

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-241

STATISTICAL REVIEW(S)

NDA 21-241

ORTHO TRI-CYCLEN Lo
Norgestimate/ethinyl estradiol

Johnson & Johnson Pharmaceutical Research & Development,
L.L.C.

3S

PM: Jennifer Mercier
HFD-580
7-4260

Statistical Review
N/A

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8/21/02

APPEARS THIS WAY
ON ORIGINAL

Statistical Review and Evaluation Clinical Studies

NDA #: 21-241
Applicant: R.W. Johnson
Name of Drug: _____ (NGM (180/215/250) and EE (25))
Indication: Oral Contraception
Medical Reviewer: Gerry Willett, M.D., HFD-580
Statistical Reviewer: Moh-Jee Ng, M.S., HFD-715
45-Day Filing Date October 3, 2000

1. Introduction

The sponsor presented the results of one clinical study to establish the efficacy of _____ for _____ is a 28-day oral contraceptive. 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. The study required at least 10,000 cycles of exposure and at least 200 women completing a minimum of 13 cycles in each of the NGM/EE treatment groups.

**Table 1
Summary of a Clinical Study**

Study Number Start/Completed Date	Trial Design	Treatment Groups Application Times	# Subjects Randomized/Evaluated
NRGLOW-OC-001 3/17/97-6/10/98	Multicenter, randomized, double-blind (except Loestrin), parallel-group study, and contraceptive efficacy study of 2 cyclophasic and one triphasic investigation treatment regimens of NGM/EE with open-label Loestrin Control	Triphasic-25 NGM 180, 215, 250/EE 25 NGM 180 g / EE 25 g days 1-7 NGM 215 g / EE 25 g days 8-14 NGM 250 g / EE 25 g days 15-21 Placebo days 22-28	1,826 randomized; 1723 evaluated for safety; 1673 evaluated for efficacy
		Cyclophasic-25 NGM 180, 250/EE 25 NGM 180 g / EE 25 g days 1,2,5,6,9,10,13,14,17,18,21 NGM 250 g / EE 25 g Days 3,4,7,8,11,12,15,16,19,20 Placebo days 22-28	1,828 randomized; 1,740 evaluated for safety; 1,700 evaluated for safety
		Cyclophasic-20 NGM 60, 180/EE 20 NGM 60 g / EE 20 g Days 3,4,7,8,11,12,15,16,19,20 NGM 180 g / EE 20 g Days 1,2,5,6,9,10,13,14,17,18,21,22 Placebo days 23-28	1,474 randomized; 1,388 evaluated for safety; 1,337 evaluated for safety
		Loestrin 100 g NETA/20 g EE days 1-21 Placebo days 22-28	1,233 randomized; 1,171 evaluated for safety; 1,141 evaluated for safety

2. Clinical Study NRGLOW-CO-001

This was a randomized, double-blind, comparative, multicenter contraceptive efficacy study of one triphasic and two cyclophasic treatment regimens of norgestimate (NGM) and ethinyl estradiol (EE) with an open-label control regimen of Loestrin.

The study was designed to include a blinded interim analysis. The objective of the interim analysis was to evaluate the cycle control of the 3 blinded regimens of NGM/EE in comparison with Loestrin and to discontinue the NGM/EE treatment group having the poorest cycle control compared with Loestrin. The interim analysis was performed on Cycle 1-3 of 1100 subjects: approximately the first 300 subjects enrolled in each of the 3 NGM/EE regimens and the first 200 subjects enrolled in the Loestrin regimen. Cyclophasic-20/60,180 was discontinued because it has the poorest cycle control at the interim analysis. Table 2 below (Vol. 1.054, Table 3 & 4) summarizes the reasons for subject discontinuation.

Table 2
Enrollment and Disposition of Study Subjects

	Loestrin	Tri 25/180,215,250	Cyc 25/180,250	Cyc 20/60,180
Number randomized	1233	1821	1828	1474
Number discontinued	300 (26%)	461 (27%)	520 (30%)	1318 (95%)
Sponsor's decision to discontinue study regimen	3 (.3%)	4 (0.2%)	5 (0.3%)	982 (71%)
Subject choice	130 (11%)	200 (12%)	205 (12%)	169 (12%)
Lost to follow-up	68 (6%)	112 (7%)	126 (7%)	69 (5%)
Adverse event	40 (3%)	73 (4%)	96 (6%)	57 (4%)
Pregnancy	22 (2%)	21 (1%)	32 (2%)	16 (1%)
Protocol violation	15 (1%)	14 (1%)	15 (1%)	6 (0.4%)
Other	22 (2%)	37 (2%)	40 (2%)	19 (2%)
Unknown	0	0	1 (0.1%)	0
Total of subj. discontinued	300 (26%)	461 (27%)	520 (30%)	1318 (95%)

Triphasic 25 (Tri-25) consists of NGM 180, 215 and 250 g in seven-day increments and daily EE 25 g. Cyclophasic 25 (Cyc-25) consists of NGM 180, 250 g and Cyclophasic 20 (Cyc-20) consists of NGM 60, 180 g. Both Cyc-25 and Cyc-20 consist of daily 25 g EE. Loestrin consists of 1 mg norethindrone acetate and 20 g EE. Both starters, who had not used oral contraceptive (OC), and switchers, who had been using another OC, were recruited.

