CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-864

STATISTICAL REVIEW(S)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIOSTATISTICS

ADDENDUM TO THE STATISTICAL REVIEW

NDA:	21-864
Drug Name:	Lybrel (Levonorgestrel/Ethinyl Estradiol)
Sponsor:	Wyeth Research
Indications:	Oral contraception
Medical Officer:	Phill Price, M.D., HFD-580
Project Manager:	John Kim
Submission Date:	May 4, 2007
Clinical Team Leader:	Shelley Slaughter, M.D., HFD-580
Statistical Reviewer:	Mahboob Sobhan, Ph.D., DB3
Biometrics Div. Director:	Stephen Wilson, Ph.D., DB3

Key Words: NDA Review, Life Table analysis.

This is an addendum to the Physician Insert Label for Lybrel (May 15, 2007). The statistical team's recommendation for the revised label pertains only to the efficacy results in the Clinical Studies section of the label. The statistical review team is in agreement with the Clinical review team with respect to sponsor's revised efficacy data (Pearl Index and life table estimates: Addendum to the statistical review, dated April 27, 2007) in the revised label.

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This is an addendum to the statistical review of Lybrel NDA 21-864, dated 6/21/2006. This submission pertains to Wyeth's adjusted life table analysis as requested by the Division, based on the same pill packs used to calculate the Pearl index in the original submission. In the original submission, approximately 3000 pill packs were excluded from the life table analysis, which were mostly due to the use of back-up contraception. Current analysis included those pill backs for a total of 12,572 pill packs. Results of the sponsor's analysis, which is confirmed by reviewer's analysis, are shown in Table 1.

Table 1

Study 313-NA Life Table Analysis: All Eligible 28-day Pill Packs: Subjects Aged 35 Years or Younger

Pregnancy Classification	Number of Pregnancies	Failure Rate	95% Confidence Interval
On-treatment plus <=14 post-treatment	23	2.39	(1.57, 3.62)
On-treatment plus <=7 post-treatment	21	2.18	(1.41, 3.36)
On-treatment excluding 1 to14 days post-treatment	19	1.99	(1.26, 3.15)
Method failure	15	1.59	(0.95, 2.67)
User failure	4	0.40	(0.15, 1.12)

Reviewer's Comment:

Based on the analysis including all pill packs that were temporarily censored for back-up contraception, the failure rates estimated by life table analysis were consistently similar to Pearl Index (shown in the original submission) in study 313-NA.

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1.0 EXECUTIVE SUMMARY OF STATISTICAL REVIEW

1.1 Conclusion

This application reports data from two studies: a North American (NA) study and a European study to support the contraceptive safety and efficacy of Lybrel (continuous-use regimen of levonorgestrel and ethinyl estradiol). In the NA study (n=2134), Lybrel was not as efficacious as other recently approved OCs as measured by Pearl index and life table analysis, while in the European study (n=323), Lybrel was efficacious despite inadequate study size. From a statistical perspective, demonstrating efficacy based on sponsor's post hoc combined analysis without exploring the plausible if not conclusive explanations for heterogeneity of results between studies by formal methods, is unacceptable.

1.2 Overview of the Study

The sponsor has submitted safety and efficacy data from two studies: Study 313-NA conducted in North America and Study 313-EU conducted in Europe to demonstrate the effectiveness of Lybrel (continuous use of the combination of LNG 90 µg/EE 20 µg) as an oral contraceptive. Of the two, the NA study was an open-label uncontrolled study while the European study was a randomized study where subjects were randomized to receive either continuous regimen or cyclic regimen of LNG 100 µg/EE 20 µg. The primary efficacy endpoint was the pregnancy rate by Pearl Index and life table method. The intent-to-treat analysis population included all on-therapy pregnancies (including pregnancies in days 1 to 14 post-treatment.

A total of 2134 subjects in the NA study and 641 subjects (323 in Lybrel and 318 in cyclic regimen) in the European study were dosed with at least 1 dose of study drugs. Of these dosed subjects, 57% and 33% discontinued from the NA and European studies, respectively. The primary reason for discontinuation was adverse event, mainly due to bleeding, and appeared higher than seen in other recently approved oral contraceptive products.

