained from the study termination CRF.

The incidence of discontinuation for specific reasons was similar across treatment groups. The most frequently stated reason for premature discontinuation was "subject choice" (Ortho Tri-Cyclen® Lo, 11.6%; Loestrin, 11.1%) and lost to follow-up (Ortho Tri-Cyclen® Lo, 6.5%; Loestrin, 5.8%). The incidence of discontinuation due to adverse events was 4.2% and 3.4%, respectively.

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Table 18: Summary of Reasons for Discontinuation
(The Safety Evaluable Population in Study NRGLOW-OC-001)

Reason for Discontinuation	Ortho Tri-Cyclen® Lo (N=1,723)		Loestrin (N=1,171)	
	N	(%)	N	(%)
Sponsor's Decision to Discontinue Study Regimen	4	(0.2)	3	(0.3)
Subject Choice	200	(11.6)	130	(11.1)
Lost To Follow-up	112	(6.5)	68	(5.8)
Adverse Event	73	(4.2)	40	(3.4)
Pregnancy	21	(1.2)	22	(1.9)
Protocol Violation	14	(0.8)	15	(1.3)
Other	37	(2.1)	22	(1.9)
Total	461	(26.8)	300	(25.6)

Medical officer's comments: Adverse events leading to discontinuation included such problems as headache, superficial phlebitis, cervical dysplasia, ovarian cyst, hypertension, depression, and erythema nodosum. The relationship between erythema nodosum and oral contraceptives originally dates to 1967 in a New England Journal article. The cases of hypertension, depression, and cervical dysplasia are different case numbers than those listed under SAE.

Other adverse events:

There was no indication that treatment with Ortho Tri-Cyclen® Lo increased the incidence of adverse events, relative to the active control group, in the Phase 3 or Phase 2 studies. Most adverse events experienced by subjects in these studies are common in women taking oral contraceptives (headache, nausea, abdominal pain, etc.). In the Phase 3 study, the incidence of treatment emergent adverse events (TEAEs) related to study medication and those categorized as "marked" was similar in the Ortho Tri-Cyclen® Lo and Loestrin treatment groups. Review of specific types of adverse events important in the evaluation of an oral contraceptive did not reveal a higher incidence in subjects treated with Ortho Tri-Cyclen® Lo than in control groups.

Between 74% and 81% of the subjects in each treatment group reported one or more adverse events during the study (table 19). The most frequently reported TEAEs in the Ortho Tri-Cyclen® Lo or Loestrin® treatment groups were headache (29.4% and 27.0%, respectively); upper respiratory tract infection (16.8% and 17.8%, respectively); nausea (14.7% and 13.8%, respectively); abdominal pain (13.7% and 14.3%, respectively); breast pain (9.8% and 7.9%, respectively); dysmenorrhea (9.7% and 7.3%, respectively); and sinusitis (9.1% and 8.4%, respectively).

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**Table 19: Incidence of TEAEs Occurring in ≥5% of Subjects in Either Treatment Group
(The Safety Evaluable Population in Study NRGLOW-OC-001)**

Body System Preferred Term	Ortho Tri-Cyclen® Lo (N=1,723)		Loestrin (N=1,171)	
	N	(%)	N	(%)
Any Adverse Event	1,347	(78.2)	915	(78.1)
Body as a whole-general disorders				
Back pain	102	(5.9)	74	(6.3)
Influenza-like symptoms	96	(5.6)	62	(5.3)
Central and peripheral nervous system disorders				
Headache	506	(29.4)	316	(27.0)
Gastrointestinal system disorders				
Abdominal pain	236	(13.7)	168	(14.3)
Nausea	253	(14.7)	162	(13.8)
Psychiatric disorders				
Emotional lability	106	(6.2)	61	(5.2)
Reproductive disorders				
Female breast pain	169	(9.8)	92	(7.9)
Dysmenorrhea	167	(9.7)	86	(7.3)
Resistance mechanism disorders				
Genital moniliasis	102	(5.9)	72	(6.1)
Respiratory system disorders				
Sinusitis	157	(9.1)	98	(8.4)
Upper respiratory tract infection	289	(16.8)	209	(17.8)
Skin and appendages disorders				
Acne	91	(5.3)	50	(4.3)

Adverse events related to oral contraceptive use:

Evaluations of certain types of TEAEs are important in the assessment of an oral contraceptive, independent of their incidence. These would include any of the following events:

