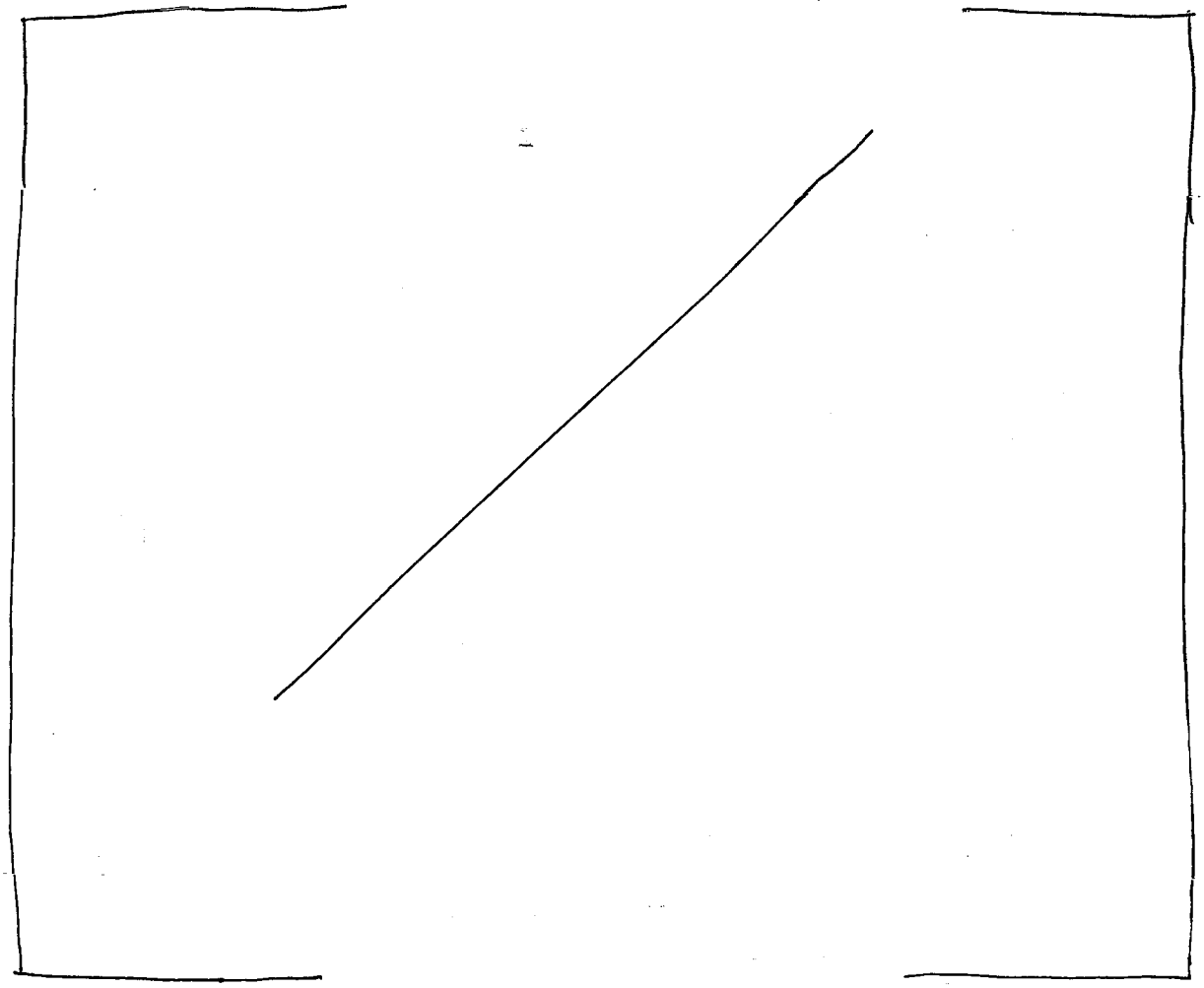
Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

Medical Review (12/14/06) (pg. 91)



Endometrial Hypertrophy:

In Study EST005, 14 estradiol gel-treated subjects were reported to have transvaginal ultrasound double-wall endometrial thickness > 4 mm at the final visit. The following Table 25 demonstrates the information available for these 14 subjects.

Table 25: Subjects With Endometrial Thickness > 4 mm at Final Visit (Study EST005) (ISS Safety Population)

Study Drug	Subject Number (study day)	Age (years) Race	Endometrial Thickness		Trough Estradiol (pg/mL)	Endometrial Histology	Comments
			Baseline	End-of-Study			
Estradiol Gel 0.87 g/day	587 (day NA)	51 White	No TVUS performed[a]	7.8 mm[b]	Baseline:<10 Week 4: <10 Week 8: <10 Week 12: 130	No endometrial biopsy performed	Subject refused final endometrial biopsy. Subject was given progestin (5 days of bleeding)

Study Drug	Subject Number (study day)	Age (years) Race	Endometrial Thickness		Trough Estradiol (pg/mL)	Endometrial Histology	Comments
			Baseline	End-of-Study			
	757 (day 87)	48 White	3.0 mm	11.5 mm	Baseline: 11 Week 4: 25 Week 8:<10 Week 12: 45	No endometrial biopsy performed	Subject received progestin (5 days of bleeding). Follow-up TVUS = 5 mm
Estradiol Gel 1.7 g/day	112 (day 85)	58 White	1.0 mm	7.0 mm	Baseline:<10 Week 4: 10 Week 8: 14 Week 12: 25	Proliferative endometrium	Subject received progestin (12 days of bleeding). Follow-up TVUS was normal
	259 (day 98)	68 White	No TVUS performed[a]	9.0 mm	Baseline:<10 Week 4: <10 Week 8: 23 Week 12: 13	No endometrial biopsy performed	Subject received progestin (no bleeding). Follow-up TVUS 6 months later = 6 mm
	269 (day 83)	58 White	No TVUS performed[a]	7.3 mm	Baseline:<10 Week 4: <10 Week 8: <10 Week 12: 32	Inactive/ atrophic endometrium	Subject received progestin (no bleeding). Repeat TVUS = 4.1 mm
	336 (day NA)	57 White	3.0 mm	5.0 mm[b]	Baseline:<10 Week 4: <10 Week 8: 13 Week 12: 10	No endometrial biopsy performed	Subject received progestin (no bleeding). No additional follow-up.
	351 (day 85)	58 White	No TVUS performed[a]	16.2 mm	Baseline:<10 Week 4: 26 Week 8: 25 Week 12: 27	No endometrial biopsy performed	Subject received progestin (8 days of bleeding). No repeat TVUS.
	637 (day 91)	48 White	No TVUS performed[a]	11.0 mm	Baseline: 41 Week 4: 38 Week 8: 40 Week 12: 13	D&C showed endometrial-type polyp and ciliated cell epithelial metaplasia	Subject did not receive progestin.
	684 (day68)	50 White	No TVUS performed[a]	18.0 mm	Baseline:<10 Week 4: 36 Week 8: 43 Week 12:<10	Proliferative endometrium	Follow-up TVUS = 4 mm.
Estradiol Gel 2.6 g/day	102 (day 95)	61 White	No TVUS performed[a]	4.1 mm	Baseline:<10 Week 4: 30 Week 8: 22 Week 12:<10	No endometrial biopsy performed	Subject received progestin (no bleeding). No follow-up TVUS.
	143 (day 88).	53 Hispanic	No TVUS performed[a]	22.0	Baseline:<10 Week 4: 11 Week 8: <10 Week 12: 14	Follow-up D&C was benign	Endometrial biopsy = insufficient tissue. Subject did not receive progestin.
	261 (day 91)	54 White	4.0 mm	6.0 mm	Baseline:<10 Week 4: 190 Week 8: 230 Week 12: 89	No endometrial biopsy performed	Cervical cyst required hospitalization 3 months after last dose of study medication. TAH & BSO performed. Pathology showed hematometrium, adenomyosis, and inactive endometrium
	271	69	No TVUS	7.3 mm[b]	Baseline:<10	Simple	Subject received

Study Drug	Subject Number (study day)	Age (years) Race	Endometrial Thickness		Trough Estradiol (pg/mL)	Endometrial Histology	Comments
			Baseline	End-of-Study			
	(day 86)	White	performed[a]		Week 4: <10 Week 8: 20 Week 12: 47	hyperplasia without atypia	progestin (3 days of bleeding).
	299 (day 85)	59 White	No TVUS performed[a]	10.4 mm[b]	Baseline:<10 Week 4: 45 Week 8: 44 Week 12: 130	Proliferative endometrium	Subject received progestin. Follow-up TVUS = 5.1 mm

Source: Adapted from NDA 21-813/S-000, Volume 62, Table 8.8.6-6, pages 133-134, and Appendix 16.2.7.2: Adverse Events, Volume 44, pages 1-114.
NA = Not available.
D&C = Dilatation and curettage.
TAH&BSO = Transabdominal hysterectomy and bilateral salpingoophorectomy.
a. Baseline endometrial biopsy was reported as normal.
b. TVUS result was not reported as an adverse event.

Medical Officer's Comments:

As shown in Table 25, seven of the 14 estradiol gel-treated subjects (50%) with an end-of-study transvaginal double-wall thickness > 4 mm did not have an endometrial biopsy performed as per protocol. However, six of these seven subjects received post-treatment progestin per protocol and three of these six subjects had repeat TVUS procedures demonstrating reduced TVUS thickness. Information available in the submission for Subject 261 in the 2.6 gram per day estradiol gel treatment group indicated that no post-treatment progestin therapy was provided. Three months post-study medication, Subject 261 underwent a transabdominal hysterectomy and bilateral salpingoophorectomy. Pathology indicated a 3-cm hematometrium, adenomyosis, and inactive endometrium.