As per sponsor's protocol, the primary efficacy analysis was based on pregnancies classified as on-therapy when the estimated date of conception occurred between the start of the study drug and 14 days after stopping study drugs in each study. Contraceptive efficacy was evaluated by Pearl index and life table analysis for each study separately and by combining both studies. The primary efficacy was based on the results from each study, rather than results from combined analysis, according to sponsor's statistical analysis plan.

1.3 Principal Findings

(1) In the larger US study, based on 23 pregnancies in subjects aged 35 years or younger, the Pearl index was 2.38 (95% CI: 1.51, 3.57) and the life table estimated rate was 0.0350 (95% CI: 0.0227, 0.0539) In the European study, based on 1 pregnancy, the Pearl index

was 0.51 (95% CI: 0.01, 2.82) and the life table estimate was 0.0098 (95% CI: 0.0014, 0.0676).

(2) The reasons for the wide variation in the pearl index could be attributable to number of subjects enrolled, and possibly due to differences in the number of pills missed and early discontinuation in NA study compared to late discontinuation in the European study. Despite the heterogeneity in discontinuation rates, the efficacy shown in the larger NA study was not similar to efficacy shown in other recently approved OCs.

(3) The sponsor's post hoc combined analysis that showed a Pearl index of 2.06 (95% CI: 1.32, 3.07) in women 35 years or younger could be subject to bias due to the reasons noted above.

2.0 INTRODUCTION

2.1 Background

This NDA pertains to clinical data to support the safety and efficacy of Lybrel (combination of the continuous-use regimen of levonorgestrel and ethinyl estradiol) as an oral contraceptive (OC). Both LNG (synthetic progestin) and EE (synthetic estrogen) have been widely used OCs, but in an effort to improve the convenience and acceptability of safe and effective OCs, the sponsor claims that their continuous-use regimen of the combination of LNG 90 µg/EE 20 µg is both effective and safe with a better bleeding profile compared to cyclic regimen of LNG 100 µg/EE 20 µg.

To support the safety and efficacy claim, data from three studies were submitted as shown in Table 2.1. Most of the efficacy evidence was from uncontrolled study 313 and controlled study 315. Although phase 2 study 208 provided some supportive data, our review will focus mostly on the two phase 3 studies. Detailed safety evaluation can be found in clinical reviewer's report.

Table 2.1
Summary of Clinical Studies

Study#	Objectives	Study Design	Study Regimen	Number enrolled
208-US	Safety	Single-center, Open-label, Phase 2.	LNG 90 µg /EE 20 µg	58
313-N. America	Safety & Efficacy	Multi-center, Open-label, uncontrolled, Phase 3	LNG 90 µg /EE 20 µg	2134
315-EU	Safety & Efficacy	Multi-center, Open-label, Randomized, Phase 3.	LNG 90 µg /EE 20 µg LNG 100 µg /EE 20 µg	328 323

2.2 Indication

The indication for this product as proposed in the package insert is:

> *Lybrel® is indicated for the prevention of pregnancy in women who elect to use an oral contraceptive.*

2.3 Approaches to the Review

During the review, the clinical and statistical teams identified the following issues:

1) Exclusion of accidental pre- and post-therapy pregnancies from the sponsor's intent-to-treat analysis that may have underestimated the pregnancy rates as measured by pearl index and life table probabilities.
2) Significantly higher rate of drop outs compared to other similar OC products.

3) Less than adequate safety profiles; and

4) Post hoc combined analysis across studies.

The Division requested additional information from the sponsor with regards to issue #1 in order to determine the status of these pregnancies and to decide whether these pregnancies should be included in the analysis or not. In this review, we will focus mostly on the efficacy results and the appropriateness of post hoc combined analysis. Safety issues will be addressed in the clinical reviewer's report. In the following section, first we will describe the study features including design and statistical methods employed, followed by efficacy results and the conclusions in view of the above limitations.

