CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-375/S-016

STATISTICAL REVIEW

Statistical Review and Evaluation
Clinical Studies[1]

Date:

NDA #: 20-375 / SE016

Applicant: BERLEX

Name of Drug: Climara® E_2-TDS (Estradiol Transdermal System)

Indication: treatment of vasomotor symptoms associated with menopause

Documents Reviewed: Vol. 32.1, 32.5-32.8, 32.20-32.25

Statistical Reviewer: Kate Meaker, M.S. (HFD-715)

Medical Input: Phill Price, M.D. (HFD-580)

Summary of Studies

This application requests the indication for the treatment of vasomotor symptoms in postmenopausal women for the Climara 6.5 cm^2 E_2-TDS patch (delivers 0.025 mg/day). Three higher doses of the Climara patch have already been approved for this indication (12.5, 18.75, and 25.0 cm^2).

There are 2 studies submitted for consideration in the application (see Table 1). The focus of the efficacy review will be the placebo-controlled study, #97074. The primary comparison to assess efficacy will be the comparison of the Climara to placebo. Study #97095 did not include a placebo group. The results from the Climara group in that study will provide supportive evidence but no comparisons will be made to the active-control conjugate equine estrogen 0.3 mg (CEE) treatment group.

Table 1: Summary of Randomized, Controlled Studies

Study Number (Dates Conducted)	# of Centers (Locations)	Treatment Arms (# Randomized)	Study Design	Duration of Treatment
97074 (1/98 – 5/99)	18 (all U.S.)	Climara 6.5 cm^2 (n=92) Placebo (n=94)	Multicenter, Randomized, Double-blind, Placebo-control	12 weeks
97095 (1/98 – 1/99)	19 (all U.S.)	Climara 6.5 cm^2 (n=95) Premarin 0.3 mg/day (n=98)	Multicenter, Randomized, Double-blind, Active-control	12 weeks

[1] Clinical studies

STUDY # 97074

Background

This is a multicenter, double-blind, placebo-controlled, randomized study designed to determine the efficacy of the Climara 6.5 cm^2 patch for the relief of vasomotor symptoms. Subjects were postmenopausal women, ages 45 or older, who experienced 7 or more moderate to severe vasomotor symptoms (MSVS) per day for 1 week or at least 60 MSVS in 1 week during the screening period. After screening, subjects were randomly assigned, using a 1:1 ratio, to one of the 2 treatment arms. Treatment was provided for 12 weeks.

There are 4 primary variables - the change from baseline in the mean daily number of MSVS at Week 4 and Week 12 on treatment, and the change from baseline in the mean daily severity of hot flushes at Week 4 and Week 12 on treatment. Efficacy on all four variables, vs. placebo, must be demonstrated to support the VMS indication. Comparisons between the Climara patch arm and the placebo arm are the primary focus for assessing efficacy. This is the only placebo-controlled study in this NDA application.

The subjects recorded the incidence and severity of vasomotor symptoms in a daily diary. The subjects then telephoned an Interactive Voice Response System (IVRS) to record their information. The frequency of MSVS is averaged over 7 days for each week in the 12-week treatment period. The severity was calculated as the mean severity per day with mild hot flushes given a score of 1, moderate a score of 2, and severe a score of 3.

A total of 186 patients were randomized to the two treatment groups, 92 to the Climara group and 94 to the placebo group. The two groups were similar with regard to demographic characteristics, and the mean number and severity of MSVS at baseline. There was a higher rate of discontinuation in the placebo group (20.2% vs. 6.5%) but this was primarily due to dropouts for lack of efficacy or withdrawal of consent (see Table 2). Also, more dropouts occurred earlier in the placebo group. These results are not unreasonable for a 12-week placebo-controlled study.

Table 2: Reason for Dropouts (Study 97074)

	Climara (N=92)	Placebo (N=94)
Reason	n (%)	n (%)
Adverse event	0 (0.0)	2 (2.1)
Lack of efficacy	3 (3.3)	7 (7.5)
Protocol deviation	0 (0.0)	2 (2.1)
Withdrawal of consent	2 (2.2)	6 (6.4)
Other	1 (1.1)	2 (2.1)
Total	6 (6.5)	19 (20.2)

Source: Vol. 5, Table 8

Applicant's Analysis

The planned analysis was to use an ANOVA model with factors for treatment and center to provide between-group comparisons for each of the four primary variables. The actual data was rather skewed, probably due to some extreme baseline values. The test for normality of the residuals did not meet the assumption necessary for the ANOVA. Therefore the applicant applied a non-parametric ANOVA model to the ranks and used the Kruskal-Wallis test instead. This is an appropriate alternative in this circumstance. The intent-to-treat (ITT) patient population was defined as all randomized subjects and was used for the efficacy analyses.

