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RESEARCH**

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STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

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1. EXECUTIVE SUMMARY

The sponsor has submitted the results of a New Drug Application (NDA) for Norethindrone Acetate 1 mg/Ethinyl Estradiol 20 mcg Oral Tablets (Loestrin-24 tablets) for the indication of prevention of pregnancy. Originally, Loestrin 1/20 was approved on April 30, 1973 under NDA 17-354. However, Loestrin-24 is a new 24-day dosing regimen of the currently marketed 21-day regimen Loestrin 1/20 tablets. This investigational product contains the same daily doses of the previously marketed Loestrin, but is administered for 3 additional days during each 28-day cycle.

One open-label, randomized, multi-center, active-controlled, Phase 3 clinical study has been submitted to the Agency to evaluate the safety and efficacy of Loestrin-24 Oral Tablets in a 24-day regimen (Protocol # PR-03903 or Report # RR-10104) for prevention of pregnancy. The duration of this study was 6 months. This review reports the results of this study based on the Sponsor's as well as this reviewer's assessments.

1.1 Conclusions and Recommendations

Based on the data provided by the sponsor, from the statistical standpoint, Norethindrone Acetate 1 mg/Ethinyl Estradiol 20 mcg Oral Tablets (Loestrin-24) seems adequate for demonstrating the effectiveness of this drug in the prevention of pregnancy for the 24-day regimen. A total of 12 pregnancies were reported in the clinical trial, 10 in subjects assigned to the 24-day regimen, and 2 in subjects assigned to the 21-day arm. In the Modified Intent-to-Treat (MITT) population (the population of subjects with at least one pregnancy assessment after the start of treatment), the 21-day treatment arm had 2 occurrences of pregnancies in a total of 873 28-day treatment-cycles, resulting in a Pearl Index (PI) of 2.98 (95% CI from 0.27 to 10.8). The Loestrin-24 treatment arm had 5 on-treatment pregnancies in a total of 3,565 28-day treatment cycles, resulting in a Pearl Index of 1.82 (95% CI from 0.51 to 4.36). If one considers an additional unconfirmed pregnancy identified by the medical reviewer (a worst case situation) there were 6 pregnancies in the Loestrin 24 treatment arm, resulting in a Pearl Index of 2.19 (95% CI from 0.77 to 4.63). Loestrin 24 demonstrates acceptable efficacy compared to the 21-day Loestrin. However, the 24-day regimen's 95% Confidence Intervals for the PI with either 5 or 6 pregnancies overlap with the 21-day regimen: with 5 pregnancies (0.51, 4.36) vs. (0.27, 10.8), and with 6 pregnancies (0.77, 4.63) vs. (0.27, 10.8). Therefore, we cannot conclude that one treatment is significantly better than the other.

1.2 Brief Overview of Clinical Study

The sponsor has conducted one controlled, multi-center, open-label, active comparator, parallel group Phase 3 study to evaluate the efficacy and safety of this new dosing regimen (24-days of active tablets followed by 4 days of placebo tablets) vs. the previous dosing of 21 days for the duration of 6 cycles, in women 18 to 45 years of age (Study PR-03903). The subjects were randomized to one of the two treatment groups, 24-day or 21-day regimens, in a 4 to 1 ratio, respectively. This clinical trial will be the focus of the statistical review.

The primary efficacy endpoint was the number of on-treatment pregnancies throughout the 6 cycles of the study. Pearl Indices and associated 95% Confidence Intervals were constructed.

1.3 Statistical Issues and Findings

The primary efficacy endpoint was the number of pregnancies throughout the 6 cycles of the study.

Efficacy was based on the Pearl Index (PI) and the associated two-sided 95% Confidence Intervals (CI) for the PI's, using number of on-treatment pregnancies in the MITT, and number of evaluable cycles of treatment during which no backup contraception was used.