- **Hypertension:** The incidence of hypertension was similar in the Ortho Tri-Cyclen® Lo treatment group (0.7%), and in the Loestrin treatment group (0.4%). Hypertension was generally categorized as mild or moderate in severity; only one subject in the Ortho Tri-Cyclen® Lo group had “marked” hypertension. The incidence of hypertension considered related to study medication was similar in the Ortho Tri-Cyclen® Lo (0.5%) and Loestrin (0.2%) treatment groups. Hypertension led to the permanent discontinuation of study medication in two subjects in the Ortho Tri-Cyclen® Lo group and one subject in the Loestrin treatment group. No subjects reported hypertension as an SAE.
- **Weight Gain:** The percentage of subjects reporting weight increase was similar in the Ortho Tri-Cyclen® Lo (2.4%) and Loestrin (2.1%) treatment groups. Most of the subjects had their weight gain categorized as mild or moderate. Marked weight gain was reported for 0.3% of subjects in both treatment groups. Weight gain was generally considered related to study medication in both treatment groups. Weight

gain was associated with the permanent discontinuation of study medication for one subject in the Ortho Tri-Cyclen® Lo group and five subjects in the Loestrin treatment group.

- **Neoplasms:** The incidence of neoplasms was similar in the Ortho Tri-Cyclen® Lo and Loestrin treatment groups (1.7% and 1.8%, respectively). Most subjects who had an event that coded as a neoplasm had a breast fibroadenoma or ovarian cyst.
- **Thrombosis:** Thrombotic events were extremely uncommon. There was no case of deep vein thrombosis or pulmonary embolus in any subject in any treatment arm of the Phase 3 study. Two subjects in the Ortho Tri-Cyclen® Lo treatment group had mild to moderate superficial phlebitis considered probably related to study medication, and one subject in the Loestrin treatment group had moderate superficial thrombophlebitis considered probably related to study medication.
- **Depression:** The incidence of depression was similar in the Ortho Tri-Cyclen® Lo (3.3%) and Loestrin® (3.4%) treatment groups. The incidence of “marked” depression also was similar among the treatment groups (Ortho Tri-Cyclen® Lo, 0.9%; Loestrin®, 0.6%). There was no notable difference in the incidence of depression related to study medication in the Ortho Tri-Cyclen® Lo treatment group (1.9%) or Loestrin treatment group (2.3%). The incidence of depression as a reason for permanent discontinuation of treatment was similar for the Ortho Tri-Cyclen® Lo regimen (0.2%) and for Loestrin® (0.3%). One subject in the Ortho Tri-Cyclen® Lo regimen reported depression as a serious adverse event.
- **Visual Disorders:** Vision abnormalities were uncommon overall. The incidence of abnormal vision was similar in the Ortho Tri-Cyclen® Lo treatment group (0.5%) and in the Loestrin treatment group (0.3%). The incidence of abnormal vision related to study medication was 0.2% in both treatment groups. Ocular hemorrhage (mild, unlikely to be related to treatment) was reported for one subject in the Ortho Tri-Cyclen® Lo group.
- **Migraine:** The percentage of subjects who reported migraine as an adverse event was similar for Ortho Tri-Cyclen® Lo and for Loestrin® (2.1% and 1.8%, respectively). About half of the subjects with migraine in both groups reported the severity as marked. Most migraine events were considered unlikely or possibly related to study treatment for both groups. Migraine as an associated reason for discontinuation of study treatment occurred in 0.1% of Loestrin subjects and 0.4% of Ortho Tri-Cyclen® Lo subjects. Only one subject reported migraine as a serious adverse event and that subject was on Loestrin®.
- **Laboratory abnormalities:** There were no clinically meaningful differences among treatment groups based on mean change from baseline or on categorical shift into or out of normal range for any laboratory analyte. There were no clinically noteworthy pre- to post-study changes in vital signs, body weight, physical or gynecologic examination findings, or PAP smears based on treatment assignment. There were no

clinically meaningful changes in mean values for any red blood cell indices, white blood cell counts or differentials, liver enzyme values, or any other laboratory tests, based on changes between baseline and Cycle 6, baseline and Cycle 13, or baseline and last visit.

- **Reproductive Disorders:** There was one subject in the Loestrin treatment group with an ectopic pregnancy. The incidence of ovarian cysts was very low overall and similar in the Ortho Tri-Cyclen® Lo (0.9%) and Loestrin® (0.6%) treatment groups. The incidence of ovarian disorders was also similar in the Ortho Tri-Cyclen® Lo (0.3%) and Loestrin® (0.6%) treatment groups.

Safety Updates:

Both the four-month safety update from Dec 15, 2000 and the final safety update from June 8, 2001 indicated that there were no additional safety concerns identified.

Phase 2 Study (K90-023)

In the Phase 2 study, safety results in the Ortho Tri-Cyclen® Lo group are compared to those in the Ortho Tri-Cyclen group.

Safety was assessed from adverse events (AEs), and changes in clinical laboratory parameters, blood pressure, and weight from pretreatment to posttreatment. Safety also was assessed from physical and gynecologic exams and Pap smears taken pre- and posttreatment.

There was one subject in the Ortho Tri-Cyclen® Lo group with a moderate level adverse event (hypertension, definitely related to study medication). A narrative appears below.