3. Sponsor's Efficacy Results

Contraceptive effectiveness was based on pregnancy rates using the Pearl Index and Life-Table analysis in the intent-to-treat (ITT) evaluation group. The ITT consists of subjects who took the study drug and were not pregnant at the initiation of therapy. However, the sponsor exclusive total of 38 subjects enrolled at the Site 011 claiming data from that site were unevaluable.

One hundred and nineteen pregnancies were reported (see Table 3):

Pre-treatment pregnancies - those in which conception occurred prior to intake of study medication: 3 in Loestrin, 2 in Tri-25, and 4 in Cyc-25.

On-therapy pregnancies - those in which conception occurred while taking study medication : 19 in Loestrin, 20 in Tri-25, 30 in Cyc-25, and 16 in Cyc-20.

Post-treatment pregnancies – those in which conception occurred after the last study medication was taken: 8 in Loestrin, 8 in Tri-25, 5 in Cyc-25, and 4 in Cyc-20.

Table 3
Summary of all Pregnancies

	Loestrin	Tri 25/180,215,250	Cyc 25/180,250	Cyc 20/60,180
Pre-Treatment Pregnancies	3	2	4	0
On-therapy pregnancies	19	20	30	16
User failure	2	6	8	1
Method failure	17	14	22	15
Post-treatment pregnancies	8	8	5	4
Total Pregnancies	30	30	39	20

The primary efficacy endpoint for this study was the Pearl Index for all on-therapy pregnancies. The Pearl Index (for all on-therapy or method failures) is defined as the number of on-therapy pregnancies (all or method failure) times 1,300 divided by the total number of on-therapy cycles.

The Pearl Indices for all on-therapy pregnancies were 3.29 for Loestrin, 2.36 for Tri-25, 3.58 for Cyc-25, and 4.07 for Cyc-20. The Pearl indices for method failure pregnancies were 2.95 for Loestrin, 1.65 for Tri-25, 1.65 for Cyc-25, and 3.81 for Cyc-20. The sponsor claimed that the Pearl Indices for all pregnancies and for method failures were lower in the Tri-25 treatment group than in the Loestrin and Cyc-25 treatment groups. The Pearl Indices were highest in the Cyc-20 treatment group (see Table 4).

The Life Table Method estimates the proportion of pregnancies in a fixed time period using a Kaplan-Meier procedure. The endpoint of interest was the 13 cycle cumulative probability of pregnancy for each of the NGM/EE treatment groups except Cyc-20 discontinued after the interim analysis. The sponsor used SAS PROC LIFETEST to compute life-table pregnancy rates. The life-table pregnancy rates of all on-therapy pregnancies were 0.976 for Loestrin, 0.985 for Tri-25, and 0.978 for Cyc-25. The Life-table pregnancy rates for method failure pregnancies were 0.976 for Loestrin, 0.98 for Tri-25, and 0.968 for Cyc-25 (see Table 4).

The sponsor implemented a proportional hazard analysis to compute the relative risks of pregnancy to contrast the NGM/EE treatment groups with the Loestrin treatment group. The endpoint of interest was at the 13 cycles for each of the NGM/EE treatment groups that were not discontinued after the interim analysis.

The relative risks for all on-therapy pregnancies were 0.717 [95% CI (0.383, 1.343)] for the Tri-25 and 1.09 [95% CI (0.613, 1.936)] for Cyc-25 treatment groups, respectively, relative to Loestrin. The sponsor claimed that these results indicate that a subject in the

Loestrin treatment group would be more likely to become pregnant than a subject in the Tri-25, but equally as likely to become pregnant as a subject in the Cyc-25 treatment group. However, these treatments comparison are not statistically significant.

The Relative Risks for method failure pregnancies were 0.56 [95% CI (0.276, 1.138)] for the Tri-25 and 0.894 [95% CI (0.475, 1.683)] for Cyc-25 treatment groups.

The medical reviewer requested (March 21, 2001) an additional sponsor analysis stratified by age (see Table 4).

