

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-998

STATISTICAL REVIEW(S)

Memorandum of Statistical Review

NDA/Serial Number: 21-998 / 000
Drug Name: Levonorgestrel 1.5 mg Tablet
Indication(s): Emergency Contraception
Applicant: Duramed Research, Inc.
Date(s): *Letter Date:* January 9, 2009 *PDUFA Date:* July 10, 2009
Review Priority: 1 Standard
Biometrics Division: Division of Biometrics 3
Statistical Reviewer: Sonia Castillo, Ph.D.
Biometrics Team Leader: Mahboob Sobhan, Ph.D.
Medical Division: Division of Reproductive and Urologic Products
Clinical Team: Daniel Davis, M.D., Clinical Reviewer
 Lisa Soule, M.D., Team Leader
Project Manager: Pamela Lucarelli

This Class 2 resubmission to an approvable letter sent to the Applicant on November 22, 2006 contains the proposed labeling. The Statistical review of the NDA submission dated January 24, 2006 was entered into DFS on September 26, 2006.

Recommendations on Labeling:

The red text from the clinical studies section of the label presented below is based on Table 1.1, which is from the statistical review of the January 24, 2006 submission for this NDA. Using this information, this portion of the clinical studies section of the label in this Class 2 labeling resubmission is acceptable from a statistical perspective.

Table 1.1
Study 97902: Observed and Expected Pregnancies with Prevented Fractions and 95% Confidence Intervals for Women Receiving Emergency Contraception from 0 to 72 Hours after Unprotected Intercourse – Full ITT Population

	N	Observed Pregnancies		Expected Pregnancies	PF* (%)	95% C.I.
		n	Rate (%)			
Levonorgestrel 1.5 mg × 1	1198	16	1.34	(0.76, 2.16)	99.7	83.95 (73.94, 90.83)
Levonorgestrel 0.75 mg × 2	1183	20	1.69	(1.04, 2.60)	94.9	78.92 (67.44, 87.12)

Source: Table 1.1 of Addendum to Statistical Review and Evaluation of submission dated January 1, 2006 and first table on page 2/10 of Amendment 1 to Statistical Report on WHO Study 97902 dated June 13, 2003

* PF = Prevented Fraction = $1.0 - (\text{Observed pregnancies} / \text{Expected pregnancies})$

14. CLINICAL STUDIES

A double-blind, randomized, multicenter, multinational study evaluated and compared the efficacy and safety of three different regimens for emergency contraception. Subjects were enrolled at 15 sites in 10 countries; the racial/ethnic characteristics of the study population overall were 54% Chinese, 34% Caucasian, and 12% Black or Asian (other than Chinese). 2,381 healthy women with a mean age of 27 years, who needed emergency contraception within 72 hours of unprotected intercourse were involved and randomly allocated into one of the two levonorgestrel groups. A single dose of 1.5 mg of levonorgestrel (Plan B One-Step) was administered to women allocated into group 1. Two doses of 0.75 mg levonorgestrel 12-hour apart (Plan B) were administered to women in group 2. In the Plan B One-Step group, 16 pregnancies occurred in 1,198 women and in the Plan B group, 20 pregnancies occurred in 1,183 women. Among women receiving Plan B One-Step, 84% of 100 expected pregnancies were prevented and 79% of 95 expected pregnancies were prevented among those women taking Plan B. The expected pregnancy rate of 8% (with no contraceptive use) was reduced to approximately 1% with Plan B One-Step.

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION Clinical Studies

NDA/Serial Number: 21-998 / 000
Drug Name: Levonorgestrel 1.5 mg Tablet
Indication(s): Emergency Contraception
Applicant: Gedson Richter, Ltd.
Date(s): Letter Date: January 24, 2006 PDUFA Date: November 24, 2006
Review Priority: 1S
Biometrics Division: Division of Biometrics 3
Statistical Reviewer: Sonia Castillo, Ph.D.
Biometrics Team Leader: Mahboob Sobhan, Ph.D.
Medical Division: Division of Reproductive and Urologic Drug Products
Clinical Team: Daniel Davis, M.D., Medical Reviewer
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Project Manager: Nenita Crisostomo

Key Words: Clinical studies, NDA review

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This study has demonstrated a prevented fraction of 81.9% (95% C.I. from 72.0% to 88.9%) for levonorgestrel 1.5 mg tablet for use as an emergency contraceptive to prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure.