The Sponsor is reporting a total of 5 on-treatment pregnancies in the 24-day arm in the MITT population. However, two additional pregnancies were discovered in this group when the data were analyzed by the statistical reviewer. The Pearl Indices (PI's) and the two-sided 95% CI's for all the subjects, the subjects who were evaluated for pregnancy at least once after beginning the study medication (the MITT population) and for women 35 years old and younger and all women were estimated.

In the MITT population, the 21-day arm had two pregnancies in a total of 873 woman-cycles and a Pearl Index of 2.98 (95% CI from 0.27 to 10.8). The 24-day regimen arm had a total of 5 pregnancies in a total of 3,562 woman-cycles with a Pearl Index of 1.82 (95% CI from 0.51 to 4.36).

2. INTRODUCTION

2.1 Overview

The sponsor has submitted the results of a New Drug Application (NDA) for Norethindrone Acetate 1 mg/Ethinyl Estradiol 20 mcg Oral Tablets (Loestrin-24 tablets) for the indication of prevention of pregnancy. Originally, Loestrin 1/20 was approved on April 30, 1973 under NDA 17-354. However, Loestrin-24 is a new 24-day dosing regimen of the currently marketed 21-day regimen Loestrin 1/20 tablets. This investigational product contains the same daily doses of the previously marketed Loestrin 1/20, but is administered for 3 additional days during each 28-day cycle.

The sponsor has conducted one controlled, multi-center, open-label, active comparator, parallel group Phase 3 study (Protocol # PR-03903, Report # RR-10104) to evaluate the efficacy and safety of this new dosing regimen (24-day) vs. the previous dosing of 21 days for the duration of 6 cycles, in women 18 to 45 years of age for prevention of pregnancy. The subjects were randomized to one of the two treatment groups, 24-day or 21-day regimens, in a 4 to 1 ratio, respectively.

The primary efficacy endpoint was the number of on-treatment pregnancies throughout the 6 cycles of the study. Pearl Indices and associated 95% Confidence Intervals were constructed.

A total of 1159 subjects were screened and 938 were randomized, 751 to Loestrin-24 and 187 to Loestrin 1/20 of whom 743 and 186 actually took drug, respectively. A total of 721 subjects completed the study, 580 on Loestrin-24 and 141 on Loestrin 1/20.

2.2 Data Sources

The Sponsor has provided the SAS data electronically, and the study report in paper version. The electronic data is located: \\Cdsesub1\n21871\N_000\2005-04-15.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

A total of 1159 women between the ages of 18 to 45 were screened and 938 were randomized, 751 to Loestrin-24 and 187 to Loestrin 1/20 of whom 743 and 186 actually took drug, respectively. The subjects were randomized to one of the two treatment groups, 24-day or 21-day regimens, in a 4 to 1 ratio, respectively. A total of 721 subjects completed the study, 580 on Loestrin-24 and 141 on Loestrin 1/20. Out of the 938 randomized subjects, there were a total of 12 pregnancies, 10 of which were in the Loestrin-24 group and 2 in the Loestrin 1/20 group. However, of the 10 pregnancies in the Loestrin-24 group, only five (5) were assessed as having occurred while on treatment with Study Drug.

The Sponsor defines the Modified Intent-to-Treat (MITT) population as the subset of all treated subjects who were evaluated for pregnancy, either positive or negative, at least once after beginning the study medication. Completers were defined as subjects who are a subset of the MITT population and completed at least 161 days of treatment based on the amount of drug returned or on data from the retrieved diaries. A per-protocol population was not included in this study.

For the primary endpoint variable, which was the number of pregnancies, the PI and the associated 95% CI were calculated.

