

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-847

MEDICAL REVIEW(S)

Medical Officer's Original Summary of NDA 20-847

NDA 20-847

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Applicant: Fournier Research Inc.
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Fairfield, NJ 07004 USA

1. General Information:

a. **Name of Drug**

(1) Generic: 17 β -Estradiol transdermal system

(2) Proposed Trade Name: Esclim®

(3) Chemical Name: Estra-1,2,5(10)-triene-3,17beta-diol

b. **Pharmacologic Category:** Steroid Hormone

c. **Proposed Clinical Indication:** The treatment of moderate to severe vasomotor symptoms associated with the menopause. Associated indications include treatment of vulvar and vaginal atrophy, and treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.

d. **Dosages and route of administration:** 0.025, 0.0375, 0.05, 0.075 and 0.1 mg of estradiol per day administered through a self-adhesive matrix-type transdermal delivery system

e. **Related Drugs:** Estrogen transdermal skin patch (Estraderm® Alora®, Climera®, Vivelle®), oral estrogens, injectable estrogens

2. Manufacturing Control Data: See Chemist Review

3. Pharmacologic Review: See Pharmacologist Review

4. Biopharmaceutics Review: The pharmacokinetics of the Esclim patches has been investigated and is adequate for approval. Esclim patches when applied to various sites (Iliac fossa, buttock, femoral triangle and upper arm) were not found to be bioequivalent. The abdomen area under the curve for the abdomen was 18% lower than that found for the buttock. This difference may be clinically significant therefore the abdomen will not be approved as a site for Esclim.

5. Consultation: See Biometric Review

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1.0 Resume

The applicant has submitted the results from three controlled clinical studies to support the following indication treatment of moderate-to-severe vasomotor symptoms associated with menopause. In addition since current guidance allows for the inclusion of treatment of vulval and vaginal atrophy, treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure as associated indications, these will automatically follow the vasomotor symptom indication. Two of the studies (TS 17 9301, TS 17 9102) were double blind and placebo controlled. A third study was open label and parallel vs. Estraderm®. These studies were submitted to support the proposed use of 17β-Estradiol transdermal system (Esclim®) for treatment of moderate to severe vasomotor symptoms associated with menopause, vaginal or vulvar atrophy, and the treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. The primary parameter of efficacy was the reduction in number of moderate to severe hot flushes per day from baseline to the fourth week of treatment. There were no unexpected issues of safety. Local skin tolerability and adhesion of the patch were acceptable for approval. The five doses of this product are approvable because efficacy and safety have been demonstrated in multiple well controlled studies.

2.0 Background

2.1 Regulatory history

Summary of Regulatory Milestones

Date	Activity
May 13,1994	Protocol for study 9301(large US study) submitted
August 1994	Protocol review completed and comments given to sponsor
December 1996	Telecon with sponsor to discuss the addition of intermediate doses
May 1997	Meeting with sponsor to discuss integrated safety summary
August 1997	NDA filing
December 1997	Submission of Safety Update Report

2.2 Clinical Background:

Relevant human experience

After menopause estrogen production decreases dramatically, leading to the occurrence of vasomotor symptoms and atrophic vaginitis. Estrogen replacement therapy can help relieve these symptoms. Risks of estrogen replacement therapy include but are not limited to endometrial hyperplasia and endometrial cancer. Oral estrogens are the most widely used form of estrogen therapy. To compensate for rapid first pass metabolism and gut wall inactivation large doses of oral estradiol must be given to achieve therapeutic blood levels. This results in estrone levels that are

higher, than those observed in premenopausal women. These higher estrone levels are of unknown clinical significance. Oral administration of estrogen also induces hepatic protein synthesis including renin substrate (angiotensinogen), sex hormone binding globulin, and thyroxin binding globulin. These changes may have important clinical effects including; theoretical risk of hypertension (hypertension has not been associated with use of oral estrogen in clinical trials), thrombotic disease and cardiovascular morbidity. Administration of estrogen with the transdermal patch appears to avoid the induction of hepatic protein synthesis and avoids the first pass hepatic effect. Theoretical benefits of transdermal estrogen over oral estrogen include the following. Transdermal estrogen: 1.) may minimize nausea 2.) may decrease the incidence of gallbladder disease.¹ 3.) can be used at a lower dose than oral estrogen (this may be related to the first pass hepatic effect or possibly because transdermal estrogen results in more consistent blood levels).² 4.) may have fewer effects on insulin metabolism 5.) may decrease thromboembolic risks.^{3,4,5} Unlike oral estrogens which increase HDL cholesterol transdermal estrogens have demonstrated minimal effects on HDL and LDL cholesterol.

2.3 Related INDs and DNAs

This product was the subject of IND NDA 20-375 Climera, NDA 20-538 Menorest, and NDA 20-665 Alora (all transdermal estrogens for similar indications) were reviewed for this NDA in preparation for this review.

2.4 International marketing experience

Marketing authorization for TS 17 (25, 50 and 100µg) was granted in France on November 7, 1994, where the products have been marketed since March 1995 under the brand name of Oesclim®. These same three doses of TS 17 were also approved for marketing in China, on January 16, 1997, and in Denmark on June 18, 1997, although marketing has not begun in these countries.

Laboratoires Fournier has a reporting system, which monitors adverse events. The period for reported cases is from March 1995 to present. During this period, total sales in patient months were The great majority (60 %) of reported events was related to skin

¹ Van K.J. Van Berge Hebgijweb GP, Verschoor L, Stoelwinder, Willekens FLH. Different hepatobiliary effects of oral and transdermal estradiol in postmenopausal women. *Gastroenterology* 191;100:482- 8

² Balfour JA, Heel RC. Transdermal estradiol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of menopausal complaints. *Drugs* 1990;40:561-82

³ Godsland IF, Gangar K, Walton C, et al. Insulin resistance, secretion, and elimination in postmenopausal women receiving oral and transdermal hormone replacement therapy. *Metabolism* 1993; 42:846-53

⁴ Chetkowski RJ, Meldrum DR, Steingold KA, et al. Biologic effects of transdermal estradiol. *New England Journal of Medicine* 1986;314:1615-20

⁵ Corson SL. A decade of experience with transdermal estrogen replacement therapy: overview of key pharmacologic and clinical findings. *International Journal of Fertility* 1993;38:79-91

and/or application site reactions. Adverse events reported to Laboratoires Fournier are listed in the table below:

Table 1. Summary of Adverse Events by Body System

Event	Number of cases
Skin and appendages	56
Vision (Conjunctivitis)	4
Reproductive	6
Body as a whole	8
Gastrointestinal	4
Liver and biliary	1
Cardiovascular (Hypertension)	2
Central and peripheral nervous	2
Urinary	2
Respiratory	1
Platelet, bleeding and clotting (Thrombotic microangiopathic syndrome)	1
Pancreatitis	1
Thrombosis	1
Pleural effusion	1

Perhaps the three most serious adverse events noted were the following three cases. A 31-year-old patient, who had been prescribed Esclim 100µg/day for the treatment of dysmenorrhea, developed thrombotic microangiopathy syndrome. The sponsor indicated that the patient was treated with a plasma exchange. She required a 1½ month hospitalization; she recovered and follow-up lab revealed no evidence of anemia or thrombocytopenia. A patient received Esclim 25µg/day as treatment for severe premenstrual headaches developed giant urticaria associated with angioedema. This patient had multiple allergies (including nickel and nylon) and the angioedema occurred one day after her last Esclim patch was discontinued. This patient was admitted to an emergency room where she was treated with oxygen and steroids. The patient recovered after hospitalization. The dates of treatment and the dosages of medication are unknown. The third case is a menopausal 63-year old female treated from November 14 to November 20, 1997 with Esclim 25µg/day, for estrogen deficiency-related symptoms. Five days after beginning Esclim treatment the patient developed a pleural effusion. She was not reported to be hospitalized but was treated with a thoracentesis. A lung scan was performed and it was normal. Treatment with Esclim was withdrawn and the event resolved. A relationship between Esclim therapy and these serious adverse events is doubtful.