3.0 STATISTICAL EVALUATION

3.1 Study 313-NA

3.1.1 Design and Methods

Design: This was a multi-center, single-treatment, open-label study of the safety and contraceptive efficacy of an OC containing a combination of LNG 90 µg/EE 20 µg in a continuous-use regimen (dispensed as 28-day pill packs). The study was conducted in 80 centers in North America and was composed of a single treatment group. The study included 2 sub studies: 1) a 3-month, cycle-related symptom sub study (CRSS); and 2) an endometrial histology sub study. Study drug was given in 28-day pill packs and each subject was to begin taking the drug (1 pill daily) on the first day of her menstrual cycle and was to continue for 13 cycles. Subjects were given diary cards to record the pills taken or missed. In case of 3 or more consecutive missed pills or any 5 pills during the 28-day pill pack period, the investigator performed a pregnancy test.

The primary objective of this study was to evaluate the safety and contraceptive efficacy of LNG 90 µg/EE 20. The secondary objectives were to evaluate the effects of the combination drugs on vaginal bleeding, endometrial histology, hemostasis measures, hemoglobin levels, discontinuation rates, subject satisfaction, and cycle-related symptoms and work productivity in subjects with these symptoms at baseline. The study was planned to enroll approximately 2000 subjects based on estimated annual drop out rate of 50%.

Primary Efficacy: The Primary efficacy outcome was the number of pregnancies defined as follows:

- On-therapy: estimated date of conception (EDC) occurred between the start of the study drug and 14 days after stopping study drug;
- Pre-therapy: EDC occurred before the start of the study drug;
- Post-therapy: EDC was more than 14 days after the discontinuation of the study drug.

On-therapy pregnancy was attributed to 'method failure' if the subject took 100% of the assigned dose within the 30 days before EDC; attributed to 'user failure' if the subject was compliant with the protocol, could have missed up to 2 consecutive days of pills or up to 4 total days within the 30 days before the EDC.

The secondary efficacy variables included vaginal bleeding and discontinuation rates. In addition, cycle-related symptoms were also evaluated.

Methods of Analysis: The contraceptive efficacy was assessed by pregnancy rates, computed by Pearl index (total, method and user failure) and by life table methods. The Pearl index was defined as number of on-therapy pregnancies divided by the number of pill packs, then multiplied by 1300. The denominator will exclude the pill packs in which:

a) Backup contraception was used,
b) Three or more consecutive days of pills missed,
c) Five or more total days of pills were missed in any pack,
d) Prohibitive medications were taken,
e) Subject was not sexually active, and
f) For subjects who become pregnant, any pack that begins after the estimated date of conception.

Pre-therapy and post-therapy pregnancies and pregnancies of subjects with protocol violations were excluded from the intent-to-treat analysis.

Life table methods describe the probability of getting pregnant over time by treating each cycle of exposure individually. The pregnancy rate was computed for each specific cycle as well as cumulatively from the first cycle to each subsequent cycle of use, by calculating the conditional probabilities of becoming pregnant. For the life table, pill packs meeting the pearl index exclusion reasons, as well as subsequent pill packs, were also excluded from the ITT analysis. Secondary efficacy variables were summarized by descriptive statistics.

3.1.2 Study Results

Subject Disposition: A total of 2134 subjects took at least 1 dose of study drug, of which 1213 (57%) discontinued and 921 (43%) completed the study. The primary reasons for discontinuation are shown in Table 3.1.2a. Two major reasons for discontinuations were subject request (15.7%) and due to adverse events (17%). Among 336 (15.7%) of the subject requests, approximately 10% were due to vaginal bleeding. The study population was predominantly white (77%) with a mean age of 29 years and who took the study drug for a mean of 240 days.