Table 4
Sponsor's Efficacy Results
Intent-to-Treat Evaluation Group

Treatment groups	Loestrin		Tri 25/180,215,250		Cyc 25/180,250		Cyc 20/60,180	
Total # of subjects	1,141		1,673		1,700		1,337	
Total cycle of exposures	7,497		11,003		10,894		5,113	
Total # of women-years	576.7		846.4		838.		393.3	
All on-therapy								
On-therapy pregnancies	19		20		30		16	
Pearl Index (95% CI)	3.29[1.81,4.77]		2.36[1.33,3.4]		3.58[2.3,4.86]		4.07[2.08,6.06]	
RR [95% CI] for pregnancy Compared to Loestrin (P-value)	-		0.717[0.383,1.343] (0.299)		1.09[0.613,1.936] (0.77)		-	
Life table Cycle 13 [95%CI]	0.974[0.958,0.989]		0.981[0.971,0.992]		0.968[0.953,0.983]			
Method Failure								
On-therapy pregnancies	17		14		22		15	
Pearl Index (95% CI)	2.95[1.55,4.35]		1.65[0.79,2.52]		2.63[1.53,3.72]		3.81[1.89,5.74]	
RR [95% CI] for pregnancy Compared to Loestrin (P-value)	-		0.561[0.276,1.138] (0.109)		0.894[0.475,1.683] (0.728)		-	
Life table Cycle 13 [95%CI]	0.976[0.961,0.99]		0.985[0.975,0.995]		0.978[0.966,0.99]			
Stratified by age (< 35 or > 35 years old)								
	Loestrin		Tri 25/180,215,250		Cyc 25/180,250		Cyc 20/60,180	
Age (years)	<35	>35	<35	>35	<35	>35	<35	>35
Total # of subjects	943	198	1351	321	1410	290	1087	249
Total cycle of exposures	6160	1337	8773	2224	8894	2000	4159	951
Total # of women-years	473.8	102.8	674.8	171.1	684.2	153.8	319.9	73.2
All on-therapy								
On-therapy pregnancies	18	1	18	2	29	1	14	2
Pearl Index	3.8	0.97	2.67	1.17	4.24	0.65	4.38	2.73
Method Failure								
On-therapy pregnancies	16	1	12	2	21	1	13	2
Pearl Index	3.38	0.97	1.78	1.17	3.07	0.65	4.06	2.73

4. Reviewer's Analyses and Comments

This reviewer's analyses are based on ITT evaluation group based on the data provided in the submission. The result of this reviewer's analysis are consistent with the sponsor's efficacy results (see Table 4).

The observed relative risks for all on-therapy pregnancies and method failure pregnancies in women who received Tri-25 are less than one (.717 and .561, respectively), indicating that a subject in the Tri-25 would be less likely to become pregnant than a subject in the Loestrin treatment group. However, the differences are not statistically significant. The results of these analyses suggest the risk of pregnancy among Tri-25 women did not appear to differ from that for Loestrin treated women.

Moh-Jee Ng, M.S.
Mathematical Statistician

Concur: Michael Welch, Ph.D.

Ed Nevius, Ph.D.

cc: Original NDA 21-241
HFD-580 / Division File
HFD-580/Gerry Willett, M.D.
HFD-580/Jennifer Mercier, B.S.
HFD-715/ENevius, MWelch, CAnello, MNg

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this page is the manifestation of the electronic signature.**

/s/

Moh-Jee Ng
6/22/01 01:24:12 PM
BIOMETRICS

Mike Welch
6/22/01 01:59:27 PM
BIOMETRICS
Concur

S. Edward Nevius
6/22/01 02:17:40 PM
BIOMETRICS
Concur with review.

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8. From a statistical perspective, is this NDA fileable? If "no", please states below why it is not.

Yes No

✓

Summary of All Clinical Studies

Study Number Start/Completed Date	Trial Design	Treatment Groups Application Times	Subjects Enrolled/Cycle of Exposures
NRGLOW-OC-001 3/17/97-6/10/98	Randomized, comparative multicenter safety and contraceptive efficacy study of 2 cyclophasic and one triphasic investigational treatment regiments of NGM/EE with open-label Loestrin Control	Tri 25/180, 215, 250 NGM 180µg / EE 25 µg days 1-7 NGM 215µg / EE 25 µg days 8-14 NGM 250µg / EE 25 µg days 15-21 Placebo days 22-28	1,826/11,003
		Cyc 25/180, 250 NGM 180µg / EE 25 µg NGM 250µg / EE 25 µg Placebo	1,828/10,894
		Cyc 20/60, 180 NGM 60µg / EE 20 µg NGM 180µg / EE 20 µg Placebo	1,474/5,113
		Loestrin 100 µg NETA/20 µg EE Placebo	1,233/7,497

For Study NRGLOW-OC-001, please provide electronic files, if possible in SAS or ASCII, containing the following variables:

- Study ID
- Subject ID
- Site ID
- Age (in years)
- Race
- Height
- Weight
- Alcohol use
- Smoking
- Body Mass Index
- Starter/Direct Switcher/Indirect Switcher
- Number of pregnancies before study entry
- Number of live births before study entry
- Date on which first study medication is taken

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If Subject became pregnant, provide: (On-therapy pregnancies/on-therapy method failure)