The applicant's results for the analyses are shown in Table 3 on the next page. The reported p-values are for the between-group comparisons of Climara to placebo at Week 4 and Week 12. The results for Week 8 are secondary and are shown for consistency, but hypothesis tests are not of interest for that timepoint.

Conclusions - Study #97074

This study provides the primary data to support the efficacy of this dose of the Climara patch. The results of the analyses show that the Climara patch was statistically significantly different from, and better than, the placebo for all 4 of the primary endpoints. This supports the efficacy of the Climara patch.

Table 3: Applicant's Results: (Study #97074)

		Climara 6.5 cm^2 patch	Placebo
Change from Baseline in Mean Daily Number of MSVS			
Week 4	N	82	83
	Mean	-6.45	-5.11
	Std. Dev.	4.65	7.43
	p-value		0.002
Week 8	N	84	71
	Mean	-7.69	-5.98
	Std. Dev.	4.76	8.63
	p-value		not applicable
Week 12	N	68	65
	Mean	-7.56	-5.98
	Std. Dev.	4.64	9.69
	p-value		0.003
Change from Baseline in Mean Daily Hot Flush Severity			
Week 4	N	82	83
	Mean	-0.81	-0.18
	Std. Dev.	0.99	0.55
	p-value		≤0.001
Week 8	N	84	71
	Mean	-1.05	-0.36
	Std. Dev.	1.10	0.76
	p-value		not applicable
Week 12	N	68	65
	Mean	-1.08	-0.53
	Std. Dev.	1.11	0.92
	p-value		≤0.001

Source: Vol. 38, Tables 15 and 21.

STUDY # 97095

Background

This is a multicenter, double-blind, active-controlled, randomized study. The primary objective was to determine the efficacy of the Climara 6.5 cm^2 patch for the relief of vasomotor symptoms in postmenopausal women. The subjects were women, 45 years of age or older, who experienced 7 or more moderate to severe vasomotor symptoms (MSVS) per day for 1 week or al least 60 MSVS in 1 week during the screening period. After screening, subjects were randomly assigned, using a 1:1 ratio, to the two treatment groups. They received treatment for 12 weeks.

This study used a double-dummy design to protect the blind. The Climara treatment group received a Climara patch to be worn continuously and placebo pills to take orally daily. The CEE group received a placebo patch to be worn continuously and Premarin 0.3 mg/day pills to be taken orally.

There are 4 primary variables - the mean change from baseline in the mean daily number of MSVS at Week 4 and Week 12 on treatment, and the mean daily severity of hot flushes at Week 4 and Week 12 on treatment. Efficacy on all four variables, vs. placebo, must be demonstrated to support the VMS indication. Patients recorded the incidence and severity of hot flushes in a daily diary.

This study did not include a placebo treatment arm. The protocol originally planned for within-group paired tests for Week 4 and Week 12 to baseline. However, within-group comparisons are not appropriate to assess efficacy for this indication. Comparisons between the Climara arm and the CEE arm to show equivalence are not appropriate because this study was not adequately designed to reach efficacy conclusions based on those comparisons. The Climara vs. CEE comparisons are not of interest to the Medical Officer. Therefore I will review only the descriptive statistics results for the Climara arm from this study as supportive evidence to the results from study #97074.

A total of 193 patients were randomized to the two treatment groups, 95 to the Climara patch group, and 98 to the Premarin arm. Since only the results from the Climara arm are of interest here, I compared the demographic characteristics of that group to the subjects enrolled in study #97074. The subjects in this study were similar on all the demographic variables and baseline number and severity of hot flushes.

I also compared the number of dropouts and reasons for discontinuing for the Climara treatment group in this study to the Climara treatment group in study #97074 and found that there was a much higher dropout rate in this study. A total of 16 (16.8%) of the 95 patients randomized to the Climara arm discontinued during treatment. As shown in Table 4, the most common reasons given were Adverse event (5; 5.3%) and Other (4;

4.2%). There was no unusual pattern to the timing of the dropouts over the treatment period.