One placebo-treated subject had an endometrial thickness > 4 mm at end-of-study. Subject 810 (60 years of age) had a week 12 TVUS reported at 59.2 mm. An endometrial biopsy showed inactive/atrophic endometrium but subject was found to have a left ovarian cyst for which surgery was indicated. This subject received post-treatment progestin with no resultant bleeding.

Overall, thirteen (13) subjects in Study EST005 with a uterus did not have an end-of-study TVUS or endometrial biopsy performed. The reasons for not having a TVUS or endometrial biopsy performed are shown in Table 26.

Table 26: Subjects Without End-of-Study Transvaginal Ultrasound or Endometrial Biopsy (Study EST005) (ISS Safety Population)

Study Drug	Subject Number	Comments
Placebo	131	No reason given
	142	Lost to follow-up
	178	Prematurely discontinued and refused end-of-study procedures
	312	Refused endometrial biopsy and TVUS
	334	Endometrial biopsy obtained showed insufficient tissue and TVUS

Study Drug	Subject Number	Comments
		was not performed
	756	Refused endometrial biopsy and TVUS was not performed
	880	Prematurely discontinued after 3 days on study medication
	890	Prematurely discontinued and no reason noted
Estradiol Gel 0.87 g/day	606	Prematurely discontinued and refused end-of-study procedures
	886	Prematurely discontinued and refused end-of-study procedures
Estradiol Gel 1.7 g/day	273	Uterus was not palpable, no cervix was visible and TVUS was inconclusive
Estradiol Gel 2.6 g/day	166	Refused gynecological examination
	291	Refused endometrial biopsy and no TVUS was performed

Source: Adapted from NDA 21-813/S-000, Section 8, Volume 62, Table 8.8.6-7, page 135 of 277.

Medical Officer's Comments:

Five of the 13 subjects without end-of-study endometrial biopsy or TVUS performed were treated with estradiol gel (38.5%) and eight were treated with placebo (61.5%). Five of the eight placebo-treated subjects had no reported adverse events. The remaining three placebo treated subjects reported the following adverse events (Subject 142, pelvic pain and vaginal discharge at study day 14; Subject 312, UTI at day 17 and breast tenderness at day 18; and Subject 880, breast swelling at day 4 and arthralgia at day 8).

One of the two subjects in the 0.87 gram per day estradiol gel treatment group reported adverse events on study day 5 (Subject 606, peripheral edema and dyspnea). The one subject in the 1.7 gram per day estradiol gel treatment group experienced arthritis at study day 12. Both subjects listed under the 2.6 gram per day estradiol gel dose reported adverse events (Subject 166, increased weight; Subject 291, vaginal discharge at day two, metrorrhagia at day 6 and day 59).

Overall, these reported findings do not raise safety concerns with the possible exception of Subject 291 in the 2.6 gram per day estradiol gel treatment group. This subject reported metrorrhagia at study day 6 and study day 59. She refused an end-of study endometrial biopsy and TVUS. However, no information is provided in the submission regarding referral to her private physician for follow-up. One must be concerned that this subject might have had concerning endometrial pathology (such as endometrial hyperplasia or cancer) as the cause of her bleeding. As reported, it appears that this subject was not adequately evaluated for her reported metrorrhagia.

Application Site Irritation:

Application site assessments were conducted during the single-blind placebo lead-in period (day -7) and throughout the 12-week double-blind treatment period. Skin irritation at the application site was graded in a five-point scale as follows:

0 = no erythema,

1 = minimal erythema,
2 = moderate erythema with sharply defined borders,
3 = intense erythema with or without edema,
4 = intense erythema with edema and erosion/blistering.

Scores ≥ 1 were recorded as adverse events. In the ISS, the number and percent of subjects with skin irritation at the application site was summarized for each treatment group at each visit for each of the reported five outcomes. The following table provides information across Studies EST004 (thighs) and EST005 (arms/shoulders) for all reported TEAE application site conditions and the investigator assessments of skin irritation (erythema).

Table 27: Application Site Treatment-Emergent Adverse Events by System Organ Class and Preferred Term During the Double-Blind Treatment Period (ISS Safety Population)

System Organ Class Preferred Term[a]	Estradiol Gel 0.625 g/day 4 weeks (N=41)	Estradiol Gel 0.87 g/day 12 weeks (N=136)	Estradiol Gel 1.25 g/day 4 weeks (N=40)	Estradiol Gel 1.7 g/day 12 weeks (N=142)	Estradiol Gel 2.5/2.6 g/day 4 weeks[b] (N=107)	Estradiol Gel 2.6 g/day 12 weeks (N=69)	Estradiol Gel All Doses 4-12 weeks (N=466	All Placebo 4-12 weeks (N=179)
Any application site TEAE	**0 (0.0)**	**11 (8.1)**	**3 (7.5)**	**9 (6.3)**	**4 (3.7)**	**4 (5.8)**	**28 (6.0)**	**9 (5.0)**
Application site burning	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.6)
Application site dermatitis	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	2 (0.4)	2 (1.1)
Application site dryness	0 (0.0)	5 (3.7)	2 (5.0)	4 (2.8)	1 (0.9)	1 (1.4)	12 (2.6)	2 (1.1)
Application site erythema	0 (0.0)	4 (2.9)	0 (0.0)	3 (2.1)	1 (0.9)	2 (2.9)	9 (1.9)	3 (1.7)
Application site irritation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Application site pruritis	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.7)	2 (1.9)	1 (1.4)	4 (0.9)	2 (1.1)
Application site reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Skin irritation (erythema)	**0 (0.0)**	**5 (3.7)**	**0 (0.0)**	**5 (3.5)**	**3 (2.8)**	**3 (4.3)**	**13 (2.8)**	**6 (3.4)**

Source: Adapted from NDA 21-813/S-000, Section 8, Volume 62, Table 8.8.6-9, page 140 and Appendix 6, pages 182-191.
TEAE = Treatment-emergent adverse event.
a. A subject with more than 1 event represented by a given Preferred Term (or the class) is counted only once for that Preferred Term (or the class). Within the class, adverse events are displayed in order of decreasing frequency in the estradiol gel All Doses group.
b. Includes Study EST004 subjects assigned to Estradiol gel 2.5 g/day for 4 weeks and Study EST005 subjects assigned to 2.6 g/day estradiol gel for 12 weeks. For Study EST005 subjects, only TEAEs that started on or before day 28 are included in this column. All TEAEs for Study EST005 subjects are presented in the estradiol gel 2.6 g/day 12 weeks and estradiol gel All Doses 4-12 Weeks columns (subjects counted once in latter column).

Per the submission, application site TEAEs were reported for the 1.25 gram per day estradiol gel treatment group (three of 40 subjects, 7.5%) and the 2.6 gram per day estradiol gel treatment group (one of 38 subjects, 2.6%), and not for the placebo or 0.625 gram per day treatment groups in Study EST004. In Study EST005, all treatment groups showed similar incidence of application site TEAEs (8.1% of the 0.87 gram per day group [11 of 136 subjects]; 6.3% of the 1.7 gram per day group [9 of 142 subjects]; 5.8% of the 2.6 gram per day group [4 of 69 subjects]; versus 6.6% of the placebo treatment group [9 of 137 subjects]). The most common type of application site disorders were dryness and erythema in Study EST005.

In total, 19 subjects had application site erythema observed by the investigator during scheduled visits across the two studies: six placebo-treated subjects (3.4%, 6 of 179 subjects) and 13 estradiol gel-treated subjects (2.8%, 13 of 466 subjects). Of these 19 subjects, only Subject 140 in the 1.7 gram per day estradiol gel treatment group in Study EST005 had moderate erythema of

the right shoulder at week 4. Skin irritation among the remaining 18 subjects was reported as minimal intensity.

Medical Officer's Comments:

In Study EST005, application site erythema observed by the investigator did not appear to be dose related (five cases in the 0.87 gram per day estradiol gel treatment group, five in the 1.7 gram per day treatment group, and three in the 2.6 gram per day treatment group).

Overall, the incidences of skin irritation and application site TEAEs were similar between estradiol gel-treated subjects and placebo-treated subjects (2.8% versus 3.4% and 6.0% versus 5.0%, respectively). No subjects discontinued double-blind treatment due to an application site disorder.

7.1.4 Other Search Strategies

No algorithm involving combination of clinical findings and a marker for a particular toxicity was developed with the exception of the interrelationship on endometrial hyperplasia and estrogen-alone use discussed in 7.1.3.3, Other Significant Adverse Events.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Per the submission, the investigator monitored each subject for evidence of study drug intolerance and for the development of clinical and/or laboratory evidence of an adverse event at each center visit. The investigator was not to suggest possible adverse events (e.g., headache, fatigue) to the subject, but rather inquire generally about how the subject felt since last seen. Subject complaints and symptoms were recorded on the adverse event form. All adverse events reported up to 30 days after stopping drug (including adverse events for subjects who received norethindrone acetate during the post-treatment period in Study EST004) were considered treatment adverse events.

Medical Officer's Comments:

The use of recall data may contribute to the under reporting of adverse events. Optimally, the subject should be requested to record adverse events in a daily diary (as well as study medication use and concomitant medication use), which is reviewed with the investigator at scheduled visits.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Per the submission, all reported adverse events were assigned a MedDRA preferred term that most closely resembled the actual adverse event as well as the system-organ class appropriate to the individual adverse event.