3.0 Description of Clinical Data Sources (IND and non-IND)

3.1 Summary of controlled trials

The three major controlled trials were:

Clinical trial TS 17 9301—a twelve to thirteen week double blind, randomized, placebo controlled, parallel group, multicenter, US study which enrolled 196 women with vasomotor symptoms; 176 women completed this trial. This study was the pivotal U.S. trial.

Clinical Trial TS 17 9102— a twelve to thirteen week, double blind, randomized parallel vs. placebo, placebo controlled, multicenter European study which enrolled 61 women; 54 women completed this trial.

Clinical Trial TS 17 9104—a sixteen week, open label, randomized, parallel vs. Estraderm®, fixed dose, discontinuous sequential, multicenter, European study in 283 women; 250 women completed this trial.

3.2 Summary of uncontrolled trials

Two uncontrolled trials were:

Clinical Trial 9103—a twelve month open label, multicenter, European study in 224 women; 175 women completed this trial. Patients were given either continuous or discontinuous treatment (patients did not use the patch for 3 to seven days each month) with TS 17 systems. Dose was initiated with TS 17 50µg. and was titrated up or down based on patients symptoms. Unlike the other clinical trials this trial required 56 moderate to severe vasomotor symptoms per week for entry, included surgically and naturally menopausal patients. Also patients in this study were more ethnically diverse, and therefore more representative of United States consumers.

Clinical Trial 9201—a 3 year, open label, multicenter, extension trial for patients who were enrolled in European trials TS 17 9102 and TS 17 9104, or US trial TS 17 9301. A total of 411 patients enrolled in this study; 314 (76.4%) completed the study. Dose adjustment was allowed at any time.

Addition details of the three pivotal trials 9301, 9102, and 9104 follow.

4.0 Clinical trial #1—Study C TS 17 9301

4.1 Objective/rationale

The primary objective of this study was to compare the efficacy of 12 weeks of treatment with three doses of TS 17 (25, 50, 100µg/24hours) with that of placebo on moderate to severe vasomotor symptoms in women presenting with menopause-related estrogen

deficiency. The secondary objectives were to evaluate the efficacy of all three doses on other postmenopausal symptoms and to assess the local tolerability, general safety and study drug acceptability.

4.2 Design

This was a twelve to thirteen week, double blind, randomized, placebo-controlled, parallel, multi-center study performed in the United States of America. Patients were evenly randomized into one of the following four arms:

- (1.) placebo
- (2.) TS 17 25 (11 square cm) delivers 0.025 mg of 17 β -estradiol over 24 hours from 5 mg contained within the matrix
- (3.) TS 17 50 (22 square cm) delivers 0.05 mg of 17 β -estradiol over 24 hours from a 10 mg contained within the matrix
- (4.) TS 17 100 (44 square cm) delivers 0.1 mg of 17- β estradiol over 24 hours from 20mg contained within the matrix.

Therapy with study drug was continuous, and the concomitant use of progestins was prohibited. Study visits were at 4, 8, and 12 to 13 weeks of treatment.

4.3 Study population

Characteristics of the study populations at baseline are summarized in the table below.

Table 2. Demographic data at baseline by treatment group

Parameter	Placebo	TS 17 25	TS 17 50	TS 17 100
Number of patients	N=54	N=48	N=47	N=47
Age (years)				
Mean \pm SD	49.8 \pm 6.6	50.7 \pm 6.3	50.1 \pm 6.8	50.1 \pm 6.7
N	54	48	47	47
Race: no. of patients (%)				
Caucasian	52 (96.3)	42 (87.5)	43 (91.5)	45(95.7)
Black	2 (3.7)	4 (8.3)	4(8.5)	2 (4.3)
Other	-	2 (4.2)	-	-
N	54	48	47	47
Height at screening (inches)				
Mean \pm SD	64.6 \pm 2.4	64.0 \pm 3.4	64.1 \pm 2.0	64.6 \pm 2.6
n	54	47	47	46
Weight at VO (lb.)				
Mean \pm SD	167.9 \pm 31.6	166.9 \pm 37.6	156.7 \pm 32.6	167.1 \pm 29.0
N	52	47	46	46
Estimated age at menopause				
Mean \pm SD	42.8 \pm 8.7	43.1 \pm 7.5	45.7 \pm 7.2	43.9 \pm 6.8
N	37	35	31	30
Type of menopause				
Number (%)				
Natural	34 (63.0)	27 (56.3)	38 (80.9)	35 (74.5)
Surgical	20 (37.0)	21 (43.8)	9 (19.2)	12(25.5)
N	54	48	47	47

A total of one hundred and ten enrolled patients had undergone a hysterectomy and were not evaluable for vaginal bleeding or endometrial hyperplasia. The two groups with the

highest percentage of surgical menopause were the placebo and the lowest dose Esclim® group, therefore bleeding and endometrial hyperplasia can still be assessed at the highest doses of Esclim® where the effects are most likely.

4.4 Inclusion and exclusion criteria

Inclusion Criteria

- may have been out-patients
- were either ovariectomized for benign pathology or had been amenorrheic for six months leading to presumption of menopause
- were likely to experience at least 56 moderate to severe vasomotor symptoms per week while not receiving estrogen replacement therapy based on the history of menopause
- presented, a priori, adequate time availability and motivation to participate in the trial as well as the ability to communicate, understand and comply with the requirements of the study
- must have read the patient informed consent form and given their written consent
- were not participating in another clinical trial, and had not been participating in a clinical trial for at least 30 days.