Table 3.1.2a **Number (%) of Subject Disposition**	

Total Enrolled (at least 1 dose)	2134 (100%)
Completed	921 (43%)
Total Discontinued:	1213 (57%)
Accidental pregnancy	19 (0.9%)
AE	363 (17%)
By Study sponsor	102 (4.8%)
Lost to follow-up	223 (10.4)
Protocol violation	140 (6.6%)
Subject Request	336 (15.7%)
Other	30 (1.4%)

Analysis Populations: A total of 18,710 pill packs (women-years of exposure) were reported for the 2134 subjects. Table 3.1.2b shows the disposition of valid pill packs available for calculating the pregnancy rates using both pearl index and life table. Seventeen (17%) percent of the pill packs for pearl index and 51% for life table analysis were not valid as per exclusion criteria noted in section 3.1.3. For life table analysis, pill packs were excluded for more than one reason.

Table 3.1.2b
Disposition of Total Pill Packs Included in the Intent-to-Treat Analysis: Study 313-NA

Disposition	Pill Packs (%)
Total	18,710 (100%)
Excluded	3249 (17%)
Valid for Analysis*:	
Pearl Index	15,461(83%)
Life Table**	9180 (49%)

* Excluding Pill packs not meeting exclusion criteria.
** Excluding pill packs for more than one reason.

Pearl Index: Sponsor's analysis included 19 on-therapy pregnancies and 23 pregnancies including on-therapy plus pregnancies that occurred during the last 14 days of post-treatment period as shown in Table 3.1.2.3c. Of these, fifteen pregnancies were due to method failure. All pregnancies were in subjects aged 35 years or younger. The Pearl index for on-therapy pregnancies was 1.60 (95% CI: 0.96, 2.49) in all subjects, and 1.96 (95% CI: 1.18, 3.07) in subjects ≤35 years of age, respectively. Including the pregnancies between 1 to 14 days post-treatment, the pearl index was 1.93 (95% CI: 1.23, 2.90) and 2.38 (95% CI: 1.51, 3.57).

Table 3.1.2c Pearl Index (95% Confidence Interval) for All Subjects and Subjects Aged ≤35 years old: Study 313-NA.				
Pregnancies classification	**Analysis Population**	**Number of**		**Pearl Index* (95% CI)**
		Pregnancies	**Pill Packs**	
On-therapy	All Ages	19	15461	1.60 (0.96, 2.49)
	Aged ≤35	19	12572	1.96 (1.18, 3.07)
On-therapy plus ≤14 days post-treatment	All Ages	23	15461	1.93 (1.23, 2.90)
	Aged ≤35	23	12572	2.38 (1.51, 3.57)
* Pearl Index = # of Pregnancy x 1300/# Pill packs.				

Life Table Analysis: Unlike Pearl index, a separate failure rate for each pill pack was calculated by life table method, and the rates were then chained together to yield cumulative failure rate within a specified cycle or pill pack in this study. Besides, in examining accidental pregnancy, it is important to censor subjects who prematurely leave observation for any other reason in order to obtain a pure measure of that cause of discontinuation. In addition, calculation of pregnancy rate by life table method is preferable over Pearl index because of the common misinterpretation that the pregnancies are distributed binomially when calculating a confidence interval for Pearl index.

Table 3.1.2d shows the cumulative accidental termination rates by pill packs in subject ≤35 years of age. With 13 pill packs, the cumulative accidental termination rate was 3.50 (CI: 2.27, 5.39), which is much higher than other approved OCs. The termination rate (not shown here) for subject of all ages (18-49 years) is 2.83 (95% CI: 1.83, 4.35).

Table 3.1.2d Life Table Analysis*: Accidental Pregnancies Termination Rate in ≤35 years: Study 313-NA		
Pill Packs	**Cumulative Termination Rates***	**95% confidence Interval**
1	0.0015	(0.0004, 0.0062)
2	0.0041	(0,0017, 0.0098)
3	0.0060	(0.0029, 0.0127)
4	0.0072	(0.0036, 0.0144)
5	0.0124	(0.0070, 0.0219)
6	0.0138	(0.0079, 0.0239)
7	0.0170	(0.0101, 0.0284)
8	0.0170	(0.0101, 0.0284)
9	0.0208	(0.0127, 0.0339)
10	0.0228	(0.0141, 0.0368)
11	0.0251	(0.0157, 0.0402)
12	0.0324	(0.0208, 0.0503)
13	0.0350	(0.0227, 0.0539)
* Rates based on Kaplan-Meier method.		