In the data set submitted to the Agency, in the MITT population for the 24-day treatment group there were a total of 705 subjects and a total of 3,565 woman-cycles assessed as at risk for pregnancy. Ten pregnancies were identified by this reviewer in the Applicant's database. However, in the study report for the same sub-population (705 subjects and 3,565 woman-cycles) the Sponsor is reporting a total of 5 pregnancies. After discussing this issue with the reviewing medical officer, he concurred with the Sponsor that, in fact, 5 pregnancies had been confirmed as occurring on-treatment. Apparently, three pregnancies occurred in women who were randomized but never started treatment and 2 pregnancies were assessed as having occurred prior to starting treatment. If we remove the 5 subjects who appear to have been, erroneously, recorded as being pregnant in the data set, then the number of pregnancies will decrease from 10 to 5. The reviewing medical officer detected one other pregnancy which was not fully confirmed, to bring the total number of pregnancies to 6. It appears that, this sixth pregnancy had occurred in a 24 year old female (subject # 022-011) who had been regarded as lost to follow-up and was not confirmed or reported as being pregnant. The data shows that she had taken the study medication for a total of 5 cycles. In this review, the Pearl Indexes, their associated number woman-cycles, as well as the 95% Confidence Intervals are reported for both the 5 pregnancies as well as the 6 pregnancies.

Loestrin subjects who became pregnant while on or within 14 days of stopping Loestrin:

- Site- subj #
1. 013-001
 2. 015-005
 3. 017-031
 4. 027-006
 5. 028-004
 6. 022-011 (possibly became pregnant while taking study medication; this pregnancy, however, was never confirmed)

The final analysis of the PI is based on these subjects' pregnancies.

Number of Subjects who Completed the Study:

Tables 1 and 2 show the number and % of subjects who completed the study, for the whole population as well as the MITT population, based on the Sponsor’s submitted data set.

Table 1: Number of Subjects - Entire Population

Treatment Arm	Non-Completers	Completers	Total
24-Day Regimen	171 (23%)	580 (77%)	751 (80%)
21-Day Regimen	46 (25%)	141 (75%)	187 (20%)
Total	217 (23%)	721 (77%)	938 (100%)

Table 2: Number of Subjects - MITT Population

Treatment Arm	Non-Completers	Completers	Total
24-Day Regimen	125 (18%)	580 (82%)	705 (80%)
21-Day Regimen	40 (22%)	141 (78%)	181 (20%)
Total	165 (19%)	721 (81%)	886 (100%)

Number of Subjects with Evaluable Cycles for Pearl Index:

In the data set submitted to the Agency, the MITT population for the 24-day treatment group consisted of a total of 705 subjects and a total of 3,565 28-day treatment-cycles during which no back up contraception was used.

Tables 3 and 4 show the number and % of subjects with evaluable cycles that were used to calculate the PI for the whole population as well as the MITT population based on the Sponsor’s submitted data set.

Table 3: Number of Subjects with Treatment Cycles - Whole Population

Treatment Arm	Cycle #							Total
	0	1	2	3	4	5	6	
24-Day Regimen	51 (7%)	58 (8%)	24 (3%)	32 (4%)	42 (6%)	60 (8%)	484 (64%)	751 (80%)
21-Day Regimen	13 (7%)	11 (6%)	8 (4%)	13 (7%)	9 (5%)	26 (14%)	107 (57%)	187 (20%)
Total	64 (7%)	69 (7%)	32 (3%)	45 (5%)	51 (5%)	86 (9%)	591 (63%)	938 (100%)

Table 4: Number of Subjects with Evaluable Cycles (based on Sponsor’s data) – Modified Intent-to-Treat Population

Treatment Arm	Cycle #							Total
	0	1	2	3	4	5	6	
24-Day Regimen	14 (2%)	49 (7%)	24 (3%)	32 (5%)	42 (6%)	60 (8%)	484 (69%)	705 (80%)
21-Day Regimen	8 (4%)	10 (6%)	8 (4%)	13 (7%)	9 (5%)	26 (14%)	107 (59%)	181 (20%)
Total	22 (2%)	59 (7%)	32 (4%)	45 (5%)	51 (6%)	86 (10%)	591 (67%)	886 (100%)

Number of Pregnancies, Number of Woman-Cycles and Pearl Index with the 95% CI:

The following two Tables show the number of pregnancies, their evaluable number of woman-cycles that was used to calculate the PI, and the associated 95% CI for the MITT population. Table 5 is for the confirmed 5 pregnancies in the Loestrin-24 group and Table 6 is based on the 6 pregnancies (which includes the one additional, unconfirmed pregnancy) in the Loestrin-24 treatment arm.