Medical Officer's Comments:

While there may be many related terms that may be selected to describe an event in the MedDRA dictionary of preferred terms, this reviewer has no concerns that the use of preferred terms resulted in a missed signal for the safety data reported in the ISS.

7.1.5.3 Incidence of common adverse events

Per the ISS, the reproductive disorders class was observed to be most affected by estradiol gel treatment, and the incidence in this class overall and individually (breast tenderness, metrorrhagia, vaginal discharge, endometrial hyperplasia, nipple pain) increased in a time and dose-dependent manner. There was a higher incidence of overall treatment-emergent adverse events (TEAEs) of this class in the estradiol gel All Doses group than in the All Placebo group and the difference was statistically significant (110 subjects [23.6%] versus 15 subjects [8.4%], respectively).

In Study EST005, adverse events occurring during the double-blind treatment period and up to 30 days thereafter were considered treatment-emergent. Treatment emergent adverse events were experienced by between 56% and 68% of all randomized subjects across the four treatment groups in Study EST005, and between 47.7% and 50.0% across the four treatment groups in Study EST004.

In Study EST005, reported TEAEs were considered to be possibly related or probably related to study medication across 27.9% and 58.0% of all randomized subjects, with those in the 2.6 gram per day estradiol gel treatment group having the highest incidence of possibly/probably related adverse events. Per the submission, most treatment-emergent adverse events were considered to be mild or moderate intensity, with severe intensity being reported among 6% to 9% of all randomized subjects across treatment groups.

7.1.5.4 Common adverse event table

Table 28: Treatment-Emergent Adverse Events by System-Organ Class (ISS Safety Population)

System Organ Class[a]	Number (%) of Subjects			
	Estradiol Gel 0.87 gram/day (N = 136)	Estradiol Gel 1.7 gram/day (N = 142)	Estradiol Gel 2.6 gram/day (n = 69)	Placebo (N = 137)
Any adverse event	80 (58.8)	92 (64.8)	47 (68.1)	77 (56.2)
Blood and lymphatic systems	1 (0.7)	0 (0)	2 (2.9)	1 (0.7)
Cardiac disorders	1 (0.7)	0 (0)	0 (0)	2 (1.5)

System Organ Class[a]	Number (%) of Subjects			
	Estradiol Gel 0.87 gram/day (N = 136)	Estradiol Gel 1.7 gram/day (N = 142)	Estradiol Gel 2.6 gram/day (n = 69)	Placebo (N = 137)
Ear and labyrinth disorders	0 (0)	2 (1.4)	0 (0)	1 (0.7)
Endocrine disorders	1 (0.7)	0 (0)	0 (0)	0 (0)
Eye disorders	0 (0)	0 (0)	2 (2.9)	1 (0.7)
Gastrointestinal disorders	19 (14.0)	16 (11.3)	9 (13.0)	9 (6.6)
General disorders and administration site conditions	15 (11.0)	18 (12.7)	9 (13.0)	12 (8.8)
Hepatobiliary disorders	0 (0)	0 (0)	1 (1.4)	0 (0)
Immune system disorders	1 (0.7)	0 (0)	0 (0)	3 (2.2)
Infections and infestations	2 (1.5)	4 (2.8)	1 (1.4)	2 (1.5)
Injury, poisoning and procedural complications	1 (0.7)	5 (3.5)	2 (2.9)	4 (2.9)
Investigations	4 (2.9)	5 (3.5)	3 (4.3)	4 (2.9)
Metabolism and nutrition disorders	3 (2.2)	1 (0.7)	1 (1.4)	0 (0)
Musculoskeletal and connective tissue disorders	17 (12.5)	11 (7.7)	8 (11.6)	15 (10.9)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.7)	1(0.7)	1 (0.7)	0 (0)
Nervous system disorders	7 (5.1)	12 (8.5)	7 (10.1)	9 (6.6)
Psychiatric disorders	0 (0)	4 (2.8)	3 (4.3)	1 (0.7)
Renal and urinary disorders	5 (3.7)	3 (2.1)	2 (2.9)	6 (4.4)
Reproductive system and breast disorders	21 (15.4)	41 (28.9)	32 (46.4)	13 (9.5)
Respiratory, thoracic and Mediastinal disorders	34 (25.0)	29 (20.4)	10 (14.5)	27 (19.7)
Skin and subcutaneous tissue disorders	10 (7.4)	8 (5.6)	4 (5.8)	9 (6.6)
Surgical and medical procedures	0 (0)	0 (0)	0 (0)	3 (2.2)
Vascular disorders	0 (0)	0 (0)	0 (0)	2 (1.5)

Source: Adapted from NDA 21-813/S-000 Section 8, Volume 26, Table 12.2-1, page 119 (page 139 of 369).
a. A subject with more than one event represented by a given system organ class is counted only once for that system organ class.

Medical Officer's Comments:

As shown in Table 28, the most common adverse events across estradiol gel doses were in the reproductive system and breast disorders class. In this system organ class, adverse events increased in incidence with increasing estradiol gel treatment groups and occurred at a frequency 2-3 times more frequently that the placebo treatment group.

The next most common class of adverse events included the system organ class of respiratory, thoracic and mediastinal disorders which showed similar incidences across all treatment groups in Study EST005 (approximately 20% for placebo and 15% to 25% across estradiol gel groups without evidence of dose-dependency).

Individual treatment-emergent adverse events occurring in ≥ 5% of subjects in 12-week Study EST005 in one or more treatment groups are shown in Table 29.

Table 29: Treatment-Emergent Adverse Events by System-Organ Class and Preferred Term Reported by ≥ 5% of Subjects in One or More Treatment Groups (ISS Safety Population)

System Organ Class/ Preferred Term[a]	Number (%) of Subjects			
	Estradiol Gel 0.87 gram/day (N = 136)	Estradiol Gel 1.7 gram/day (N = 142)	Estradiol Gel 2.6 gram/day (n = 69)	Placebo (N = 137)
Gastrointestinal disorders				
Nausea	6 (4.4)	4 (2.8)	5 (7.2)	2 (1.5)
General disorders and administration site conditions	1 (0.7)	0 (0.0)	4 (5.8)	0 (0.0)
Reproductive system and Breast disorders				
Breast tenderness	9 (6.6)	11 (7.7)	15 (21.7)	5 (3.6)
Metrorrhagia	6 (4.4)	13 (9.2)	14 (20.3)	3 (2.2)
Vaginal discharge	2 (1.5)	5 (3.5)	5 (7.2)	1 (0.7)
Nipple pain	1 (0.7)	3 (2.1)	4 (5.8)	0 (0.0)
Endometrial hyperplasia	0 (0.0)	1 (0.7)	5 (7.2)	0 (0.0)
Respiratory, thoracic and mediastinal disorders				
Nasopharyngitis	14 (10.3)	12 (8.5)	3 (4.3)	10 (7.3)
Upper respiratory tract infection	8 (5.9)	5 (3.5)	2 (2.9)	5 (3.6)

Source: Adapted from NDA 21-813/S-000, Section 8, Volume 26, Table 12.2-2, page 121 (page 141 of 369).

a. A subject with more than one event represented by a given Preferred Term (or System Organ Class) is counted only once for that Preferred Term (or System Organ Class).

Medical Officer's Comments:

The common adverse events reported in Study EST005 are not unknown with estrogen-alone therapy and have been reported to occur in other clinical trials of hormone therapy conducted for VMS [ ]

The incidence of overall and possibly-related TEAEs of the reproductive system and breast disorders class increased with increasing Estradiol gel dosage strengths:

- *At the 0.87 gram per day estradiol gel dose, the only TEAE occurring with >5% incidence was breast tenderness (6.6%).*
- *At the 1.7 gram per day estradiol gel dose, TEAEs occurring with >5% incidence included metrorrhagia (9.2%) and breast tenderness (7.7%).*
- *At the 2.6 gram per day estradiol gel dose, TEAEs occurring with a >5% incidence included breast tenderness (21.7%), metrorrhagia (18.8%), endometrial hyperplasia (11.1% when only women with uteri are included), vaginal discharge (7.2%), and nipple pain (5.8%).*

The incidence of endometrial hyperplasia demonstrated in Study EST005 is discussed in Section 7.1.3 Dropouts and Other Significant Adverse Events, Sub-section 7.1.3.3 Other significant adverse events.

The overall number of subjects with one or more treatment-emergent adverse events (TEAEs) during the double-blind treatment period in the ISS population is summarized below by study and treatment groups. Table 8.8.4-1 in Section 8, Volume 62, page 49 of NDA 21-813/S-[ ] served as the source of this data:

Study EST004:

Estradiol Gel	Estradiol Gel	Estradiol Gel
0.625 g/day	1.25 g/day	2.5/2.6 g/day
4-week	4-week	4-week
(N = 41)	(N = 40)	(N = 107, EST004/EST005 pooled)
20 (48.8%)	20 (50.0%)	51 (47.7%)

Study EST005:

Estradiol Gel	Estradiol Gel	Estradiol Gel
0.87 g/day	1.7 g/day	2.6 g/day
12-week	12-week	12-week
(N = 136)	(N = 142)	(N = 69)
80 (58.8%)	92 (64.8%)	47 (68.1%)

Study EST004/Study EST005:

All Placebo	Estradiol Gel (All doses)
4-12 weeks	4-12 weeks
(N = 179)	(N = 466)
94 (52.5%)	278 (59.7%)

Medical Officer's Comments:

As shown above, the overall incidence of adverse events across all doses of estradiol gel combined in Studies EST004 and EST005 was 59.7% (278 of 466 subjects) verses 52.5% (94 of 179 subjects) in all placebo groups. Based on descriptive statistics, the findings are not statistically significantly different between the two groups.