1.2 Background

The Sponsor has submitted one randomized, double-blind, multinational, parallel group study to demonstrate the safety and efficacy of two regimens of a total of 1.5 mg of levonorgestrel (LNG) for emergency contraception in women requesting emergency contraception within 120 hours after unprotected intercourse. One regimen is the administration of one 1.5 mg tablet and the other is the administration of two 0.75 mg tablets taken 12 hours apart.

The Sponsor's proposed indication is:

Levonorgestrel 1.5 mg tablet is an emergency contraceptive that can be used to prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure. To obtain optimal efficacy, the tablet should be taken as soon as possible within 72 hours of intercourse.

1.3 Statistical Issues and Findings

There are no statistical issues with this submission. Efficacy is based on calculation of the prevented fraction or the fraction of pregnancies that were prevented. The prevented fraction for LNG 1.5 mg tablet is 81.9% (95% C.I. from 72.0% to 88.9%).

2 INTRODUCTION

2.1 Overview

The Sponsor has submitted one randomized, double-blind, multinational, parallel group study (97902) designed to demonstrate the safety and efficacy of two regimens of a total of 1.5 mg of LNG for emergency contraception in women requesting emergency contraception within 120 hours after unprotected intercourse. The rationale for developing the single 1.5 mg dose of LNG was that it would simplify the treatment and increase the compliance and acceptability of the product. Table 2.1 presents a brief summary of the study.

Brief Summary of Study 97902

Dates of Study Conduct (No. of Centers / Country)	Subject Population	Treatment / Regimen (Taken only once)	Number Enrolled	Design ²
5-18-1998 to 3-15-2001 (6 for China, 1 for each: India, Mongolia, Slovenia, Sweden, Switzerland, United Kingdom, Finland, Georgia, Hungary)	Women requesting emergency contraception within 120 hours after unprotected intercourse	Mifepristone 10 mg / 1 dose LNG ¹ 0.75 mg / 2 doses 12 hrs apart LNG ¹ 1.5 mg / 1 dose	1380 1377 1379	DB, R, PG, MC

Source: Statistical Reviewer's listing.

¹ LNG = Levonorgestrel

² DB = Double-blind, R = Randomized, PG = Parallel Group, MC = Multicenter

The Division of Reproductive and Urologic Drug Products agreed to accept one study because one LNG 1.5 mg tablet, or the LNG 1.5 mg × 1 regimen, is the same dose as two LNG 0.75 mg tablets, or the LNG 0.75 mg × 2 regimen, which is the currently approved product. The difference is in the regimen for the product, a single dose of 1.5 mg LNG taken once during a treatment cycle versus 0.75 mg LNG taken 2 doses 12 hours apart once during a treatment cycle.

Since the Sponsor is seeking approval for the LNG 1.5 mg × 1 regimen, this review will focus on the results for LNG 1.5 mg × 1 regimen and LNG 0.75 mg × 2 regimen, the comparator.

2.2 Data Sources

The study reports and additional information for this study are available in electronic and paper formats. The SAS data sets are complete and well documented. These items are located in the Electronic Document Room at

\\Cdsub\N21998\N 000 under submission dates 1-24-2006 and 3-20-2006 and two paper submissions are dated 1-11-06 and 6-29-06.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Study 97902 is a randomized, double-blind, multinational (15 non-U.S. centers), parallel group study comparing three treatment regimens in emergency contraception each administered in two doses 12 hours apart: (i) one dose of 10 mg of mifepristone plus one placebo dose; (ii) two doses of 0.75 mg of LNG; and (iii) one dose of 1.5 mg of LNG plus one placebo dose. The treatment regimens were given orally during one treatment cycle, with the first dose swallowed in the presence of a member of the study team who recorded the date and time of administration and the second dose taken off site 12 hours later. Women requesting emergency contraception within 120 hours of unprotected intercourse who satisfied the inclusion criteria, which included a negative pregnancy test and willing to abstain from further acts of intercourse during that cycle, were randomly assigned to one of three treatment groups.