Subject 1025, a 37-year-old woman in the Ortho Tri-Cyclen® Lo treatment group, had hypertension (moderate, related to study drug) reported as a serious adverse event. At the prestudy visit on 20 August 1991 her blood pressure was 108/62 mmHg. At the Cycle 1 visit on 16 September 1991 (Study Day 22) her blood pressure was 144/92 mmHg, and at the Cycle 3 visit on 5 November 1991 (Study Day 72, the last cycle of this study), it was 160/88 mmHg. This adverse event was considered by the investigator to be definitely drug related and the severity was classified as moderate. She was advised not to take oral contraceptives. At a poststudy follow-up on 24 January 1992, her blood pressure was 136/70 mmHg.

Discontinuations in Study K90-023 are listed in the following table.

**Table 20: Discontinuations Due to Adverse Events
(Safety Evaluable Population in Study K90-023)**

Treatment Group	Subject No.	Adverse Events Leading to Discontinuation
Tri 35/180,215,250	914	Headaches
	522	Nausea and breast tenderness
Tri 25/180,215,250	715	Pain in chest
	907	Breakthrough bleeding
	504	Vaginal bleeding
	605	Nausea and vomiting
	419	Right leg bruising, numbness, tingling, warm sensation, aching

Two of the above cases are described in greater detail:

Subject 419, a 33-year-old woman in the Ortho Tri-Cyclen® Lo treatment group, was discontinued from the study on Day 18 due to aching, numbness, tingling, a warm feeling, and increased bruising in the right leg that had started the previous day. All of these adverse events were of moderate severity and were considered possibly drug related. A physical examination on the day of discontinuation showed bruising on the right leg, but no phlebitis or clots. On examination four months later, no bruising was evident.

Subject 715, a 33-year-old woman in the Ortho Tri-Cyclen® Lo treatment group, was discontinued from the study on Day 5 due to mild chest pain which started on study Day 2, and which was considered to be possibly drug related. The chest pain was later evaluated as evidently due to physical activity.

The most frequently reported adverse events in the Ortho Tri-Cyclen® Lo and Ortho Tri-Cyclen treatment groups were headache (35% and 38%, respectively) and nausea (28% and 27%, respectively). There were few notable differences between treatment groups in the incidence of common adverse events

Phase 1 Study (NRGLOW-PHI-001)

Safety evaluations were based on changes in physical and gynecologic examination findings, vital signs, clinical laboratory tests (hematology, serum chemistry, and urinalysis) from prestudy to poststudy, and TEAEs reported throughout the study.

There were no serious adverse events in the Phase 1 studies.

Fourteen (88%) of the 16 subjects reported at least one TEAE during the study. As seen in Table 23, the most common TEAEs were headache (9 subjects, 56%), nausea (5 subjects, 31%), and vomiting (4 subjects, 25%). Most events were rated as moderate or mild in severity, and considered probably or possibly related to study medication.

D. Adequacy of Safety Testing

Medical officer's comments: The safety testing was adequate and appropriate for an oral contraceptive study. No toxicologic or clinical findings indicate the need for further assessment.

E. Summary of Critical Safety Findings

There were no deaths in the Ortho Tri-Cyclen® Lo or the Loestrin treatment arms of the pivotal study. There was one death in the Cyclophasic 25/180,250-treatment arm secondary to gastric adenocarcinoma. This death is unlikely to be related to study medication.

There were a total of 13 serious adverse events recorded for Ortho Tri-Cyclen® Lo (12 in the pivotal phase 3 trial and one in the phase 2 trial). Of these 13, only one case of hypertension and one case of depression are felt by this reviewer to be related to study medication. The case of hypertension resolved on study medication discontinuation. There were no cases of deep vein thrombosis or pulmonary embolism reported in any of the clinical studies.

In the adverse events leading to discontinuation there was no significant findings apart from those events that would either be known events related to oral contraceptive use or common for this age group.

VIII. Dosing Regimen, and Administration Issues

There are no concerns in regard to dosing or administration.

IX. Use in Special Populations

Although increasing body weight and body surface area showed a slight trend toward decreased AUC and C max, there was no indication in the pivotal study that increased BMI was unduly represented in the subjects who became pregnant.

Although the clinical studies indicated a higher pregnancy rate among non-white subjects, further analysis did not reveal that this was related to method failure.

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X. Conclusions and Recommendations

Despite some reservations on the clinical benefit of the lower estrogen dose, this product can be approved based on the following arguments:

- Historically the agency has approved products with equal or higher Pearl Indices (Estrostep® 2.4, Trinorinyl® 2.6, Brevicon® 5.18, and Norinyl® 2.51)
- Ortho Tri-Cyclen® Lo demonstrated a lower pregnancy rate than an approved oral contraceptive Loestrin® in the pivotal phase III trial for efficacy and safety.
- Though no strong benefit was demonstrated in either cycle control or estrogenic side effects by the pivotal study or historical comparison there may be benefits for individual patients in taking a lower amount of estrogen.
- There are no safety concerns for this product over and above the risks typically associated with low dose oral contraceptive products.