Table 4: Reason for Dropouts (Study 97095)

	Climara (N=95)
Reason	**n (%)**
Adverse event	5 (5.3)
Lack of efficacy	2 (2.1)
Protocol deviation	2 (2.1)
Withdrawal of consent	3 (3.2)
Other	4 (4.2)
Total	16 (16.8)

Source: Vol. 20, Table 8

Applicant's Analysis

The Intent-to-Treat (ITT) patient population was defined as all patients randomized to treatment. The descriptive results are presented in Table 5 below. I have not reported the results from the CEE active-control arm, nor the applicant's comparisons to that arm, because this study was not adequately designed to make efficacy conclusions based on those comparisons and they are not of interest to the Medical Officer.

Table 5: Applicant's Results: (Study #97095)

		Climara 6.5 cm^2 patch
Change from Baseline in Mean Daily Number of MSVS		
Week 4	N	88
	Mean	-7.07
	Std. Dev.	4.17
Week 8	N	83
	Mean	-7.91
	Std. Dev.	4.74
Week 12	N	75
	Mean	-8.39
	Std. Dev.	4.53
Change from Baseline in Mean Daily Hot Flush Severity		
Week 4	N	88
	Mean	-0.67
	Std. Dev.	0.88
Week 8	N	83
	Mean	-1.02
	Std. Dev.	1.03
Week 12	N	75
	Mean	-1.33
	Std. Dev.	1.09

Source: Vol. 38, Tables 16 and 22.

Conclusions - Study #97095

The results of the Climara group from this study are similar to the results for the Climara group in study #97074. This provides supportive evidence for the efficacy of this dose of Climara.

Combined Results - Study #97074 and #97095

In the ISE the applicant combined the subjects from the Climara treatment arms in studies #97074 and #97095, and compared them to the placebo treatment arm from study #97074. These results are shown in Table 6 below. The applicant has proposed that the combined results be presented in the label. The studies had the same patient population, screening criteria, and treatment regimens. However, in other labels for this indication only the results from placebo-controlled studies have been presented. The results from study #97074 are sufficient to support this indication for this dose level, so I feel only those results, from the placebo-controlled study, should be presented in the label.

Table 6: Applicant's Results: 97074 and 07095 Combined

		Climara 6.5 cm^2 patch	Placebo
Change from Baseline in Mean Daily Number of MSVS		97074 & 97095	97074 only
Week 4	N Mean Std. Dev. p-value	170 -6.77 4.40	83 -5.11 7.43 ≤0.001
Week 8	N Mean Std. Dev. p-value	167 -7.80 4.74	71 -5.98 8.63 not applicable
Week 12	N Mean Std. Dev. p-value	143 -8.00 4.58	65 -5.98 9.69 ≤0.001
Change from Baseline in Mean Daily Hot Flush Severity			
Week 4	N Mean Std. Dev. p-value	170 -0.74 0.93	83 -0.18 0.55 ≤0.001
Week 8	N Mean Std. Dev. p-value	167 -1.03 1.06	71 -0.36 0.76 not applicable
Week 12	N Mean Std. Dev. p-value	143 -1.21 1.10	65 -0.53 0.92 ≤0.001

Source: Vol. 38, Tables 14 and 20.

Conclusions

Study #97074 provides the only direct comparison of Climara to placebo. The Climara arm was statistically significantly different from, and better than, the placebo arm for all four primary endpoints. This study clearly supports the efficacy of the Climara patch at the proposed dose.

In Study #97095 the lack of a placebo arm precludes formal comparisons for efficacy; however, the Climara group provides descriptive statistics which are comparable to those for the Climara treatment group from study #97074. This study thus provides additional support for the efficacy of Climara.

In study #97095 and in the ISE the applicant performed between-group comparisons of Climara to the active-control (CEE) treatment group. In the ISE, the applicant also presented confidence intervals for the difference between the Climara and CEE treatment groups and concludes the groups are equivalent. These are not appropriate comparisons or conclusions, as study 97095 was not adequately designed to be able to determine equivalence. These comparisons should not be used to imply efficacy of the Climara treatment.

Therefore, the results of the CEE treatment group from study #97095 should not be tabulated in the label, and statements regarding comparisons to CEE should not be included in the label text. If p-values are printed in the table, the only p-values to include would be for Week 4 and Week 12 for the between-group comparison of placebo to Climara. Moreover, the table should be consistent with other labels for this indication.

This application is requesting approval of a dose of Climara which is lower than the three doses already approved. The results from study #97074 indicate that this dose of Climara is efficacious compared to placebo. That conclusion is supported by the results of the Climara arm in study #97095. Thus, I feel there is sufficient evidence to support efficacy of this lowest dose.

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Concur: Dr. Welch
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cc:
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