In 12-week Study EST005, the proportion of subjects experiencing one or more TEAEs was highest in the 2.6 gram per day estradiol gel treatment group (68.1%, 47 of 69 subjects) and lowest in the 0.87 gram per day estradiol gel treatment group (58.8%, 80 of 136 subjects). Similar findings are observed in Study EST004 with the lowest dose of estradiol gel (0.625 gram per day) reporting the lowest TEAEs (48.8%, 20 of 41 subjects). These findings suggest an estradiol gel dose response.

7.1.5.5 Identifying common and drug-related adverse events

The overall number of subjects with one or more treatment-related TEAEs during the double-blind treatment period in the ISS population is summarized below by study and treatment groups. Table 8.8.4-1 in Section 8, Volume 62, page 49 of NDA 21-813/S-000 served as the source of this data:

Study EST004:

Estradiol Gel	Estradiol Gel	Estradiol Gel
0.625 g/day	1.25 g/day	2.5/2.6 g/day
4-week	4-week	4-week
(N = 41)	(N = 40)	(N = 107, EST004/EST005 pooled)
8 (19.5%)	11 (27.5%)	34 (31.8%)

Study EST005:

Estradiol Gel	Estradiol Gel	Estradiol Gel
0.87 g/day	1.7 g/day	2.6 g/day
12-week	12-week	12-week
(N = 136)	(N = 142)	(N = 69)
38 (27.9%)	49 (34.5%)	40 (58.0%)

Study EST004/Study EST005:

All Placebo	Estradiol Gel (All doses)
4-12 weeks	4-12 weeks
(N = 179)	(N = 466)
35 (19.6%)	159 (33.5%)

7.1.5.6 Additional analyses and explorations

In the ISS, the most common TEAEs were of the reproductive system and breast disorders organ class (8.4% to 46.4% of subjects), with the highest occurrence in the 2.6 gram per day estradiol gel treatment group in 12-week Study EST005 and the lowest occurrence in the all placebo treatment group. The following individual adverse events were reported by > 2.0% of subjects in one or more treatment groups: breast tenderness, metrorrhagia, vaginal discharge, endometrial hypertrophy, nipple pain, genital pruritus female, vaginal mycosis, uterine spasm, endometrial hyperplasia, breast pain, and adnexa uteri pain. Data adapted from Table 8.8.4-2 in Section 8, Volume 62, pages 53-55 of NDA 21-813/S-000 is presented below:

Study EST004:

Estradiol Gel	Estradiol Gel	Estradiol Gel

0.625 g/day 4-week (N = 41) 4 (9.8%)	1.25 g/day 4-week (N = 40) 7 (17.5%)	2.5/2.6 g/day 4-week (N = 107, EST004/EST005 pooled) 25 (23.4%)

Study EST005:

Estradiol Gel 0.87 g/day 12-week (N = 136) 21 (15.4%)	Estradiol Gel 1.7 g/day 12-week (N = 142) 41 (28.9%)	Estradiol Gel 2.6 g/day 12-week (N = 69) 32 (46.4%)

Study EST004/Study EST005:*

All Placebo 4-12 weeks (N = 179) 15 (8.4%)	Estradiol Gel (All doses) 4-12 weeks (N = 466) 110 (23.6%)

* $p \leq 0.05$ for estradiol gel All Doses 4-12 weeks" versus "All Placebo 4-12 weeks" using descriptive statistical testing with Fisher's exact test.

7.1.6 Less Common Adverse Events

See the discussion regarding estradiol gel use and endometrial hypertrophy and endometrial hyperplasia in Section 7.1.3 Dropouts and Other Significant Adverse Events, Sub-section 7.1.3.3 Other significant adverse events.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

In Study EST005, markedly abnormal laboratory values were specified by the applicant as being below or equal to the lower safety limit or above or equal to the upper safety limit. See the normal ranges for clinical laboratory tests implemented in Study EST005 (Final Study Report Appendix 16.2.8.1: Normal Ranges for Clinical Laboratory Tests, Volume 59, page 76).

Laboratory safety assessments scheduled to be obtained were:

Hematology	hematocrit, hemoglobin, platelet count, red blood cells, white blood cells with differential, mean corpuscular volume (MCV),

	mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and reticulocytes in Study EST005 only.
Chemistry:	sodium, potassium, chloride, glucose, calcium, blood urea nitrogen (BUN), creatinine, total bilirubin, total protein, albumin, alkaline phosphatase, phosphorus, lactate dehydrogenase (LDH), serum glutamic-oxaloacetic transaminase (AST/SGOT), and serum glutamic-pyruvic transaminase (ALT/SGPT).
Lipid Profile:	triglycerides, total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL).
Urinalysis:	appearance, color, pH, specific gravity, leukocytes, nitrites, protein, glucose, ketones, and blood.
Coagulation (EST004):	(activated) partial thromboplastin time (aPTT), and prothrombin time (PT).
Coagulation profile: (EST005)	protein-C activity, protein-S antigen (protein S), antithrombin III activity, and Factor V Leiden (activated protein-C resistance).
Miscellaneous: (EST005)	C - reactive protein

In Study EST005, there were no statistically significant differences from placebo in the mean change from baseline to week 12 evaluations for any hematology parameter in subjects receiving the 0.87 gram per day estradiol gel dose. There were mean statistically significant differences ($p \leq 0.05$) in the 1.7 gram per day estradiol gel group in decreased platelets (mean change from baseline -8.2 [SD 32.4] 10^3/UL; p=0.0021) and in the 2.6 gram per day estradiol gel group (decreased platelets; mean change from baseline -6.0 [SD 26.9] 10^3/UL; p=0.0372) and increased MCH (mean change from baseline 0.19 [SD0.62] PG; p=0.0045) and increased MCV (mean change from baseline 0.72 [SD 1.93] FL; p=0.0012). Overall, the reported changes were small.

In Study EST004, there were no statistically significant mean changes from baseline to week 4 for any of the hematology parameters.

Medical Officer's Comments:

The statistically significant mean changes in hematology parameters reported in Study EST005 were small and are not considered clinically meaningful.

Few subjects had clinically significant serum chemistry values at the end of Study EST005. Statistically significant decreases from baseline to week 12 for the 0.87 gram per day, 1.7 gram per day, and 2.6 gram per day estradiol gel dosage strengths, relative to placebo, were observed for calcium (-0.19, -0.27 and -0.38 versus -0.05 mg/dL, respectively); BUN (-1.0, -0.7, and -0.7 versus 0.4 mg/dL, respectively); phosphorus (-0.36, -0.40, and -0.45 versus -0.01 mg/dL, respectively); and LDH (-4.6, -9.9, and 014.5 versus 3.3 mg/dL, respectively). In addition, statistically significant differences ($p \leq 0.05$) from placebo were also observed in mean change from baseline to week 12 for the 1.7 gram per day estradiol gel group for serum creatinine

(decrease), total protein (decrease), and albumin (decrease); and for the 2.6 gram per day estradiol gel group for sodium (decrease), potassium (increase), total protein (decrease), total bilirubin (increased), and alkaline phosphatase (decrease).

In Study EST004, statistically significant differences ($p \leq 0.05$) from placebo were observed in mean change from baseline to week four for the 1.25 gram per day estradiol gel group for serum calcium (decrease), and for the 2.5 gram per day estradiol gel group for calcium (decrease), sodium (decrease), total protein (decrease), albumin (decrease), and phosphorus (decrease).

Medical Officer's Comments:

None of the descriptive statistically significant mean changes in chemistry parameters were considered clinically important, and mean values at last visit were within the normal range.

Statistically significant differences ($p<0.05$) from placebo in mean change from baseline to week 12 for the 1.7 gram per day estradiol gel treatment group was observed for total cholesterol (decrease) and LDL (decrease) in Study EST005. No similar statistically significant decreased were observed in Study EST004. These results suggest a favorable duration-response relationship.

In Study EST005, there was a small but statistically significant difference from placebo in mean change from baseline to week 12 for protein S activity (decrease) and protein C activity (decrease) for the 1.7 gram per day and 2.6 gram per day estradiol gel treatment groups, and for antithrombin III activity (decrease) for the 2.6 gram per day estradiol gel treatment group. The magnitude of mean changes from baseline increased for these parameters with increased doses of estradiol gel.

In Study EST004, no statistically significant differences from placebo were observed in mean change from baseline to week 4 in the estradiol gel treatment groups for either aPTT or PT.

Medical Officer's Comments:

Changes in coagulation parameters (activated partial thromboplastin time [aPTT], protein S antigen-free, and prothrombin time) were the most common type of the clinically significant laboratory shifts although these changes were not associated with TEAEs. Significant mean decreases in coagulation parameters occurred with the higher doses of estradiol gel in Study EST005 thus appearing to be dose dependent. No change in coagulation parameters occurred at the 0.87 gram per day estradiol gel dosage strength.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Controlled comparisons provide the best data for deciding whether there is a signal of an effect of a drug on a laboratory test. In Study EST005, there does not appear to be any laboratory safety signal upon evaluation of the safety data.