The labeling for this product should reflect the contraceptive efficacy results from the pivotal phase 3 trial.

XI. Appendix

Abbreviations:

AE = Adverse event
ALT = Alanine transaminase
AST = Aspartate transaminase
Alk Phos = Alkaline phosphatase
 β subunit HCG = β -subunit human chorionic gonadotropin
BBS = Breakthrough bleeding and/or spotting
BMI = Body mass index
BUN = Blood urea nitrogen
CI = Confidence interval
CIS = Carcinoma-in-situ
COC = Combination oral contraceptive
CRF = Case report form
DRUDP = Division of Reproductive and Urologic Drug Products
DSG = desogestrel
EE = Ethinyl estradiol
EWF = Early withdrawal flow
FDA = United States Food and Drug Administration
GCP = Good Clinical Practice
HCT = Hematocrit
HGB = Hemoglobin
IM = Intermenstrual

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ITT = Intent-to-Treat (population)
ISE = Integrated summary of efficacy
ISS = Integrated summary of safety
kg = Kilogram(s)
lb = Pounds(s)
LDH = Lactic dehydrogenase
LMP = Last menstrual period
Loestrin = Loestrin • Fe 1/20
mmHg = Millimeters of mercury
mg = Milligram(s)
mL = Milliliter(s)
ng = Nanogram(s)
NETA = Norethindrone acetate
NGM = Norgestimate
NGMN = Norelgestromin
OC = Oral contraceptive
OR = Odds Ratio
Pap = Papanicolaou smear
RBC = Red blood cell(s)
RIA = Radioimmunoassay
RR = Relative risk
RWJPRI = The R. W. Johnson Pharmaceutical Research Institute
SAE = Serious adverse event
SD = Standard deviation
SE = Standard error
SGOT = Serum glutamic oxaloacetic transaminase (same as AST)
SGPT = Serum glutamic pyruvic transaminase (same as ALT)
STD = Sexually transmitted disease
TEAE = Treatment-emergent adverse event
WHOART = World Health Organization Adverse Reaction Terminology

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Definitions:

Amenorrhea = Two consecutive cycles without bleeding or spotting in the absence of pregnancy

Breakthrough bleeding = Vaginal bleeding that requires sanitary protection (at least one pad or tampon per day)

Breakthrough bleeding and/or spotting (BBS) = For each cycle, bleeding or spotting during the active tablet-taking interval that is neither early withdrawal flow or withdrawal flow continuing from the previous cycle

Early withdrawal flow (EWF)= Any bleeding or spotting during the active tablet-taking interval that begins during the active tablet-taking interval and continues without interruption into the inactive tablet-taking interval

Intermenstrual bleeding (IMB) Any BBS and/or EWF that occurs during the active tablet-taking interval that is not withdrawal flow continuing from the previous cycle

ITT evaluation = Intent to treat evaluation that includes all subjects who received at least one dose of study medication and all on-therapy cycles during which study medication was taken

Latent period = Number of days with no bleeding/spotting from the beginning of the treatment-free interval to the first day of withdrawal flow.

Life table analysis = Estimate of the cumulative probability of not becoming pregnant while receiving study medication

Method failure = Pregnancy resulting from failure of the study medication to prevent conception under conditions of use enumerated in the instructions to subjects

Odds ratio = Contrast of pregnancy rates with test regimen versus reference regimen

Overall failure = Includes all on-therapy pregnancies, i.e., the sum of method failures and user failures

Pearl Index = Estimate of the number of pregnancies per 100 woman-years of product use, calculated as (# on-therapy pregnancies X 1300) / # on-therapy cycles

Perfect compliance = A cycle in which 21 active tablets are taken during a 21-day active tablet-taking interval followed by 7 inactive tablet-taking days

Breakthrough spotting = Vaginal bleeding that does not require sanitary protection

User failure = Pregnancy resulting from the subject's failure to use the study medication according to the instructions to subjects

Related INDs

IND 11,391 = Norgestimate/ethinyl estradiol tablets

IND 50,488 = 17-deacetylnorgestimate/ethinyl estradiol transdermal contraceptive patch

Related NDAs

NDA 19-697 = Ortho Tri-Cyclen (Approval date: Jul 3, 1992) - contraceptive

NDA 19-653 = Ortho-Cyclen 21, Ortho-Cyclen 28 (Approval date: Dec 29, 1989) -
contraceptive

NDA 21-040 = Ortho-Prefest (Approval date: Oct 22, 1999) – vasomotor, vulvo-vaginal
atrophy, prevention of osteoporosis

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