Women who had previously been or were currently being treated for menopausal symptoms with any product were eligible to enter the screening period. For those patients already receiving a hormonal treatment (estrogen and/or progestin), a wash-out period of at least two months was to be observed before the baseline visit when the patient was allocated to treatment

Exclusion criteria

- biliary lithiasis.
- personal past history of idiopathic jaundice or pruritus during pregnancy.
- presence or symptoms of pituitary tumor (galactorrhea)
- ongoing and/or past history of thromboembolic disease.
- history or presence of breast cancer.
- current and/or past history of gynecological malignant pathology.
- current symptomatic or large volume fibroma.
- endometriosis, apart from adenomyosis in hysterectomized patients.
- unexplained metrorrhagia.
- cardiovascular disease: valvulopathies and/or thrombogenic rhythm disorders and/or myocardial infarction and/or cardiac insufficiency.
- severe uncontrolled hyperlipidemia.
- uncontrolled hypertension.
- diabetes mellitus.
- current or past history of cerebrovascular disorder.
- epilepsy.
- ocular pathology of vascular origin.
- known allergy to estrogen therapy.

- pregnancy.
- known alcoholism and/or drug abuse.
- irregular metrorrhagia during HRT (apart from withdrawal bleeding in the case of discontinuous treatment).
- chronic skin disease (e.g. eczema, psoriasis). Likely to interfere with evaluation of skin tolerability.
- past history of cutaneous contact allergy to adhesives, cosmetics or topical medications including to transdermal delivery systems.
- patients receiving hepatic enzyme inducers: barbiturates, hydantoins, carbamazepine, meprobamate, phenylbutazone, rifampin.
- patients receiving troleandomycin (risk of cholestatic hepatitis).
- patients receiving systemic corticoids (however patients receiving systemic cortioids for an acute pathology for no more than one week were allowed in the trial) and/or thyroid hormone.
- current or past history of psychiatric illness and/or major depression not related to menopause.

4.5 Screening period.

During a screening period that was variable but greater than 14 days, informed consent was obtained from the patient. A physical examination was performed, which included measurement of height, weight, blood pressure, pulse, gynecological exam including vaginal smears and breast exams to assess the patients eligibility. Laboratory tests and mammography were requested. Patients previously treated for menopause were required to undergo a washout period of eight weeks from last dose of hormonal treatment or four weeks from non-hormonal treatment (including Clonidine). The number and severity of vasomotor symptoms that occurred daily for the last fourteen days of the screening period were recorded. Treatment was to begin within seven days of completing the fourteen day baseline evaluation.

4.6 Treatment period

Baseline visit

Qualified patients were randomly assigned to receive one of four treatments: TS 17 25, TS 17 50, TS 17 100, or matching placebo. Patients were given a Follow-Up Diary and were instructed in how to record their symptoms.

Treatment:

Treatment regimens were identical for treated and placebo groups. Therapy was continuous and unopposed. Patients applied a new transdermal patch twice a week (patches were changed after three days and after four days). Each patient was instructed to apply a patch to the upper part of the buttock. Successive applications were not to be made to the same buttock.

Visit 1 (week 5) and visit 2 (week 9)

Interim physical examinations were performed, diary data were reviewed, the patient was asked about any change in symptoms, and the patch sites were examined. Data was extracted from the diary and case report forms when completed. An assessment of safety and adverse events was obtained. Hormone levels were monitored.

Visit 3 (week 13) end of trial

Evaluations done at visit 1 and 2 were again performed. A complete physical including gynecological exam, breast exam and endometrial biopsy was performed. Laboratory safety tests were obtained. Evaluation and documentation of safety and efficacy was accomplished.

4.7 Evaluation criteria

The primary efficacy endpoint was a comparison of the mean number of moderate to severe vasomotor symptoms per 24 hours recorded in the fourteen day baseline period to those which occurred during week four of the trial.

Reviewer's comments:

Though the primary efficacy endpoint of this trial was assessed at four weeks (and this was agreed upon between sponsor and the FDA), it is usual for approval that statically significant differences in moderate to severe vasomotor symptoms be demonstrated at week 12. This review will also assess the week 12 evaluation of efficacy.

Secondary efficacy criteria included:

- the assessment of changes from baseline in the mean severity score and in the mean number of moderate to severe vasomotor symptoms recorded daily by the patient throughout the 12 weeks of treatment
- gynecological assessment based on the trophicity of the vaginal smears maturation index, the trophicity of the vulva and the presence of mucus
- the assessment of changes in general condition globally assessed by the patient during the final visit by evaluating any change in vitality and well-being
- the assessment of overall study on signs of estrogen deficiency evaluated by the investigator and by the patient during the final visit
- the assessment of other accompanying symptoms such as sleep disorders, asthenia, mood disorders, headaches, osteoarticular pain, libido disorders, sensation of vaginal dryness, urinary continence disorders evaluated at each visit by the patient

4.8 Withdrawal and compliance:

Of the 196 patients enrolled, 176 completed the full 12 week study. Reasons for discontinuation of treatment are summarized below.

Table 3
Number (%) of patients discontinued from double-blind treatment (all treated patients)

Reason for discontinuation	Placebo (N=54)	TS17 25 (N=48)	TS 17 50 (N=47)	TS17 100 (N=47)	Total (N=196)
Adverse event	-	2(4.2)	3(6.4)	2(4.3)	7(3.6)
Ineligible patient whose safety may be jeopardized by the study	-	-	-	1(2.1)	1(0.5)
Lack of efficacy	5(9.3)	-	1(2.1)	-	6(3.1)
Consent withdrawn	2(3.7)	1(2.1)	-	-	3(1.5)
Lost to follow-up	-	1(1.2)	-	1(1.2)	2(1.0)
Other reasons	1(1.9)	-	-	-	1(0.5)
Total	8(14.8)	4(8.3)	4(8.5)	4(8.5)	20(10.2)

The adverse events resulting in discontinuation in the TS 17 25 group were;

- spotting in one patient ,
- A concussion and a broken ankle after an auto accident in the other.

In the TS 17 50 group the adverse events were:

- vaginal bleeding in two patients. One patient with vaginal bleeding was diagnosed with atypical and complex hyperplasia. She was ultimately transfused two units of blood and underwent a hysterectomy
- a patient with various symptoms including cardiac chest pain, metallic taste in her mouth, nausea, headache, weakness, chills, fatigue and diarrhea.

The 2 adverse events in the TS 17 100 group were;

- vaginal bleeding in one subject,
- a rash and edema in the other subject.

Reviewer's comments: The discontinuation rates in the active treatment groups were less than 10%. Most of the reasons for discontinuation in the placebo arm were related to lack of efficacy, while those in the active treatment arm were related to adverse events. This supports the activity of Esclim®. There were no unexpected treatment-related adverse events responsible for discontinuation in the active treatment groups.

4.9 Efficacy analyses:

The primary efficacy variable was the number of moderate to severe vasomotor flushes per day comparing baseline to the fourth week of treatment for all evaluable patients. For patients who discontinued prematurely, their final value was carried forward in the ITT analysis. Secondary efficacy evaluations included other evaluations of vasomotor symptoms, evaluation of other symptoms of menopause, gynecological assessments and assessments of hormonal levels.