The primary objectives of the study were to compare the efficacy and safety of the three treatments listed above. The primary efficacy outcome was prevention of pregnancy. The prevented fraction (PF), or the proportion of expected pregnancies prevented by the treatment, is the primary efficacy variable and is defined as follows:

$$\text{Prevented Fraction} = [1.0 - (\text{Observed pregnancies}/\text{Expected pregnancies})] \times 100$$

The method used to calculate the expected number of pregnancies and the 95% confidence interval for the PF is described in Appendix 1. The pregnancy rate (PR), or percentage of women who became pregnant, and its 95% confidence interval were also calculated. No formal statistical comparisons or threshold to meet were planned.

3.1.1 Overall Study Descriptive Statistics

Table 3.1 presents the number of randomized subjects and the disposition of subjects in the full ITT set. The full ITT set included all who had been randomized and for whom any assessment of efficacy was available. The full ITT set did not include subjects with pregnancy status undetermined (lost of follow-up or had intercourse after missed menses). Discontinuation rates were similar in both treatment groups (1.7% and 1.5%). The primary reason for study discontinuation is loss to follow-up, with similar percentages in each treatment group.

Table 3.1
Study 97902: Randomized Subjects and Disposition of All Treated Subjects

	LNG 1.5 mg x 1	LNG 0.75 mg x 2
Randomized/Treated	1379	1377
Full ITT	1356	1356
Discontinued n (%*)	23 (1.7)	21 (1.5)
Primary Reason for Discontinuation n (%**):		
Lost to Follow-up	22 (95.6)	20 (95.2)
Had Intercourse After Missed Menses	1 (4.4)	1 (4.8)

Source: pages 1-2 of Appendix 16.2.3 Patient Excluded from the Efficacy Analysis from Clinical Study Report dated February 24, 2003.

* With respect to number of Full ITT subjects.

** With respect to number of all discontinuations.

Baseline characteristics were similar for the two treatment groups in the full ITT population: women had a mean age of 27 years. More than half of the women were Chinese (54%) and 34% were Caucasian.

3.1.2 Study Results

Table 3.2 presents the pregnancy rate and, in the highlighted area, the prevented fraction (PF) in the full ITT population. The Reviewer concurs with the Sponsor's results. There were 44 pregnancies observed, 20 (1.5%) in the LNG 1.5 mg x 1 group and 24 (1.8%) in the LNG 0.75 mg x 2 group. There were 216 pregnancies expected if no contraceptive measures were taken, 111 in the LNG 1.5 mg x 1 group and 106 in the LNG 0.75 mg x 2 group. So, the percentage of pregnancies that was prevented was 81.9% (95% C.I. from 72.0% to 88.9%) for the LNG 1.5 mg x 1 regimen and 77.3% (95% C.I. from 66.3% to 85.5%) for the LNG 0.75 mg x 2 regimen.

Table 3.2
Study 97902: Observed and Expected Pregnancies with Prevented Fractions and 95% Confidence Intervals – Full ITT Population

	N	Observed Pregnancies		Expected Pregnancies	
		n	Rate (%)	95% C.I.	n
Levonorgestrel 1.5 mg x 1	1356	20	1.47	(0.90, 2.27)	110.5
Levonorgestrel 0.75 mg x 2	1356	24	1.77	(1.14, 2.62)	105.8

Source: Table 11-12, page 51/116 of Clinical Study Report dated February 24, 2003
 * PF = Prevented Fraction = $1.0 - (\text{Observed pregnancies} / \text{Expected pregnancies})$

3.2 Evaluation of Safety

There is no statistical evaluation of safety necessary for this review. For additional information, reference the clinical review evaluation of safety section.

4. FINDINGS IN SUBGROUP POPULATIONS

Two subgroup populations are of interest in this submission, age and ethnic group. The age groups are 35 years of age or less and 36 years of age or more; and the ethnic groups are Chinese and non-Chinese.

4.1 Age Subgroup

Table 4.1 presents the pregnancy rate and, in the highlighted area, the prevented fraction in the full ITT set by two age groups: 35 years of age or less and 36 years of age or more. The Reviewer concurs with the Sponsor's results.

More than 85% of the women were 35 years of age or less. There were 40 pregnancies observed in this age group, 19 (1.6%) in the LNG 1.5 mg x 1 group and 21 (1.8%) in the LNG 0.75 mg x 2 group. There were 185 pregnancies expected if no contraceptive measures were taken, 94 in the LNG 1.5 mg x 1 group and 91 in the LNG 0.75 mg x 2 group. So, the percentage of pregnancies that was prevented was 79.7% (95% C.I. from 68.3% to 87.8%) for the LNG 1.5 mg x 1 regimen and 76.8% (95% C.I. from 64.6% to 85.6%) for the LNG 0.75 mg x 2 regimen.