7.1.7.3 Standard analyses and explorations of laboratory data

Abnormal laboratory values are listed by subject in Table 30.

Table 30: Estradiol Gel Treated Subjects With Clinically Significant Shifts From Normal Baselines to Abnormal Levels in Clinical Safety Laboratory Parameters (ISS Safety Population)

Profile Parameter (Normal Range)	Subject Number	Estradiol Gel Dose	Study Day	Result	Flag[a]
Hematology					
Hematocrit (25-47%)	299	2.6 g/day	-21	39.2	
			88	31.4	L;CS
Hemoglobin (11.7-16 g/dL)			-21	13.1	
			88	10.4	L;CS
Red blood cells ($3.8\text{-}5.3x10^6$/ul)			-21	4.2	
			88	3.29	L;CS
Coagulation					
Protein S antigen free activity (62-146%)	668	0.87 g/day	-21	98	
			86	55	L;CS
	104	2.6 g/day	-21	80	
			86	56	L;CS

Source: Adapted from NDA 21-813/S-000; Section 8, Volume 26, Table 12.4-2, page 138 (page 158 of 369).
a. L: low value (below normal range); CS: value considered clinically significant by the investigator.

Medical Officer's Comments:

Table 30 shows specific laboratory values for the parameters that shifted from normal to abnormal in three subjects in Study EST005. Subject 299, who received the 2.6 gram per day estradiol gel dose had a normal to low shift in hematology values, experienced intermittent mild to moderate metrorrhagia beginning on day 37 which became severe on day 78 and then remained moderate for 21 days. Per the submission, her bleeding resolved, without treatment, 21 days after completing the study (day 106). This subject had a post-treatment endometrial biopsy with a diagnosis of proliferative endometrium. She received post-treatment progestin per protocol.

Subject 668 (0.87 gram per day estradiol gel) had a normal to low shift in protein S. This subjects also had a low white blood cell count at baseline ($4x10^3$/uL) and day 86 ($3.5x10^3$/uL). Per the submission, Subject 668 had no thromboses-related adverse events and was not treated for the abnormal laboratory values.

Subject 104 (2.6 gram per day estradiol gel) had a similar low shift in protein S on day 56. Per the submission, this subject had no thromboses-related adverse events. A repeat assessment on day 120 was within the normal range (74%).

An increased incidence of shifts from baseline TVU measurements ≤ 4 mm to > 4 mm at the end-of-study visit in Study EST005, and normal to abnormal endometrial biopsies was observed

with the 1.7 gram per day and the 2.6 gram per day estradiol gel treatment groups in 12-week Study EST005.

Medical Officer's Comments:

See the discussion regarding estradiol gel use and endometrial hypertrophy and endometrial hyperplasia in Section 7.1.3 Dropouts and Other Significant Adverse Events, Sub-section 7.1.3.3 Other significant adverse events.

7.1.7.3.1 Analyses focused on measures of central tendency

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

7.1.7.4 Additional analyses and explorations

Other subjects in Study EST008 who showed clinically significant abnormal values for lipid parameters at the end-of-study were reported to have abnormal baseline values:

- Subject 630 (0.87 g/day estradiol gel): cholesterol (272 mg/dL at baseline and 325 at end-of study) and LDL (179 mg/dL at baseline and 203 at end-of-study).
- Subject 669 (0.87 g/day estradiol gel); cholesterol (245 mg/dL at baseline and 256 at end-of study) and LDL (171 mg/dL at baseline and 185 at end-of-study).
- Subject 844 (0.87 g/day estradiol gel); cholesterol (296 mg/dL at baseline and 353 at end-of study) and triglycerides (518 mg/dL at baseline and 693 at end-of-study).
- Subject 615 (1.7 g/day estradiol gel); triglycerides (287 mg/dL at baseline and 405 at end-of study).
- Subject 638 (1.7 g/day estradiol gel); cholesterol (241 mg/dL at baseline and 227 at end-of study).
- Subject 109 (2.6 g/day estradiol gel); cholesterol (270 mg/dL at baseline and 327 at end-of study) and LDL (192 mg/dL at baseline and 248 at end-of-study).
- Subject 171 (2.6 g/day estradiol gel); LDH (217 IU/L at baseline and 228 at end-of-study but both values were obtained from non-fasting blood samples.
- Subject 601 (placebo): cholesterol (225 mg/dL at baseline and 258 at end-of-study); LDL (166 mg/dL at baseline and 194 at end-of-study; alkaline phosphatase (106 IU/L at baseline and 136 IU/L at end-of-study and glucose (154 mg/dL at baseline and 195 at end-of-study).
- Subject 823 (placebo): ALT 62 IU/L at baseline and 80 at end-of-study) and AST (53 IU/L at baseline and 67 at end-of-study).

7.1.7.5 Special assessments

Study EST006 was a Phase 1, open-label, study of skin-to-skin transfer between estradiol gel treated subject and an untreated male partner. Two parallel groups were randomized. Group 1 couples engaged in five minutes of skin-to-skin contact two hours after the 2.6 gram per day

estradiol gel dose was applied to the upper arm of the female subject. Group 2 couples engaged in contact eight hours after the application of estradiol gel to the upper arm. Twelve couples were assigned to group 1 and 12 couples were assigned to group 2.

To establish baseline estradiol levels, males in both groups underwent serum estradiol sampling on day 1 prior to skin contact at 1, 2, 4, 8, and 24 hours relative to the projected skin contact.

To determine residual estradiol on the skin, group 1 females applied an additional 2.6 gram dose to the opposite arm and separate 20 cm^2 areas were swabbed two hours and eight hours after application. The arm was immediately washed and swabbed again and assayed for estradiol content. Cotton swabs were extracted into a methanol: water (50:50) solution.

PK parameters for AUC_{0-24}, C_{max}, C_{ave}, C_{min}, T_{max}, AUC_{inf}, K_{el}, and $t_{1/2}$ were analyzed for serum estradiol concentrations in the male subjects.

Study EST006 reported that PK parameters in the untreated males were not significantly different compared to before skin contact at 2 or 8 hours. The adjusted AUC_{0-24} and C_{ave} after skin contact were negative (that is a decreased exposure to estradiol compared to baseline). The mean percent of estradiol recovered from the skin at 2 and 8 hours post-application was 4.6 ± 4.0% and 7.8 ± 5.8% of the applied dose of estradiol, respectively.

[redacted] percent of the applied dose of estradiol was recovered from the female subject at two hours and [redacted]% at eight hours post application. [redacted]1% of the applied dose was recovered after washing the site.

Medical Officer's Comments:

No detectable absorption of estradiol in male partners after 5 minutes of skin-to-skin contact with estradiol gel indicates that the potential for estradiol transfer is negligible. A low amount of residual estradiol (< 10% of the applied dose) was demonstrated at two and eight hours after Estradiol gel application. Washing the application site with soap and water resulted in [redacted] 1% of the dose remaining at the application site and suggest that washing of the application site area substantially decreased the potential for transfer of estradiol gel.

Study EST008 was a Phase 1, randomized, open-label, 2-period crossover, multiple-dose study to determine concentrations of estradiol when estradiol gel was applied either before or after the application of sunscreen. Twelve (12) postmenopausal women applied 2.6 grams of estradiol gel daily to 320 cm^2 of the upper arm for 15 days. Blood draws were performed pre-dose on days 13-14 to determine trough steady-state serum hormone levels ($C_{min, ss}$ or $trough_{ss}$). Serial blood draws were taken throughout a 24 hour period on day 15 for hormone analyses ($SUC_{0-24, ss}$).

Sunscreen ([redacted]; SPF 30, UVA, UVB) was applied 10 minutes before each application of estradiol gel to the same upper arm site of days 16-22 (group one, sequence one, six subjects). Serial blood draws were taken pre-dose and throughout a 24-hour period on day 22.

Following another 15 days of once daily dose application of estradiol gel (days 23-37), serial blood draws were taken again throughout a 24 hour period on day 37. Subsequently, these subjects applied sunscreen 25 minutes after the application of estradiol gel for the final seven days (days 38-44). On the day of final application of estradiol gel and sunscreen (day 44), serial blood draws were taken pre-dose and throughout a 24 hour period.

The second group of six subjects (sequence two) received the therapies, but received the sunscreen application in the opposite sequence: sunscreen application 25 minutes after the estradiol gel application on days 16-22 and sunscreen application 10 minutes before estradiol gel application for days 38-44.

The PK parameters of AUC_{0-24}, C_{max}, and C_{ave} were calculated for steady-state, serum estradiol, estrone and estrone sulfate concentrations during applications of estradiol gel alone and in combination with sunscreen.

Adverse events were assessed prior to each drug application and for six days following the last application.

Study EST008 reported that when sunscreen was applied 10 minutes before applying estradiol gel for seven days C_{ave} and AUC_{0-24} for estradiol, estrone, and estrone sulfate increased by 55%, 34%, and 36%, respectively compared when applied alone.

When the sunscreen was applied 25 minutes after estradiol gel application for seven days, no significant change in C_{ave} and AUC_{0-24} for estradiol or its metabolites were observed.

Medical Officer's Comments:

See Section 5 Clinical Pharmacology, Sub-Section 5.1 Pharmacokinetics for additional information on Studies EST006 and EST008.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs (blood pressure, pulse, respiration rate, and temperature) were measured at screening and final visits during Studies EST004 and EST005. The data were not pooled due to the differences in double-blind treatment period between these two studies. Body weight was assessed at screening in both studies.