Primary efficacy analyses

Mean reduction in moderate to severe vasomotor symptoms (MSVS) per day from baseline to week four compared to placebo

Table 4

Number of MSVS per day at baseline and week 4 of treatment and reduction from baseline in patients evaluable for efficacy at week 4: mean±SD

Number of vasomotor symptoms per day	Placebo (n=54)	TS 17 25 (n=48)	TS 17 50 (n=47)	TS 17 100 (n=47)
All treated patients up to four weeks				
Baseline Number of MSVS	11.4±3.7	11.6±5.4	10.9±4.2	11.2±2.8
Week 4 Number of MSVS	6.1±5.3	3.0±3.5	1.7±2.7	1.0±2.0
Reduction from baseline week 4	5.3±4.1	8.6±5.7*	9.2±4.5*	10.2±2.9*

Modified from Table 43: page 8-6568

*Statistically significant difference from placebo in mean reduction in MSVS (Dunnett's test $p < 0.05$)

The mean baseline frequency of moderate to severe vasomotor symptoms was more than seventy five per week.

Reviewer's comments:

A statistically significant reduction in vasomotor symptoms ($p < 0.05$) was seen in all three actively treated groups compared to placebo by week four. All these doses therefore meet the primary endpoint. The above information and table is based on all treated patients. The reduction in the number of vasomotor symptoms from baseline was also dose proportional. This supports the predictability of dosage response and supports the approval of intermediate doses (37.5 µg/day and 75 µg/day), even though these doses were not specifically studied.

Secondary efficacy analyses

1. Vasomotor symptoms

The four treatment groups were compared with respect to the mean reduction from baseline of MSVS at each week of treatment. In the table below are the results at week 4, 8, and 12 compared to baseline, for the evaluable subgroup of patients.

Table 5.

Number of MSVS per day over the 12 week treatment period and reduction from baseline: mean \pm SD and percentage reduction from baseline in the number of MSVS per day: Evaluable patients.

	Placebo	TS 17 25	TS 17 50	TS 17 100
Number of patients	(N=48)	(N=42)	(N=39)	(N=38)
Baseline				
Number of MSVS per day	11.5 \pm 3.8(n=48)	12.0 \pm 5.4(n=42)	11.1 \pm 4.5(n=39)	11.0 \pm 2.7(n=38)
Week 4				
Number of MSVS per day	5.8 \pm 5.4(n=48)	2.8 \pm 3.3(n=42)	1.5 \pm 2.7(n=39)	1.0 \pm 2.0(n=38)
Reduction: baseline to week 4	5.8 \pm 4.0	9.3 \pm 5.7*	9.6 \pm 4.6*	10.0 \pm 2.7*
%reduction in number of MSVS per day week 4	52.9 \pm 33.5	76.2 \pm 29.0	87.7 \pm 19.3	91.4 \pm 15.6
Week 8				
Number of MSVS per day	5.6 \pm 5.9(n=46)	2.1 \pm 3.0(n=40)	0.4 \pm 1.0(n=39)	0.5 \pm 1.4(n=38)
Reduction: baseline to week 8	5.9 \pm 4.6	9.9 \pm 5.7*	10.6 \pm 4.4*	10.5 \pm 2.6*
%reduction in number of MSVS per day week 8	54.5 \pm 38.6	82.2 \pm 24.7	96.0 \pm 9.8	95.6 \pm 10.2
Week 12				
Number of MSVS per day	6.1 \pm 7.0(n=46)	1.6 \pm 3.0(n=40)	0.4 \pm 0.7(n=37)	0.4 \pm 0.9(n=36)
Reduction: baseline to week 12	5.4 \pm 5.2	10.3 \pm 5.8*	10.8 \pm 4.4*	10.5 \pm 2.7*
%reduction in number of MSVS per day week 12	52.3 \pm 42.3	86.1 \pm 25.0	97.2 \pm 6.0	96.9 \pm 7.5

*statistically significant difference from placebo in mean reduction in MSVS (Dunnett's test) modified table 44&45(page 8-6571)

By week five all three TS 17 groups achieved an eighty percent reduction in moderate to severe vasomotor symptoms. TS 25 reduced the mean number of vasomotor symptoms at weeks 4, 8 and 12 by 76, 82 and 86% respectively. TS 50 reduced the mean number of moderate to severe vasomotor symptoms at weeks 4, 8, and 12 by 88, 96 and 97%, respectively. TS 100 reduced the mean number of moderate to severe vasomotor symptoms weeks 4, 8, and 12 by 91, 96 and 97%, respectively.

Reviewer's comment:

It is clear that all three active treatment groups showed a significant benefit over placebo in the reduction of VMS by week 4. These effects were essentially maintained at weeks 8 and 12.

The percent of patients with complete relief of symptoms again showed a dose proportional response. Data for complete relief of symptoms at four and twelve weeks is presented below (for evaluable patients only).

Table 6
Patients Evaluable for Efficacy up to Week 4 and 12: complete relief of VMS

	Placebo	TS 17 25	TS 17 50	TS 17 100
Number of patients	n=48	n=42	n=39	n=38
Week 4 Number(%) of patients with complete relief	1(2.1)	7(16.7)	16(41.0)	21(55.3)
Week 12 Number(%) of patients with complete relief	6(13.0)	23(57.5)	24(64.9)	29(80.6)

Table modified from table 47: page 6578

A mean symptom score (per patient) was used to evaluate changes in severity. The following algorithm was used

$$\frac{\text{Number of mild VS} \times 1 + \text{number of moderate VS} \times 2 + \text{number of severe VS} \times 3}{\text{Total number of VS}}$$

The mean severity score for all four treatment groups was approximately 2.4 ± 0.2 . In the TS 17 100 subjects the reduction in severity from baseline was 0.6 ± 0.6 at week 2, which was statistically significant. The TS 17 50 group reached statistical significance at week three with a reduction from baseline in mean severity of 0.8 ± 1.0 . The TS 17 25 group reached statistical significance at week six with a reduction from baseline in mean severity score of 0.9 ± 0.8 .

2. Other symptoms of menopause

The incidence and severity of urinary incontinence disorders, vaginal dryness, libido disorders, headaches, osteoarticular pain, sleep disorders, asthenia, dysparunia and mood disorders were evaluated at baseline and at each visit. Table 7 describes some of these analyses in small subsets of patients who had these symptoms at baseline.