About 15% of the women were 36 years of age or more. There were 4 pregnancies observed in this age group, 1 (0.5%) in the LNG 1.5 mg x 1 group and 3 (1.5%) in the LNG 0.75 mg x 2 group. There were 32 pregnancies expected if no contraceptive measures were taken, 17 in the LNG 1.5 mg x 1 group and 15 in the LNG 0.75 mg x 2 group. So, the percentage of pregnancies that was prevented was 94.1% (95% C.I. from 67.1% to 99.9%) for the LNG 1.5 mg x 1 regimen and 80.4% (95% C.I. from 42.7% to 96.0%) for the LNG 0.75 mg x 2 regimen.

Table 4.1
Study 97902: Observed and Expected Pregnancies with Prevented Fractions and 95% Confidence Intervals – 35 Years of Age or Less and 36 Years of Age or More Groups - Full ITT Population

	N	Observed Pregnancies		Expected Pregnancies	
		n	Rate (%)	95% C.I.	n
35 Years of Age or Less					
Levonorgestrel 1.5 mg x 1	1166	19	1.63	(0.98, 2.53)	93.6
Levonorgestrel 0.75 mg x 2	1151	21	1.82	(1.13, 2.78)	90.6
36 Years of Age or More					
Levonorgestrel 1.5 mg x 1	190	1	0.53	(0.01, 2.90)	16.9
Levonorgestrel 0.75 mg x 2	205	3	1.46	(0.30, 4.22)	15.3

Source: Two tables for Full ITT Population in Section 1.1.1 on page 6 of submission dated 6-29-06.
 * PF = Prevented Fraction = $1.0 - (\text{Observed pregnancies} / \text{Expected pregnancies})$

4.2 Ethnic Subgroup

Table 4.2 presents the pregnancy rate and prevented fraction (PF) for all treated subjects by two ethnic groups: Chinese and non-Chinese. The Reviewer concurs with the Sponsor's results.

Fifty-four percent of the women were Chinese. There were 27 pregnancies observed in this ethnic group, 11 (1.5%) in the LNG 1.5 mg x 1 group and 16 (2.2%) in the LNG 0.75 mg x 2 group. There were 112 pregnancies expected if no contraceptive measures were taken, 58 in the LNG 1.5 mg x 1 group and 54 in the LNG 0.75 mg x 2 group. So, the percentage of pregnancies that was prevented was 80.9% (95% C.I. from 65.8% to 90.5%) for the LNG 1.5 mg x 1 regimen and 70.4% (95% C.I. from 51.9% to 83.1%) for the LNG 0.75 mg x 2 regimen.

Forty-six percent of the women were non-Chinese. There were 17 pregnancies observed in this ethnic group, 9 (1.4%) in the LNG 1.5 mg x 1 group and 8 (1.3%) in the LNG 0.75 mg x 2 group. There were 105 pregnancies expected if no contraceptive measures were taken, 53 in the LNG 1.5 mg x 1 group and 52 in the LNG 0.75 mg x 2 group. So, the percentage of pregnancies that was prevented was 83.0% (95% C.I. from 67.7% to 92.2%) for the LNG 1.5 mg x 1 regimen and 84.6% (95% C.I. from 69.6% to 93.3%) for the LNG 0.75 mg x 2 regimen.

Table 4.2
Study 97902: Observed and Expected Pregnancies with Prevented Fractions and 95% Confidence Intervals - Chinese and non-Chinese Groups - Full ITT Population

	N	Observed Pregnancies			Expected Pregnancies	
		n	Rate (%)	95% C.I.	n	
<i>Chinese</i>						
Levonorgestrel 1.5 mg x 1	733	11	1.50	(0.75, 2.67)	57.6	
Levonorgestrel 0.75 mg x 2	732	16	2.19	(1.25, 3.52)	54.0	
<i>Non-Chinese</i>						
Levonorgestrel 1.5 mg x 1	623	9	1.44	(0.66, 2.72)	52.9	
Levonorgestrel 0.75 mg x 2	624	8	1.28	(0.56, 2.51)	51.9	

Source: Tables 11-33 and 11-34 on page 58 of Clinical Study Report dated February 24, 2003

* PF = Prevented Fraction = $1.0 - (\text{Observed pregnancies} / \text{Expected pregnancies})$

5. CONCLUSIONS

From a statistical standpoint, the Sponsor has provided an adequate study that resulted in a prevented fraction of 81.9% (95% C.I. from 72.0% to 88.9%) for levonorgestrel 1.5 mg tablet for use as an emergency contraceptive to prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure.