Per the submission, no statistically significant or clinically meaningful differences between estradiol gel treatment groups and placebo were observed in mean change from baseline for any vital signs parameter or body weight in Study EST004. In Study EST005, significant differences from placebo treatment were observed in mean decreases from baseline to week 12 for systolic

blood pressure in the 2.6 gram per day estradiol gel treatment group; and diastolic blood pressure in the 0.87 gram per day estradiol gel treatment group. The reported mean changes from baseline were small (≤ 3.2 mm Hg decrease).

All four treatment groups in 12-week Study EST005 showed mean increases in weight of 0.9 to 1.8 pounds at the final visit which were statistically significant ($p<0.0001$) in the 0.87 gram per day and 1.7 gram per day estradiol gel treatment groups (1.8 pounds and 1.6 pounds, respectively). Increases in weight were reported as treatment-emergent AEs of mild to moderate severity in all treatment groups in Study EST005 (one cases in 0.87gram/day treatment group, two cases in the 1.7 gram/day treatment group, two cases in the 2.6 gram/day treatment group, and one in placebo treatment group).

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The ISS pooled safety population included all randomized subjects who received at least one dose of double-blind study drug for Phase 2 (Study EST004) and Phase 3 (Study EST005) studies. In total, there were 161 subjects included in the ISS safety population (41 subjects in the 0.625 gram per day estradiol gel group, 40 subjects in the 1.25 gram per day estradiol gel group, 38 subjects in the 2.5 gram per day estradiol gel group, and 42 subjects in the placebo group in Study EST004. There were 484 subjects enrolled into Study EST005 and included in the ISS safety population (136 subjects in the 0.87 gram per day estradiol gel group, 142 subjects in the 1.7 gram per day estradiol gel group, 69 subjects in the 2.6 gram per day estradiol gel group, and 137 subjects in the placebo group.

7.1.8.3 Standard analyses and explorations of vital signs data

There were no clinically important findings for the assessments of vital signs, weight, and application site reactions.

7.1.8.3.1 Analyses focused on measures of central tendencies

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

7.1.8.4 Additional analyses and explorations

No additional analyses of vital signs data was performed by this reviewer.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

No electrocardiograms were obtained at baseline or at any scheduled post-treatment visit in 12-week, primary Study EST005.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

No overall drug-control comparisons were made.

7.1.9.3 Standard analyses and explorations of ECG data

No standard analyses and exploration of ECG data were performed/conducted.

7.1.9.3.1 Analyses focused on measures of central tendency

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

7.1.9.4 Additional analyses and explorations

No QT or QT_c interval data in included in the submission. No cases of arrhythmia, atrial fibrillation, atrial flutter, tachycardia, bradycardia, or ventricular fibrillation were reported in any completed estradiol gel clinical trial. No cases of Torsades de pointes or ventricular tachycardia were reported in the ISS.

7.1.10 Immunogenicity

No human immunogenicity studies, data, or published literature were submitted with the NDA.

7.1.11 Human Carcinogenicity

No human carcinogenicity studies were conducted under IND [ ] for estradiol gel. No data or published literature was submitted with the NDA on human carcinogenicity.

The Agency's draft 2003 estrogen-class labeling guidance document recommends that the following information be included in labeling: "Long-term continuous administration of estrogen, with or without progestin, in women with or without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver."

7.1.12 Special Safety Studies

In the drug development program for Estradiol gel, a partner transfer study was conducted. Study EST006 was a Phase 1, open-label, study of skin-to-skin transfer between estradiol gel-treated subject and an untreated male partner. Two parallel groups were randomized. Group 1 couples engaged in five minutes of skin-to-skin contact two hours after the 2.6 gram per day estradiol gel dose was applied to the upper arm of the female subject. Group 2 couples engaged in contact eight hours after the application of estradiol gel to the upper arm. Twelve couples were assigned to group 1 and 12 couples were assigned to group 2.

PK parameters for AUC_{0-24}, C_{max}, C_{ave}, C_{min}, T_{max}, AUC_{inf}, K_{el}, and $t_{1/2}$ were analyzed for serum estradiol concentrations in the male subjects. Study EST006 reported that PK parameters in the untreated males were not significantly different compared to before skin contact at 2 or 8 hours. The adjusted AUC_{0-24} and C_{ave} after skin contact were negative (that is a decreased exposure to estradiol compared to baseline). The mean percent of estradiol recovered from the skin at 2 and 8 hours post-application was 4.6 ± 4.0% and 7.8 ± 5.8% of the applied dose of estradiol, respectively.

In addition, Study EST006 determined residual estradiol on the skin of the female subject after an additional 2.6 gram dose estradiol gel application to the opposite arm. Separate 20 cm^2 areas were swabbed two hours and eight hours after application. The arm was immediately washed and swabbed again and assayed for estradiol content. Cotton swabs were extracted into a methanol: water (50:50) solution.

Per the submission, [ ] percent of the applied dose of estradiol was recovered from the female subject at two hours and [ ]% at eight hours post application. [ ] 1% of the applied dose was recovered after washing the site.

Medical Officer's Comments:

No detectable absorption of estradiol in male partners after 5 minutes of skin-to-skin contact with estradiol gel indicates that the potential for estradiol transfer is negligible. A low amount of residual estradiol (< 10% of the applied dose) was demonstrated at two and eight hours after estradiol gel application. Washing the application site with soap and water resulted in [ ] 1% of the dose remaining at the application site and suggest that washing of the application site area substantially decreased the potential for transfer of estradiol gel.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Per the submission, there were no cases of overdose with the study medication in the clinical development program of estradiol gel.

7.1.14 Human Reproduction and Pregnancy Data

Given that the[ ] indications being sought in NDA 21-813/S-000 are the treatment of moderate to severe vasomotor symptoms associated with the menopause[ ] [ ] no formal studies in humans on the effects of estradiol gel in human reproduction or pregnancy were performed.

Primary Phase 3 Study EST005 did not provide any information on drug exposure in pregnant women.

7.1.15 Assessment of Effect on Growth

Estradiol gel has not been tested in pediatric subjects. Estrogen drug product class labeling states that the safety and efficacy of estrogen drug products has not been established in pediatric patients.

7.1.16 Overdose Experience

No cases of overdose with estradiol gel have been reported during the clinical development program.

7.1.17 Postmarketing Experience

Estradiol gel is not marketed, either in the U.S. or internationally.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The table of clinical studies that appears in Section 4.2 Table of Clinical Studies in this review summarizes the clinical trials submitted to support the safety and efficacy of estradiol gel. Primary Phase 3, 12-week Study EST005 was used in the evaluation of efficacy. Study EST005 and Phase 2, 4-week Study EST004 both collected safety data. There was adequate representation for postmenopausal women in both studies.

7.2.1.1 Study type and design/patient enumeration

Refer to Section 4.2 Table of Clinical Studies for table that lists the clinical trials and summarizes the study design and number of subjects in each study.

7.2.1.2 Demographics

The demographics characteristics of all subjects who were randomized to study medication in Phase 3 Study EST005 are shown in Table 31.

Table 31: Demographic Characteristics (Study EST005) (All Randomized Subjects)

Characteristic	Estradiol Gel 0.87 g/day (N = 136)	Estradiol Gel 1.7 g/day (N = 142)	Estradiol Gel 2.6 g/day (N = 69)	Placebo (N = 137)
Age (years)				
Mean ± SD	54.4 ± 6.3	53.9 ± 6.2	55.3 ± 8.5	54.4 ± 5.8
Range	31 – 73	30 - 69	28 – 74	40 - 71
Race, n (%)				
White	120 (88.2)	119 (83.8)	57 (82.6)	113 (82.5)
Black	10 (7.4)	11 (7.7)	9 (13.0)	17 (12.4)
Hispanic	5 (3.7)	10 (7.0)	3 (4.3)	7 (5.1)
American Indian	1 (0.7)	1 (0.7)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
BMI (kg/m^2)				
Mean ± SD	26.4 ± 4.0	26.2 ± 3.8	26.6 ± 3.6	25.8 ± 3.8
Range	18 – 35	17 – 35	20 - 35	19 - 35
Height (in)				
Mean ± SD	64.0 ± 3.0	64.0 ± 2.6	64.6 ± 2.7	64.3 ± 2.9
Range	53 - 71	53 - 71	59 - 73	59 - 72
Weight (lb)				
Mean ± SD	154.1 ± 25.7	152.2 ± 26.0	157.8 ± 25.8	151.9 ± 27.6
Range	107 – 240	88 – 224	111 - 207	101 – 250
Time since last menses (years)				
Mean ± SD	9.2 ± 8.4	8.1 ± 7.9	8.3 ± 8.5	8.9 ± 8.3
Range	0.4 – 36.9	0.9 – 39.2	0.5 – 43.4	0.9 – 32.4
Menopausal history, n (%)				
Oophorectomy only	1 (.7)	0 (0.0)	0 (0.0)	0 (0.0)
Hysterectomy only	24 (17.6)	17 (12.0)	2 (2.9)	17 (12.4)
Oophorectomy/hysterectomy	31 (22.8)	30 (21.1)	22 (31.9)	37 (27.0)
Neither procedure	80 (58.8)	95 (66.9)	45 (65.2)	83 (60.6)

Source: Adapted from NDA 21-813/S-000, Section 8, Volume 26, Table 11.2-1 on page 77 (page 97 of 369) and Table 11.2-2 on page 79 (page 99 of 369).

Demographics and baseline characteristics in the ISS population is shown in Table 32.