Table 7
Changes from baseline to week 12 in other symptoms of menopause: number (%)

Menopausal symptom	Placebo	TS 17 25	TS 17 50	TS 17 100
all treated patients				
Number of patients	(n=54)	(n=48)	(n=47)	(n=47)
Urinary continence				
Worse	1(4.8)	-	1(7.1)	1(5.0)
Same	10(47.6)	7(53.9)	4(28.6)	6(30.0)
Improved	10(47.6)	6(46.2)	9(64.3)	13(65.0)
N	21	13	14	20
Dysparunia				
Same	4(57.1)	2(20.0)	-	3(30.0)
Improved	3(42.9)	8(80.0)	6(100)	7(70.0)
N	7	10	6	10
Mood disorders				
Worse	1(3.5)	2(6.5)	-	1(3.5)
Same	6(20.7)	8(24.2)	6(18.8)	6(20.7)
Improved	22(75.9)	23(69.7)	26(81.3)	22(75.9)
N	29	33	32	29
Libido disorders				
Worse	1(6.7)	3(15.0)	1	-
Same	6(40.0)	3(15.0)	1(5.6)	6(31.6)
Improved	8(53.3)	14(70.0)	16(88.9)	13(68.4)
N	15	20	18	19
Sensation of vaginal dryness				
Worse	2(7.7)	1(3.9)	-	-
Same	7(26.9)	3(15.4)	7(25.0)	5(19.2)
Improved	17(65.4)	21(80.8)	21(75.0)	21(80.8)
n	26	26	28	26

Modified from table 95 page 8-6659

Reviewers comments: The sponsor claims the data “ further demonstrated a clear trend towards a beneficial effect in symptomatic patients for each of the TS 17 treatment groups when compared to placebo for dysparunia, libido disorders and vaginal dryness.” The data from these subsets of patients evaluated are limited, and the trends are not that clear or convincing. Placebo also appears to have a high level of effectiveness for most of the symptoms evaluated. Conclusions about the effectiveness of Esclim® on these symptoms are therefore difficult to make.

Evaluation of vaginal smears

There was a statistically significant difference between all active treatment groups and the placebo group with regard to vaginal trophicity. By week 12/13 100% of evaluable patients in each of the three treatment groups had a trophic vaginal smear.

Table 8

Changes in vaginal smears between baseline and endpoint for patients with a non trophic smear at baseline: number (%) of patients

Changes in vaginal smear between baseline and endpoint	Placebo	TS 17 25	TS 17 50	TS 17 100
Patients evaluable for efficacy up to 12/13 weeks				
Worse	1(12.5)	-	-	-
Same	5(62.5)	-	-	-
Improved	2(25.0)	7(100.0)	8(100.0)	8(100.0)
N	8	7	8	8

Table 52 page 8-6589

Reviewers comment: There are only 7 to 8 patients with non-tropic smears in each treatment group. One hundred percent of actively treated patients showed improvement in vaginal smear compared to only 25% of patients in the placebo control group. These results suggest a beneficial effect of all three doses of Esclim® for the treatment of vaginal atrophy, although the available sample size is very small.

Presence or absence of mucus:

For patients evaluable for efficacy, all actively treated patients had a statistically significant improvement in mucus over the placebo group by the end of study.

Hormone evaluation

Hormone levels were evaluated between 24 and 72 hours after application of the last patch at week 5, week 9 and week 13. A linear relationship was observed between dose given and serum estradiol and estrone sulfate levels. Estrone sulfate levels increased only slightly with increasing doses. The E2/E1 ratio increased to values observed in normal pre-menopausal women. FSH levels decreased in a dose related fashion for each of the actively treated groups.

4.10 Safety analyses

Safety analyses included evaluation of adverse events, specific estrogen replacement tolerability, laboratory safety, general tolerability, laboratory safety, local skin tolerability, adhesion of the transdermal system, overall acceptability.

All adverse events were recorded. An adverse event was defined as any unwanted change in the clinical condition of the patient or a significant change in a safety determination during the trial. Adverse events were classified into a standardized terminology using the COSTART Coding Symbols for Thesaurus of Adverse Reactions Terms.

The percentage of patients with at least one adverse event was 87% for the placebo group, 81.3% for the TS 17 25 group, 91.5% for the TS 17 50 group and 95.7% for the TS 17 100 group. There were no deaths during the course of the study.

Seven patients discontinued the protocol because of adverse events:

1. One patient was in an auto accident. She was hit by a car and suffered a right parietal hematoma. This occurred only four days after beginning the TS 17 25 patch.
2. One patient a 53 year old in the TS 17 50 group, noted moderate to heavy bleeding per vagina at visit 2. The bleeding resulted in anemia. Approximately eleven weeks later the patient had a hysterectomy. The pathology report revealed simple hyperplasia.
3. Three other patients one from each active treatment group had nonserious adverse events of vaginal bleeding or spotting which was probably related to treatment. Two patients had allergic syndromes. Patient was in the TS 17 50 group. Patient as in the TS 17 100 group.

The following table describes the incidence of menorrhagia and hyperplasia in the subset of patients who had a uterus.

Table 9
Patients with a uterus who had an estrogen related adverse event

COSTART diagnosis	Placebo	TS 17 25	TS 17 50	TS 17 100
Number of patients	(N=17)	(N=14)	(N=22)	(N=18)
Menorrhagia	4(23%)	6(42%)	15(68%)	15(83%)
Hyperplasia of endometrium	0	1(7%)	12(54.5%)	9(50%)

Modification of table 64 page 8-6609 and table 71 page 8-6620number

Endometrial hyperplasia was reported in one patient (7%) in the TS 17 25 group and by 12 patients (44.5%) in the TS 17 50 group and by 9 patients (50%) in the TS 17 100 group. Endometrial hyperplasia was not reported in the placebo group.

An additional estrogen related adverse event of breast pain was experienced by 22.9% of the patients in the TS 17 25 group, by 44.7% of the patients in the TS 17 50 group, and by 40.4% of patients in the TS 17 100 group.

Reviewers comment:

Two of the patients included in the TS 17 50 as having hyperplasia did not actually have endometrial biopsies. Their inclusion in the analysis was based solely on a thickening of the endometrium by ultrasound. Nonetheless, it appears that the higher doses of Esclim® (0.05mg and 0.1 mg) had a greater rate of hyperplasia when compared to the low dose Esclim® group.

Local skin tolerability

Application site reaction was defined as the appearance of at least one of the following: redness, spots, swelling, itching or burning.

Table 10
Percentage of all applications causing application site reaction in all treated patients

Application site reactions	Placebo	TS 17 25	TS 17 50	TS 17 100	All treatment groups
Number of patients	(N=54)	(N=48)	(N=47)	(N=47)	(N=194)
Number of applications	1282	1194	1197	1207	4880
Number of site reactions	95	59	119	129	402
Number of site reactions as a percentage of applications	7.4%	4.9%	9.9%	10.7%	8.2%
Number (percent) of patients with site reaction	22(41.5)	11(23.4)	20(42.6)	26(55.3)	79(40.7)

Table 72 page 8-6626 and table 72 page 8-6627

4.11 Reviewer's assessment of safety and efficacy.

This U.S. trial is considered the pivotal trial since it had the most stringent entry criteria regarding symptom frequency and severity. In addition this trial is the only controlled trial that included a racially diverse patient population, and was the only controlled trial to evaluate the efficacy using 3 different doses of Esclim®. The results of this study demonstrate that all three treatment groups are clinically effective in reducing vasomotor symptoms by the third week of therapy. The effectiveness of treatment resulting in a complete relief of symptoms was dose proportional with the lowest dose treatment group providing complete relief to over 50% of the subjects by week twelve. Serum levels of estradiol, estrone and FSH are supportive of a clinical effect for the three patches tested. There were no unexpected drug related safety issues.