Table 5: Number of Confirmed Pregnancies, Number of Woman-Cycles* and Pearl Index with the 95% CI – Modified Intent-to-Treat Subjects

	No. of Pregnancies	No. of Women-Cycles	Pearl Index (PI)	95% CI for PI
24-Day n=705	5	3,565	1.82	(0.51, 4.36)
21-Day n=181	2	873	2.98	(0.27, 10.8)

*Number of cycles without Backup Contraception

Table 6: Number of Confirmed and Unconfirmed Pregnancies, Number of Woman-Cycles* and Pearl Index with the 95% CI – Modified Intent-to-Treat Subjects

	No. of Pregnancies	No. of Women-Cycles	Pearl Index (PI)	95% CI for PI
24-Day n=705	6	3,565	2.19	(0.77, 4.63)
21-Day n=181	2	873	2.98	(0.27, 10.8)

*Number of cycles without Backup Contraception

As can be observed in both Tables 5 and 6, the 21-day treatment arm had two pregnancies in a total of 873 woman-cycles and a Pearl Index of 2.98 (95% CI from 0.27 to 10.8). Loestrin-24 with a total of 5 pregnancies and a Pearl Index of 1.82, or with 6 pregnancies and a Pearl Index of 2.19 demonstrates an acceptable efficacy compared to 21-day Loestrin, with a PI of 2.98. However, the 24-day regimen's 95% Confidence Intervals for the PI using either 5 or 6 pregnancies overlap with the 21-day regimen: with 5 pregnancies (0.51, 4.36) vs. (0.27, 10.8), and with 6 pregnancies (0.77, 4.63) vs. (0.27, 10.8). Therefore, we cannot conclude, that one treatment is significantly better than the other.

3.2 Evaluation of Safety

For evaluation of safety, please refer to the Medical Officer's review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Due to the nature of this indication, all the subjects were female. In addition, based on the age group, only one pregnancy was observed in the 35 and older group. This subject was 36.6 years of age and was in the Loestrin-24 treatment arm and only had one evaluable cycle. This subject was Hispanic. Among the 18 to 35 age group, 3 were Black, 2 were Caucasian and one was Hispanic. No subgroup analysis for gender was performed.

5. SUMMARY AND CONCLUSIONS

5.1 Conclusions and Recommendations

Based on the data provided by the sponsor, from the statistical standpoint, Norethindrone Acetate 1 mg/Ethinyl Estradiol 20 mcg Oral Tablets (Loestrin-24) seems adequately effective for the prevention of pregnancy. A total of 12 pregnancies were reported to have occurred in the clinical trial; 10 in 24-day regimen, and 2 in the 21-day arm. However, 5 of the 10 pregnancies in the Loestrin 24 arm were not assessed as having occurred while the subjects were on treatment with Study Drug. In the Modified Intent-to-Treat (MITT) population, the 21-day treatment arm had 2 occurrences of pregnancies in a total of 873 28-day treatment cycles, resulting in a Pearl Index (PI) of 2.98 (95% CI from 0.27 to 10.8). The Loestrin-24 treatment arm had a total of 5 pregnancies in a total of 3,565 28-day treatment cycles, resulting in a Pearl Index of 1.82 (95% CI from 0.51 to 4.36); if the one unconfirmed pregnancy is

considered, there were 6 pregnancies, resulting in a Pearl Index of 2.19 (95% CI from 0.77 to 4.63), also demonstrating acceptable efficacy compared to the 21-day Loestrin, with a PI of 2.98. However, the 24-day regimen's 95% Confidence Intervals for the PI using either 5 or 6 pregnancies overlap with the 21-day regimen: with 5 pregnancies (0.51, 4.36) vs. (0.27, 10.8), and with 6 pregnancies (0.77, 4.63) vs. (0.27, 10.8). Therefore, we cannot conclude that one treatment is significantly better than the other.

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