Comments: *Study 313-NA was an open-label study designed to enroll approximately 2000 subjects assuming a discontinuation rate of 50%. It appeared excluding pill packs for reasons a-c (section3.1.1), would make the results more conservative since the denominator becomes smaller and the numerator remains the same. In addition, the power of the study was compromised because the observed discontinuation rate was more than what was expected, and the total women-years of exposure (pill packs) of approximately 12575 was less than adequate to rule out the upper limit of a 95% CI to be less <3. It would require approximately 20,000 women-years of exposure to rule out a Pearl index of <3.*

3.2 Study 315-EU

3.2.1 Design and Methods

This study was a randomized, multi-center, open-label, controlled study conducted in 44 centers in Europe. The objective of this study was to evaluate the safety and contraceptive efficacy of Lybrel compared to a 21-day cyclic regimen of LNG 100 µg/EE 20 µg. A total of 641 subjects were randomized: 323 in Lybrel and 318 in LNG 100 µg/EE 20 µg to receive the study drugs for approximately 13 months.

The **primary efficacy** outcome was the number of pregnancies attributed to method failure. The contraceptive efficacy assessment included the computation of the pregnancy rate by Pearl Index and life table method.

3.2.2 Results

Subject Disposition: A total of 641 took at least 1 dose of study drug: 323 in the continuous regimen and 318 in the cyclic regimen, of which 176 (27%) discontinued early from the study. The primary reason for discontinuation were due to adverse events and was statistically significantly higher in the continuous regimen (22% vs. 9.7%, p<.001) as shown in Table 3.2.2a. But unlike the US study, substantially lower discontinuation rates were noted in this European study. The study population was predominantly white (96%) with a mean age of 27 years and who took the study drug for a mean duration of approximately 300 days.

Analysis Populations: The women-years of exposure were measured by the number of cycles (pill packs) during the study duration. A total of 3461 and 3698 cycles were reported in the continuous and cyclic regimen, respectively (Table 3). An equal number of pill packs by regimen were included in the calculation of pregnancy rate in the total population and in subjects under 35 years of age.

Table 3.2.2a Number of Subject Disposition: Study 315-EU		
Subjects	**Lybrel N (%)**	**LNG 100 µg/EE 20 N (%)**
Total Enrolled (at least 1 dose)	**323**	**318**
Completed	216 (67)	249 (78)
Total Discontinued:	107 (33)	69 (22)
Accidental pregnancy	0 (0.0)	3 (0.9)
AE	72 (22.3)	31 (9.7)
By Study sponsor	1 (0.3)	2 (0.6)
Lost to follow-up	5 (1.5)	2 (0.6)
Planning pregnancy	3 (0.9)	3 (0.9)
Protocol violation	9 (2.8)	11 (3.5)
Subject Request	17 (5.3)	17 (5.3)

Table 3.2.2b Dispositions of Pill Packs Valid for Intent-to-Treat Analysis: Study 315-EU		
Dispositions	**Lybrel**	**LNG 100 µg/EE 20**
Total	3461 (100%)	3698 (100%)
Excluded	389 (11%)	428 (12%)
Valid for Analysis:		
Pearl Index	3072 (89%)	3270 (88%)
Life Table*	2360 (68%)	2627 (71%)
* Excluded for more than one reason.		

Pearl Index: There were 4 on-therapy (including days 1 to 14 post-treatment) pregnancies: 1 in continuous regimen and 3 in cyclic regimen. All pregnancies were in subjects aged 35 years or younger. The Pearl indexes in the ≤ 35 year group were 0.51 (95% CI: (0.01, 2.82) and 1.43 (95% CI: 0.29, 4.17) for lybrel and LNG, respectively. Although the Pearl index in this study was similar or even lower to approved OCs, the study was under powered since only approximately 3000 pill packs of exposure were valid for the analysis when in fact close to 14000 pill packs would be necessary for the upper limit of a 95% CI to be <1.4.