Table 32: Demographic and Baseline Characteristics (ISS Safety Population)

	Number (%) of Subjects						
Subject Characteristics	**Estradiol Gel 0.625 g/day 4 weeks (N=41)**	**Estradiol Gel 0.87g/day 12 weeks (N=136)**	**Estradiol Gel 1.25 g/day 4 weeks (N=40)**	**Estradiol Gel 1.7 g/day 12 weeks (N=142)**	**Estradiol Gel 2.5/2.6 g/d 4 weeks[a] (N=107)**	**Estradiol Gel 2.6 g/day 12 weeks (N=69)**	**All Placebo 4 weeks/12 weeks (N=179)**
Age (years)							
Mean ± SD	53.7 ± 6.0	54.4 ± 6.3	52.7 ± 5.1	53.9 ± 6.2	54.4 ± 7.5	55.3 ± 8.5	54.0 ± 6.5

Subject Characteristics	Number (%) of Subjects						
	Estradiol Gel 0.625 g/day 4 weeks (N=41)	Estradiol Gel 0.87g/day 12 weeks (N=136)	Estradiol Gel 1.25 g/day 4 weeks (N=40)	Estradiol Gel 1.7 g/day 12 weeks (N=142)	Estradiol Gel 2.5/2.6 g/d 4 weeks[a] (N=107)	Estradiol Gel 2.6 g/day 12 weeks (N=69)	All Placebo 4 weeks/12 weeks (N=179)
Range	39 - 65	31 - 73	44 - 65	30 - 69	28 - 74	28 - 74	28 - 74
Race, n (%)							
White	33 (80.5)	120 (88.2)	35 (87.5)	119 (83.80	89 (83.2)	57 (82.6)	146 (81.6)
Black	7 (17.1)	10 (7.4)	4 (10.0)	11 (7.7)	13 (12.1)	9 (13.0)	26 (14.5)
Hispanic	1 (2.4)	5 (3.7)	1 (2.5)	10 (7.0)	5 (4.7)	3 (4.3)	7 (3.9)
Other	0 (0.0)	1 (0.7)	0 (0.0)	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
BMI (kg/m^2)							
Mean ± SD	28.1 ± 4.3	26.4 ± 4.0	27.1 ± 3.3	26.2 ± 3.8	26.7 ± 3.8	26.6 ± 3.9	26.0 ± 3.9
Range	20 - 36	18 - 35	21 - 34	17 - 35	20 - 35	20 - 35	19 - 35
Weight (lb)							
Mean ± SD	160.4±27.0	154.1±25.7	160.9±21.6	152.2±26.0	157.2±26.1	157.8±25.8	152.5±27.0
Range	108-219	107-240	123-208	88-224	111-209	111-207	101-250
Menopausal history, n (%)[b]							
Natural	21 (51.2)	80 (58.8)	25 (62.50	95 (66.9)	68 (63.60	45 (65.20	109 (60.9)
Surgical	20 (48.8)	56 (41.2)	15 (37.5)	47 (33.1)	39 (36.4)	24 (34.8)	70 (39.1)
Prior therapy n (%)							
Hormone	28 (68.30	103 (75.7)	24 (60.0)	120 (84.5)	77 (72.0)	54 (78.3)	141 (78.8)
Estrogen	22 (53.7)	76 (55.9)	19 (47.5)	86 (60.6)	62 (57.9)	44 (63.8)	110 (61.50

Source: Adapted from NDA 21-813/S-000, Section 8, Volume 62, Table 8.8.3-1, page 41of 277.
SD = Standard deviation
a. Includes EST004 subjects assigned to 2.5 g/day estradiol gel for four weeks and EST005 subjects assigned to 2.6 g/day estradiol gel for 12 weeks. EST005 subjects are also presented in the estradiol gel 2.6 g/day 12 weeks and the estradiol gel All Doses 4-12 weeks columns (subjects counted once in latter column).
b. Natural = no oophorectomy or hysterectomy; Surgical = hysterectomy with or without oophorectomy.

Medical Officer's Comments:
Overall, the treatment groups were similar with respect to demographic and baseline characteristics across Studies EST004 and EST005.

7.2.1.3 Extent of exposure (dose/duration)

Overall, 484 subjects received at least one application of study medication in Study EST005. The median duration of exposure to study medication was 85 days. A summary of exposure to double-blind study medication is shown in Table 32.

Table 33: Duration of Double-Blind Treatment (Study EST005)

Variable[a]	Estradiol Gel 0.87 gram/day (N = 136)	Estradiol Gel 1.7 gram/day (N = 142)	Estradiol Gel 2.6 gram/day (N = 69)	Placebo (N = 137)
Duration of treatment (days)				
Mean ± SD	84.4 ± 12.8	83.4 ± 11.7	84.3 ± 10.8	82.0 ± 16.5
Median	85.0	85.0	85.0	85.0

Variable[a]	Estradiol Gel 0.87 gram/day (N = 136)	Estradiol Gel 1.7 gram/day (N = 142)	Estradiol Gel 2.6 gram/day (N = 69)	Placebo (N = 137)
Range	5 - 99	16 - 00	24 - 99	2 - 101
Duration ranges (days)				
1-28	3 (2.2%)	1 (0.7%)	1 (1.4%)	6 (4.4%)
29-56	1 (0.7%)	6 (4.2%)	2 (2.9%)	3 (2.2%)
57-84	36 (26.5%)	61 (43.0%)	21 (30.4%)	50 (36.5%)
≥85	96 (70.6%)	74 (52.1%)	45 (65.2%)	78 (56.9%)

Source: Adapted from NDA 21-813/S-000, Section 8, Volume 26, page 116 (page 136 of 369).
a. Duration (days) of double-blind treatment is calculated from date of last dose of study drug and date of first dose of double-blind study drug.

The duration of double-blind treatment exposure presented in the ISS population is shown in Table 34.

Table 34: Duration of Double-Blind Treatment (ISS Safety Population)

	Number (%) of Subjects						
Variable[b]	**Estradiol Gel 0.625 g/day 4 weeks (N=41)**	**Estradiol Gel 0.87g/day 12 weeks (N=136)**	**Estradiol Gel 1.25 g/day 4 weeks (N=40)**	**Estradiol Gel 1.7 g/day 12 weeks (N=142)**	**Estradiol Gel 2.5/2.6 g/d 4 weeks[a] (N=107)**	**Estradiol Gel 2.6 g/day 12 weeks (N=69)**	**All Placebo 4 weeks/12 weeks (N=179)**
Duration of treatment (days)							
Mean ± SD	28.3±1.3	84.4±12.8	26.9±5.6	83.4±11.7	28.2±1.0	84.3±10.8	69.3±27.2
Median	28	85.0	28.0	85.0	28.0	85.0	84.0
Range	24 -32	5 – 99	3 - 32	16 – 100	23 – 31	24 – 99	2 - 101
Duration ranges (days), N (%)							
1-28	27 (65.9)	3 (2.2)	27 (67.5)	1 (0.7)	89 (83.2)	1 (1.4)	30 (16.8)
29-56	14 (34.1)	1 (0.7)	13 (32.5)	6 (4.2)	18 (16.8)	2 (2.9)	21 (11.7)
57-84	0 (0.0)	36 (26.5)	0 (0.0)	61 (43.0)	0 (0.0)	21 (30.4)	50 (27.9)
≥85	0 (0.0)	96 (70.6)	0 (0.0)	74 (52.1)	0 (0.0)	45 (65.2)	78 (43.6)

Source: Adapted from NDA21-813/S-000, Section 8, Volume 62, Table 8.8.2-1, page 37 of 277.
SD = Standard Deviation
a. Includes EST004 subjects assigned to estradiol gel 2.5 g/day for four weeks and EST005 subjects assigned to estradiol gel 2.6 g/day for 12 weeks. In this column, EST005 subjects with a treatment duration > 4 weeks were counted as duration=28 days. Entire treatment durations for Est005 subjects are presented in the estradiol gel 2.6 g/day 12 weeks and the estradiol gel All Doses 4-12 weeks columns (subjects counted once in latter column).
b. Duration (days) of double-blind treatment = date of last dose of double blind study drug – date of first dose of double-blind study drug + 1 day.

Medical Officer's Comments:

If all of the estradiol gel doses demonstrated in Table 34 are combined, 46.1% of estradiol gel subjects were treated for a period of ≥ 85 days (215 of 466 subjects) compared with 43.6% (78 of 179 subjects) in the all placebo groups.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Secondary safety source data is provided in four-week Study EST004 and in five of the six PK studies conducted during the estradiol gel development program (Studies [ ], EST003, EST006, EST007, and EST008). Safety information on integrated Studies EST004 and EST005 is located throughout the ISS section of this review.

Of the 111 subjects in the five PK studies with safety information (including 24 male subjects), 15 subjects had at least one adverse event assessed as possibly or probably related to treatment. The most common adverse event was breast pain and tenderness in six subjects. The next most common adverse events were dyspepsia (two subjects), nausea (two subjects), and headache (two subjects). A single case of application site reaction (dryness and redness on the fingers of the hand used to apply the gel) was reported. Other treatment-related adverse events included vomiting, thirst, fatigue, agitation, insomnia, stress symptoms, and hyperhidrosis. Per the submission, no subjects discontinued from the PK studies because of TEAEs.

7.2.2.2 Postmarketing experience

Estradiol gel is not marketed in the U.S. or internationally.