5.0 Clinical trial #2 TS 17 9102

5.1 Objective/rationale

The primary objective of this study was to evaluate the efficacy of twelve to thirteen weeks of treatment with TS 17 50 (22 square cm.) on the reduction in mean number of vasomotor symptoms per day in women presenting with menopause-related estrogen

deficiency. The secondary objectives were to evaluate the efficacy of TS 17 50 on other symptoms of menopause, vaginal smears, hormone levels and to assess the local skin tolerability, general safety and treatment acceptability.

5.2 Design

This was a 12 week, double blind, randomized, placebo controlled, multicenter study conducted in France. The study compared placebo to TS 17 50 (22 square cm.). TS 17 50 delivers 50µg/24 hr of 17β-estradiol from the 10 grams contained in the patch.

5.3 Study population

All patients in the study were Caucasian outpatients who had onset of natural menopausal more than three months prior to study participation, and had not been previously treated with hormonal medication for their menopause. The mean age in both treatment groups was 51 years (range 46 to 60 years with distribution similar for each group). The estimated age of onset of menopause was 48 years for both groups. At the time of selection for this study 28 patients had been menopausal less than nine months. For all included patients, the distribution of BMI was similar for the two treatment groups, with a range across the groups of 17.40 to 32.42 kg/meter squared, and means of about 23 kg/meter squared. The mean weight for both groups was about 60 kg with ranges of approximately 44 to 85 kg. The mean and range of pulse and blood pressure were well matched between the groups. There were no statistically significant differences between treatment groups in any baseline biological values. The mean baseline estradiol and FSH concentrations were also comparable in both groups.

The estimated duration of menopause is outlined below

Table 11.
Estimated duration of menopause

Estimated duration of menopause (years)	TS 17 50 (N=32)	Placebo (N=29)
Mean (SD)	2.63(3.44)	2.37(3.40)
Median (Range)	1.04(0.74

modified from page 8-17345

Two patients in each treatment group had a history of essential hypertension. Seven patients in the TS 17 50 and ten patients in the placebo group had a past history of uterine leiomyoma. Eleven of the patients had a hysterectomy and/or unilateral oophorectomy (6 in the TS 17 50 and 5 in the placebo group).

5.4 Inclusion and exclusion criteria

Inclusion criteria

- be followed -up as an outpatient

- be white
- be at least 48 years old
- have been amenorrheal for at least 3 months
- present signs of estrogen deficiency, and in particular vasomotor disorders (hot flushes, nocturnal sweating) related to natural menopause (women who have undergone bilateral ovariectomy cannot be selected for the trial: conversely, women presenting with natural menopause after unilateral ovariectomy or patients having undergone hysterectomy may participate in the trial)
- declare a mean of at least 5 hot flushes per 24 hours at least 4 out of 7 days, and at least one episode of nocturnal sweating 4 nights out of 7, during the seven day symptom self-evaluation period which precedes the inclusion visit.
- present, *a priori*, adequate availability and motivation to participate in the trial as well as an adequate command of the French language
- have read the patient information leaflet and given their written consent
- do not present any cutaneous lesions on the buttocks
- have undergone a recent mammography (in the last year) which did not reveal any benign mastopathy nor any malignant growth.
- have undergone a vaginal smear (endocervix and ectocervix) with vaginal cytochemical examination, which did not reveal any major abnormality.
- have undergone the progesterone test (10 days of progestogen treatment) carried out between the selection and inclusion visits, and gave a negative result (no gynecological bleeding after the progestogen was withdrawn),
- have undergone a set of laboratory safety tests performed after the selection visit and before the progestogen treatment of the above-mentioned test began, in the patient who had been fasting since the previous evening, and comprising:
 - a. Hormone assay demonstrating the low plasma levels of estradiol and the high levels of FSH, compatible with postmenopausal diagnosis and dependent upon the norms of the various laboratories of medical analyses employed,
 - b. liver function tests that do not demonstrate any severe hepatic disorder:
 - gamma GT \leq 3 times the upper limit of the laboratory range (IU/l)
 - transaminase (SGOT, SGPT) \leq 2 times the upper limit of the laboratory range (IU/l)
 - total bilirubin \leq 2 times the upper limit of the laboratory range (μ mol/ml)
 - c. assay of lipid levels including HDL cholesterol and LDL cholesterol, not revealing severe hyperlipidemia
 - total cholesterol total \leq 3 g/l (7.8 mmol/l)
 - triglycerides $<$ 4g/l (4.57 mmol/l)
 - d. biological, hematological and biochemical tests which do not reveal severe anemia or diabetes
 - hemoglobin \geq 10 g/100ml
 - glycemia $<$ 1.4 g/l (7.77 mmol/l)
 - e. coagulation tests normal (according to the norms of the analytical laboratory):
 - prothrombin
 - activated partial thromboplastin time

antithrombin III

- f. 2 tumor markers: CA 125 and SCCTA4 < upper limits of the normal laboratory range

Reviewers comment: The inclusion criteria require all patients to be white. This is inconsistent with the desire to test the product in a population reflecting a diverse population of consumers, such as those in the United States. Women who undergo surgical menopause will be candidates of this product and should not have been excluded from this protocol. The inclusion criteria for the number of vasomotor symptoms and length of amenorrhea and the lack of a defined FSH differ from the Agency guidance, and may have resulted in the inclusion of some perimenopausal patients. Therefore, this trial can be considered supportive, but not pivotal, to this application.

Exclusion criteria

- known disorders which constitute a contraindication to estrogen
 - a. biliary litiasis
 - b. personal past history of idiopathic jaundice or pruritus during pregnancy
 - c. pituitary tumor: unless clinical signs suggest otherwise, prolactin assay would not appear justified in the context of this trial
 - d. porphyria
 - e. otospongiosis
 - f. connectivitis
 - g. ongoing and/or personal past history of thromboembolic disease
 - h. breast cancer and/or past history of gynecological malignant pathology
 - i. large volume fibroma and/or symptomatic
 - j. endometriosis, apart from adenomyosis discovered fortuitously by histological examination of hysterectomy sample
 - k. undocumented metrorrhagia
 - l. personal past history of galactorrhea; unless clinical signs suggest otherwise prolactin assay would not appear to be justified in the context of this trial
 - m. cardiovascular disease: valvulopathy and/or thrombogenic rhythm disorders and/or myocardial infarction and/or cardiac insufficiency
 - n. severe uncontrolled hyperlipidemia
 - o. uncontrolled hypertension
 - p. diabetes
 - q. cerebrovascular disorder
 - r. epilepsy
 - s. tetany
 - t. ocular pathology of vascular origin
 - u. known allergy to estrogen therapies
- other exclusion criteria
 - v. pregnancy

- w. known alcoholism and/or drug abuse
- x. chronic skin disease (e.g. eczema, psoriasis)
- y. patients who have already received postmenopausal treatment (hormone treatment and/or non-hormonal treatment)
- z. personal history of cutaneous contact allergy
- aa. any known pathology likely to put at risk the short term vital prognosis of the patient
- bb. patients receiving hepatic enzyme inducers: barbituates, hydantoins, carbamazepine, meprobamate, phenbutazone, rifampicin
- cc. patients receiving troleandomycin (risk of cholestatic hepatitis)
- dd. patients receiving corticoids and/or thyroid hormones
- ee. current treatment which could give false positives on the evaluation criteria: clonidine, anticholinergics, type B MAO inhibitors, levodopa, dopamine agonists and antagonists
- ff. past history of major depression not related to the menopause and/or psychiatric illness

5.5 Screening period

During the screening period the investigator determined that the patients met the inclusion and exclusion criteria. All patients underwent a history and physical examination including pap smear; laboratory tests including blood chemistries and CBC; a mammogram if not performed within the previous 12 months. The study design and purpose was explained to the patients and a 10-day progesterone challenge test was performed. The patient was given forms to record number and severity of vasomotor symptoms for the 7-day period preceding the inclusion visit, but after the progesterone challenge. A quality of life questionnaire was also completed.