Table 3.2.2c Pearl Index (95% Confidence Interval) for Subjects Aged ≤35 years in by Study 315-EU				
Pregnancy classification	**Regimen**	**Number of**		**Pearl Index (95% CI)**
		Pregnancies	**Pill Packs**	
On-therapy (excluding days 1-14 Post-treatment)	Lybrel	0	2564	0.00 (0.00, 1.87)
	LNG 100 µg/EE 20	3	2733	1.43 (0.29, 4.17)
On-therapy (including days 1-14 post-treatment)	Lybrel	1	2564	0.51 (0.01, 2.82)
	LNG 100 µg/EE 20	3	2733	1.43 (0.29, 4.17)

Life Table Analysis: The cumulative rates of accidental pregnancies by therapy and pill packs are shown in Table 3.2.2d for subjects aged 35 years or younger. At 13 pill packs, the termination rate for accidental pregnancy was 0.08 (95% CI: 0.11, 5.46) for the continuous regimen compared to 1.65 (95% CI: 0.53, 5.05) for the cyclic regimen.

Table 3.2.2d Life Table Analysis: Accidental Pregnancies Termination Rate in ≤35 years: Study 315-EU		
Pill Pack	**Cumulative Pregnacy Rates* (95% confidence Interval)**	
	Lybrel	LNG 100 µg/EE 20
1	0.0000 (0.0, 0.0)	0.0 (0.0, 0.0)
6	0.0000 (0.0, 0.0)	0.0 (0,00, 0.00)
9	0.000 (0.0, 0.0)	0.0105(0.0026, 0.0413)
12	0.0000 (0.0, 0.0)	0.0165 (0.0053, 0.0505)
13	0.0079 (0.0011, 0.0546)	0.0165 (0.0053 0.0505)
*Rates based on Kaplan-Meier method.		

Comments: *Despite a low Pearl index (0.51) supported by a low pregnancy rate of 0.008 at 13 pill packs in this study, the upper limit of the 95% CI for the pregnancy rate was similar to the NA study.*

3.3 Sponsor's combined analysis

The sponsor also presented the combined (studies 313-NA and 315-EU) Pearl index of 2.06 (95% CI: 1.32, 3.07) in 35 years or younger subjects and made an argument that the efficacy of Lybrel was consistently similar to recently approved products such as Ortho Tri-Cyclen Lo (PI=2.39); Estrostep (PI=2.4); and Seasonale (PI=1.98). But they have not given much

importance to combined analysis in the submission until we raised the issue of the high Pearl index seen in the bulk of the data they submitted, especially, in the larger 313-NA study. In recent communications they made their focus based mostly on post hoc combined analysis, without giving rationale for presenting such analyses.

From a statistical perspective, a combined analysis can be used as supportive only when the efficacy is demonstrated adequately in individual studies. In this application, there appeared to be substantial heterogeneity of the study results: study 315-EU showing a Pearl index of 0.51, while the study 313-NA showing a Pearl index of 2.38. It is obvious that when a study with a low point estimate is combined with a study with a large point estimate, an analysis of the combined data will fall in-between. It is important to explore the plausible if not conclusive explanations for heterogeneity of results by formal methods. Therefore, efficacy results from combined analysis should not be considered as the totality of evidence in this application.

4.0 REVIEWER'S CONCLUSION

Study 313-NA was an open-label study designed to enroll approximately 2000 subjects assuming a discontinuation rate of 50%. It appeared the power of the study was compromised since the observed discontinuation rate was more than what was expected, and the total women-years of exposure (pill packs) of approximately 12575 was less than adequate to have sufficient power in order to rule out a true Pearl index rate of 3. For a Pearl rate of 3, approximately 20000 women-years of exposure would be required.

Although the Pearl index in the European study was much lower than the NA study, the study size was not adequate to rule out a true rate of 0.51 with adequate power.

The sponsor's post hoc decision to use results of an unplanned combined analysis as collective evidence is unacceptable. From a statistical perspective, the rationale for using results of such pooled analysis had to be pre-specified in the protocol. Proper statistical methods need to be used to perform such an analysis once the condition that each study stands on its own merit is met.

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Lisa A. Kammerman
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I concur with review.