APPENDIX 1

The methods used to calculate the pregnancy rate, the expected number of pregnancies, the prevented fraction (PF, or the proportion of expected pregnancies prevented by the treatment), and their 95% confidence intervals are described below.

a) Pregnancy proportion = $O/\text{total number of subjects}$, where O is the number of observed pregnancies. This multiplied by 100 is the percentage.

b) 95% confidence intervals for the pregnancy rates: use exact 95% CI given by the binomial distribution (Armitage and Berry, 1994, page 121). These can be obtained using the inverse of the beta distribution, obtained by the BETAINV function in SAS:

$$\text{LCL} = \text{BETAINV}(0.025, O, n-O+1),$$

$$\text{UCL} = \text{BETAINV}(0.975, O+1, n-O),$$

where n is the number of volunteers and O is the number of pregnancies.

c) Number of expected pregnancies (E): obtained by multiplying the number of women having unprotected intercourse on each day of the menstrual cycle (n_i) by the probability of conception on that cycle day ($prob_i$) and summing all these products over coital day (i):

$$E = \sum n_i prob_i$$

The ovulation date for each woman will be estimated by subtracting 14 days from the expected date of next menstrual period. For $prob_i$ the following pooled recognizable conception (rc) probabilities will be used (Pooled-rc in Trussell et al, 1998):

Coital day (i)	-5	-4	-3	-2	-1	0	1
Pooled-rc ($prob_i$)	0.035920	0.136387	0.155106	0.276833	0.297993	0.123348	0.044959

d) Prevented fraction or effectiveness: $PF = (1-O/E)$. This multiplied by 100 is the percentage.

e) 95% confidence intervals for the prevented fraction Method 1: use the Poisson distribution as described in Gardner and Altman (1989), page 59, for the indirect method of standardization.

REFERENCES

- Armitage, P and Berry, G (1994). Statistical Methods in Medical Research, Third Edition. London: Blackwell.
- Gardner, MJ and Altman, DG (1989) Statistics with Confidence. London: British Medical Journal.
- Trussell S, Rodriguez G, Ellertson C. New estimates of the effectiveness of the Yuzpe regimen of emergency contraception. Contraception 1998; 57:363-69.

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**Screening of New NDA for Statistical Filing
Division of Biometrics II**

NDA #: 21-998 (Serial 000)

Applicant: Gideon Richter, Ltd. (Duramed Research, Inc. is the authorized U.S. agent)

Trade/Generic Name: Plan B (Levonorgestrel 1.5 mg Tablet)

Indication: Emergency Contraception

Date of Submission: January 24, 2006

Filing Date: March 25, 2006

User Fee Goal Date: September 25, 2006

Project Manager: Jennifer Mercier

Medical Reviewer: Daniel Davis, M.D. (DRUDP)

Comments: This NDA is fileable from a statistical perspective.

The Sponsor still needs to address the following comment from statistics that was included in the January 13, 2006 meeting minutes with the Sponsor:

Confirm that the pregnancy status for the subjects listed in the memos on pages 14, 18, and 19 of Attachment 3 (WHO Stat Plan.pdf) from your submission dated 1-11-06 is reflected in the efficacy data set sent with your application. For example, in Attachment 5 (pregnancies.pdf) from the 1-11-06 submission, Subject 060-E from Center 6 is not listed as one of the pregnancies while the memo on page 14 from Attachment 3 lists the subject as being pregnant.

Checklist for Fileability	Remarks (NA if not applicable)
Index sufficient to locate study reports, analyses, protocols, ISE, ISS, etc.	OK
Original protocols & subsequent amendments submitted	OK
Study designs utilized appropriate for the indications requested	OK
Endpoints and methods of analysis spelled out in the protocols	OK
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	NA
Appropriate references included for novel statistical methodology (if present)	NA
Data and reports from primary studies submitted to EDR according to Guidances	EDR data present
Safety and efficacy for gender, racial, geriatric, and/or other necessary subgroups investigated	See Medical Reviewer's filing document

Reviewer: S. Castillo

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