5.6 Treatment period

Inclusion visit

At the inclusion visit, the results of all the laboratory tests, mammography, Pap smear, and the progesterone challenge test were reviewed. A physical exam was performed and the patient diary was reviewed. Patients were randomized and appropriate patches were given.

Monitoring visits V1 (week 5) and V2 (week 9)

At these visits interim physical examinations were performed including examination for local skin reactions, measurement of blood pressure, pulse and weight. History is reviewed including adverse events, assessment of tolerability, and asking the patient about any change in symptoms. The information from the diary is copied into the CRF.

Final visit Vf (week 13)

At this visit a physical exam including gynecologic check, pap smear, and examination of application sites were performed. Laboratory safety tests were reviewed. Patients were questioned about changes in symptoms, tolerability and compliance. Specific questions

on vasomotor symptoms, patch adhesive qualities, and quality of life questionnaire were completed

5.7 Evaluation Criteria

Primary efficacy criteria

The primary criteria for measurement of efficacy was a comparison of the mean number of vasomotor symptoms per 24 hours recorded in the 7 days preceding the inclusion visit to those noted during week 12 of the trial.

Secondary efficacy criteria

- changes in postmenopausal symptomatology, particularly the number of vasomotor symptoms evaluated by the patient in the course of the 4th, 8th, and 12th week of treatment as recorded in her diary
- the number of women still awakened by one or more episodes of nocturnal sweating after twelve weeks of treatment
- the general intensity of hot flushes which occur in the 7 day self-rating period preceding the inclusion visit and during the 4th, 8th, and 12th weeks of treatment, and demonstrating a sensation which is classified as:
 - a. mild: a sensation of transient heat without sweating
 - b. moderate: a sensation of heat and sweating which does not interfere with current activity
 - c. severe: a sensation of intense heat with sweating that stops current activity
- vaginal dryness
- vaginal mucosa
- vaginal cytology
- changes in general condition, assessed by the patient during the end-of-trial visit
- overall treatment efficacy on signs of estrogen deficiency evaluated by the investigator during the end-of-trial visit

5.8 Withdrawal and compliance

Of the 105 patients who underwent a selection visit 63 were enrolled into the trial and allocated a treatment number. Two of these patients, both in the TS 17 50 group did not receive treatment. One patient was diagnosed with a superficial phlebitis at the inclusion visit, the other was wrongly included: she did not have sufficient vasomotor symptoms, and laboratory tests were not done at baseline. Both patients were excluded from analyses since they never received study drug. Of the 61 patients receiving treatment, 7 withdrew prematurely. Three placebo patients withdrew due to inadequate efficacy while two other placebo subjects were felt to have been enrolled inappropriately by the investigator. Of the TS 17 50 patients, one withdrew because of

metrorrhagia and one was inappropriately enrolled. (Data obtained from vol 81 page 8-18038).

Reviewer's comment:

It is somewhat concerning that three patients were discontinued from the study because of being inappropriately enrolled. This leads to concern regarding the quality of the study in regards to how it was carried out.

5.9 Efficacy analyses

Vasomotor symptoms:

Comparison of the mean number of daily vasomotor symptoms between baseline (the 7 day period prior to inclusion in the study) and week 12 (the 7 day period prior the final visit) between TS 17 50 and placebo was the primary evaluation criteria for this study. The change in vasomotor symptoms from baseline to Week 4 and from baseline to Week 13 were both statistically significant when compare to placebo. The sponsor also assessed vasomotor symptoms at each visit. By the patient's first visit (Week 4) TS 17 50 patients had an 89.15% decline in vasomotor symptoms from mean to baseline. There was a mean of 9.31 vasomotor symptoms per day at baseline and a mean of 1.15 vasomotor symptoms at week four. There was a continued but less dramatic decline in mean daily vasomotor symptoms from week 4 until the end of study. Table 12. summaries the actual study information.

Table 12.

Effectiveness Results: Change in Vasomotor Symptoms from Baseline to Week 4 visit and from Baseline to Final Visit – patients evaluable for efficacy

	Placebo	TS 17 50
Number of patients	(N=25)	(N=28)
Baseline		
Number of MSVS per day	8.3±3.4(n=25)	9.3±4.2(n=28)
Week 4		
Number of MSVS per day	4.0±3.9(n=25)	1.2±2.1(n=28)
Reduction: baseline to week 4	4.3±3.2	8.2±3.8*
%reduction in number of MSVS per day week 4	54.9	89.2
Week 13		
Number of MSVS per day	3.2±5.0(n=25)	0.3±0.8(n=25)
Reduction: baseline to week 13	5.1±6.0	9.1±4.1*
%reduction in number of MSVS per day week 13	60	97.5

*Statistically significant difference from placebo in mean reduction in MSVS between TS 17 50 and control ($p \leq 0.01$, Wilcoxon Rank Sum test) modified from table 19(page 8-338)

Reviewer's comments: This study required only 5 vasomotor symptoms per day whereas the agency guidelines recommend 7 to 8 vasomotor symptoms per day. In general, however, this would make it more difficult (rather than less difficult) for a drug to show a significant effect compared to placebo. A significant reduction in the number of vasomotor symptoms per day at each visit (week 4, 8, and 12) was demonstrated for the TS 17 50 patients when compared to placebo. These results support efficacy of the TS 17 50 patch for the relief of vasomotor symptoms.

Hormone Levels

Levels of estradiol and FSH were evaluated at baseline and at week twelve. Significant differences ($p = .0001$ for both parameters) between baseline and endpoint visits were noted for the TS 17 50 group but were not noted in the placebo group. Data is outlined in the table below.

Table 13.

Hormone levels measured at baseline and at week 13 (all included patients)

Hormone level	TS 17 50 (n=32)	Placebo (n=29)
Estradiol (pmol/l) baseline (SD)	81.10(63.85)	117.71(209.68)
Estradiol (pmol/ml) endpoint (SD)	323.78(204.83)	208.81(357.76)
FSH(mIU/ml) baseline (SD)	83.37(29.17)	83.91(40.47)
FSH(mIU/ml)endpoint (SD)	29.17(13.42)	80.45(48.69)

Modified from sponsor table 50 page 8-17419

Reviewer's comments: There are several issues, which may have affected evaluation of hormone levels. The inclusion criteria permitted the possible inclusion of perimenopausal patients. Patients only needed three months of amenorrhea to be included in the study. There were no defined FSH and estradiol levels required for inclusion. Laboratory evaluation was not carried out at a central site resulting in large ranges of values and large standard deviations. Thus it is difficult to meaningfully interpret these analyses.

5.10 Safety analyses

The sponsor defined an adverse event as any serious or mild clinical or laboratory event experienced by the patient during a clinical trial, irrespective of whether it was considered to be related to trial treatments or not. All included patients were analyzed for adverse events, which were categorized by their relationship to estrogen therapy. Local skin reactions were evaluated separately. A total of 17(53 %) patients in the TS 17 50 group and 9(31%) patients in the placebo group presented at least one adverse event attributed to the study treatment by the investigators. The most common event was metrorrhagia which was seen in 14 (48%) patients in the TS 17 50 group and 8 (33%) in the placebo

group (based on patients with a uterus). The most frequent adverse event associated with hyperestrogenism was breast pain which presented in 7(22%) patients in the TS 17 50 group and in 1 (3%) in the placebo group.

Four serious events occurred, three in the TS 17 50 group versus one in the placebo group. In the placebo group one patient was hospitalized for removal of an IUD. All serious events in the TS 17 50 group required hospitalization. They included; one patient requiring laparoscopy for uterine leiomyoma, one patient had menometrorrhagia and one required a phlebectomy of varicose veins.

Application site reactions were evaluated and compared to the placebo group. An application site reaction was defined by the appearance of at least one of the following signs or symptoms: redness, spots, swelling, itching or burning sensation. Local erythema which lasted for less than sixty minutes after patch removal was not included as an adverse event. In the TS 17 50 group there were 35 site reactions noted after 831 applications (one reaction in every 24 applications). In the placebo group there were 29 site reactions in 732 applications (one reaction in every 25 applications). The percentage of patients with at least one site reaction was 28% in the TS 17 50 group and 17% in the placebo group. Itching and redness were the most common application site reactions in both groups. The duration of application site reactions was a mean of 10.1 hours in the TS 17 50 group and 1.77 hours in the placebo group. A total of 23 (2.8%) and 31(4.2%) of applications became detached from patients using TS 17 50 and placebo, respectively.

5.11 Reviewer's assessment of safety and efficacy:

As noted in previous comments there are many issues raised in the study, which make the data difficult to evaluate. Therefore we have not considered this a primary pivotal study. This study does, however, add support to the effectiveness of the 0.05 mg/day dose of Esclim® versus placebo in white women. There were no unexpected or unusual issues related to safety in this trial.

6.0 Clinical trial #3—Study TS 91 04

6.1 Objective.

The primary objective of this study was to compare the number of application site reactions relative to the total number of applications between TS 17 50 and Estraderm TTS®50 after 16 weeks of therapy. Secondary endpoints included efficacy and general tolerability and adhesion of TS 17 50 compared to Estraderm TTS ®50.

6.2 Design

This was a 16 week, open label, randomized, parallel, active controlled, multicenter study. The study was conducted in 48 centers in six European countries. During the week prior to active treatment the patients kept a daily diary of vasomotor symptoms.

Treatment consisted of four 28 day cycles, during which patients received 24 days of estrogen (either TS 17 50 or Estraderm TTS ® 50). The patients also received a progestin during the last 12 days of estrogen therapy.

6.3 Study population

The study population consisted of 285 Caucasian women who were randomized to TS 17 50 or Estraderm TTS ® 50. Two of the 285 patients did not receive the correct treatment in the third cycle and were removed from the primary analysis. Of the remaining 283 patients 143 were treated with TS 17 50 and 140 were treated with Estraderm TTS® 50. Both study populations had similar mean ages, body mass index, and mean body weights. The study population included patients both surgically and naturally menopausal.

6.4 Inclusion and exclusion criteria

Women selected for the trial were to meet the following criteria:

- out-patients;
- white;
- have signs of estrogen deficiency (particularly hot flushes) consecutive to the natural menopause or menopause due to surgical or radiotherapeutic bilateral ovariectomy performed without additional hormonal implants;
- present, *a priori*, adequate availability and motivation to participate in the trial;
- had read the information leaflet and given oral or written consent, depending on the legislation of the country where the trial was being conducted.

Exclusion criteria:

— Known disease contraindicating the use of estrogens:

- biliary lithiasis;
- past history of idiopathic jaundice or pruritus during pregnancy;
- pituitary tumor; an assay of prolactin levels was not required unless clinical signs rendered it useful;
- porphyria
- otospongiosis
- connectivitis;
- ongoing and/or past history of thromboembolic disease;
- breast cancer and/or past history of breast cancer/
- malignant uterine disease (on October 2nd, 1992 protocol was amended to replace “malignant uterine disease” with “current and/or past history of gynecological malignant pathology”)
- large volume fibroma and/or symptomatic;
- endometriosis (on October 2nd, 1992 protocol was amended to replace “endometriosis” with “endometriosis, apart from adenomyosis discovered fortuitously by histological examination of hysterectomy sample”);
- undiagnosed metrorrhagia;

- past history of galactorrhea
- cardiovascular disease: valvulopathies and/or thrombogenic rhythm disorders and/or myocardial infarction and/or cardiac insufficiency;
- uncontrolled severe hyperlipidemia
- uncontrolled hypertension
- diabetes;
- cerebrovascular disease;
- epilepsy;
- tetany;
- ocular pathology of vascular origin.
- known allergy to estrogen treatment;
- pregnancy
- known alcoholism and/or drug abuse
- chronic skin disease (e.g. eczema, psoriasis);
- patients previously treated with a transdermal system delivering estradiol;
- non-hysterectomised patients who had recently been treated for more than three months for menopause by estrogens alone
- previous history of cutaneous contact allergy;
- any known pathology likely to put at risk the short term vital prognosis of the patient;
- patient receiving hepatic enzyme inducers: Barbiturates, hydantoins, carbamazepine, meprobamate, phenylbutazone, rifampicin;
- patients receiving troleandomycin (risk of cholestatic hepatitis);
- patients receiving corticoids and/or thyroid hormones;
- current treatment which could give false positives on the evaluation criteria: clonidine, anticholinergics, type B MAO inhibitors, levodopa, dopamine agonists and antagonists;
- past history of major depression not related to the menopause and/or psychiatric illness

Inclusion criteria

- presented with at least one hot flushes and one episode of nocturnal sweating during the 7 day symptom self-evaluation period which preceded the inclusion visit;
- had not received any postmenopausal hormone (estrogen or progesten or non-hormone treatment for at least one month before the beginning of the seven-day self-evaluation of symptoms;
- did not present any skin lesions on the buttocks;
- had undergone mammography during the past year (or during the past 3 months in The Netherlands), which had not revealed any marked benign mastopathy nor any malignant growth;
- had undergone a vaginal smear with vaginal cyto hormonal examination which had not revealed any major abnormality;
- if menopause had been of surgical origin, had undergone surgery at least one month before the inclusion visit;