7.2.2.3 Literature

Publications in the Journal of the American Medical Association (JAMA) and in the Obstetrics and Gynecology literature have extensively documented the potential risk and benefits of estrogen and estrogen plus progestin therapy for the treatment of vasomotor symptoms and symptoms of vulvar and vaginal atrophy associated with the menopause. These publications have raised appropriate safety concerns about dose and duration of hormone therapy for menopausal symptoms. See page 22 for the review of findings of the National Institutes of Health (NIH) Women's Health Initiative (WHI) studies.

7.2.3 Adequacy of Overall Clinical Experience

A total of 484 subjects were exposes to estradiol gel in 12-week Study EST005 (136 subjects to 0.87 gram per day estradiol gel, 142 subjects to 1.7 gram per day estradiol gel, 69 subjects to 2.6 gram per day estradiol gel, and 137 subject to placebo). One hundred sixty-one (161) subjects were exposed to estradiol gel in four-week Study EST004 (41 subjects to 0.625 gram per day estradiol gel, 40 subjects to 1.25 gram per day estradiol gel, 38 subjects to 2.5 gram per day estradiol gel, and 42 subjects to placebo). In addition, 111 subjects were exposed to estradiol gel in [ ] PK studies including 24 male subject partners (Study EST006) [ ]

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The pharmacology, PK, and toxicology of estradiol treatment in general (including oral and topical administration) have been thoroughly characterized over 24 years of experience. It is recognized that long-term continuous administration of estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testes, and liver.

Per the submission, only one *in vivo* animal study was conducted using the [ ] formulation (Study [ ]). As reported, the single-dose topical application was non-irritating in a rabbit skin irritation test. In addition, two *in vitro* skin permeation studies were conducted with this same formulation (Study [ ] on human cadavers and Study [ ] on guinea pigs).

One *in vitro* skin permeation study was conducted with the to-be-marketed [ ] formulation of estradiol gel. Per the submission, no additional animal studies were conducted or require by the FDA, and no additional studies or repetitions of existing studies involving data pertinent to human safety are planned.

See the Pharmacology/Toxicology review of NDA 21-813/S-[ ] for a full discussion of *in vivo* animal and *in vitro* skin permeation findings.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing in Studies EST004 and EST005 subjects presented in the submission, including efforts to monitor laboratory parameters, vital signs, and efforts to elicit adverse event data is adequate. Laboratory parameters were collected at baseline and week four (Study EST004) and week 12 (Study EST005) and subjects were compared to their baseline values. There were very few shifts in laboratory values, and no cause for concern for subject safety was identified.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Section 5 of this review gives a brief summary of the clinical pharmacology for estradiol gel. See the Clinical Pharmacology and Pharmacokinetics Review for a more complete discussion. The metabolism and excretion of estrogen drug products are sufficiently understood to ease concerns about safety problems in patients with impaired excretory or metabolic function and problems resulting from drug-drug interactions.

In vitro and in vivo studies of other estrogen drug products have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations, phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effect and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole,

itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects. None of these issues raised concerns that require further testing for estradiol gel.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The gynecologic safety data submitted is generally adequate. BioSante Pharmaceuticals, Inc. was requested to provide additional endometrial hyperplasia safety information. The applicant responded promptly with the requested information.

7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of the safety data submitted with NDA 21-813/S-000 for the safety cohort of 756 postmenopausal women, with and without a uterus, was adequate. Phase 3, 12-week Study EST005 fulfills the Agency's requirement to conduct a 12-week safety and efficacy study for the treatment of moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.

7.2.9 Additional Submissions, Including Safety Update

A four-month safety update was submitted August 2, 2006. Per this submission, "Since our NDA submission, there are no new safety data, no ongoing Estradiol gel studies, and no new safety data. Consequently, there is no information suggesting a change in the safety profile or the labeling for this compound."

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Drug-related adverse events have been discussed previously in Section 7.1.3 Dropouts and Other Significant Adverse Events, Sub-section 7.1.3.3 Other significant adverse events. Refer to these sections for information on selected drug-related adverse events.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

In the submission, the Applicant provided estradiol gel safety data based on individual dosage strengths utilized during the estradiol gel development program with the exception of pooled results for the 2.5 gram per day estradiol gel dose in Study EST004 and the 2.6 gram per day estradiol gel dose utilized in Study EST005. The ISS combines the data for the 2.5/2.6 gram per day estradiol gel dosage strengths and the placebo groups. In the safety review, the source of the data has been identified in each section.

The individual study reports and the ISS were reviewed by this reviewer.

7.4.1.2 Combining data

The ISS combines the data for the 2.5/2.6 gram per day estradiol gel dosage strengths.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The issue of dose dependency of reported adverse events has been discussed in several sections of this review, particularly in Section 7.1.2 Other Serious Adverse Events, and Section 7.1.3 Dropouts and Other Significant Adverse Events.

Medical Officer's Comments:

Overall, the incidence of TEAEs were higher in the 2.6 gram per day estradiol gel treatment group than in the treatment groups treated with lower doses of estradiol gel in 12-week Study EST005. A relationship of increased incidence was observed for events in the reproductive system and breast disorder class. A higher incidence of breast tenderness (21.7%, 15 of 79 subjects), metrorrhagia (31.1%, 14 of 45 [of 69] subjects with a uterus), and endometrial hyperplasia (11.1%, 5 of 45 [of 69] subjects with a uterus) was observed in the 2.6 gram per day estradiol gel treatment group.

7.4.2.2 Explorations for time dependency for adverse findings

Exploration of time-dependent adverse event was limited to 12-week study EST005.

7.4.2.3 Explorations for drug-demographic interactions

Subjects ranged in age from 28 to 74 years across treatment groups in Studies EST005 and EST004. The majority of subjects across all placebo groups and all estradiol gel groups were 50 to 59 years of age (58% to 64%). A small percentage of subjects were ≥ 65 years (2.5% to 13%). In the submission, treatment-emergent adverse events were summarized by age accordingly, < 50 years of age (estradiol gel = 98 subjects, placebo = 38 subjects), 50 to 59 years of age (estradiol gel = 290 subjects, placebo = 110 subjects), 60 to 64 years of age (estradiol gel = 53 subjects, placebo = 25 subjects), and ≥ 65 years of age (Estradiol gel = 25 subjects, placebo = 6 subjects).

The most frequently occurring TEAEs for any of the estradiol gel age groups, or for which a statistically significant difference was seen in any age group analysis between estradiol gel and placebo-treated subjects is summarized below:

- **Eye disorder class:** The overall incidences of events of this class between estradiol gel all doses and all placebo groups for subjects ages 50 to 59 years was statistically significant (zero subjects versus three subjects, 2.7%, respectively; p=0.0204).
- **Gastrointestinal disorders class:** The incidence of overall TEAEs of this class was greater for estradiol gel subjects ages 60 to 64 years (nine subjects, 17.0%) than for other age groups (8.0% to approximately 12.2%). The incidence of nausea was highest for subjects aged < 50 years (six subjects, 6.1%).
- **General disorders and site administration class:** The overall incidences of TEAEs in this class were greater in the estradiol gel all doses group than in the all placebo group for all aged subjects. Overall, events in this class occurred in 9.0% to 15.1% of subjects in the estradiol gel all doses group, with the highest occurrences in subjects aged 60 to 64 years of age.
- **Musculoskeletal and connective tissue disorders class:** The incidence of overall TEAEs between estradiol gel all doses and all placebo groups in this class for subjects aged < 50 years was significant (12 subjects, 12.2% versus zero subjects, respectively).
- **Nervous system disorders class:** The highest incidence of TEAEs in the estradiol gel group was in the < 50 years of age group (headaches).
- **Reproductive system and breast disorder class:** The incidences of TEAEs in this class in each age category of the estradiol gel all doses group (21.7% to 28.3% of subjects) were higher than those of subjects in the all placebo group (7.9% to 16.7%). Endometrial hyperplasia was seen only in subjects treated with estradiol gel and an age trend was observed: three subjects (1.0%) aged 50 to 59 years, two subjects (3.8%) aged 60 to 64 years, and one subject (4.0%) aged ≥ 65 years. The incidence of nipple pain was greatest in subjects ≥ 65 years of age and treated with estradiol gel (8.0%, two of 25 subjects).
- **Respiratory, thoracic and mediastinal disorders class:** The overall incidence of events was higher in the estradiol gel all doses group for subjects < 50 years of age and aged 60 to 64 years, and higher in the all placebo group for subjects 50 to 59 years and ≥ 65 years of age.

Medical Officer's Comments:

See Section 8.8.4.8 (Volume 62, pages 78 to 82) Treatment-Emergent Adverse Events in Subgroups in the submission, particularly Table 8.8.4-1, for complete information on TEAEs by age subgroups in Studies EST005 and EST004.

The incidence of TEAEs in subjects with any dose of estradiol gel who were aged ≥ 65 years of age was slightly higher than that seen in the younger age categories and in all subjects (68.0%, 17 of 25 subjects compared with 33.3%, two of six subjects in the all placebo group ≥ 65 years. This finding, however, may be attributed to the relatively small number of subjects in the oldest age category rather than a treatment effect.

7.4.2.4 Explorations for drug-disease interactions

Per the submission, no drug-disease interactions were studied in the estradiol gel clinical development program.

7.4.2.5 Explorations for drug-drug interactions

In Study EST008, sunscreen applied 10 minutes before application of estradiol gel increased the absorption of estradiol by approximately 55%, but no [ ] in estradiol absorption was observed when sunscreen was applied 25 minutes after estradiol gel application.

See the Clinical Pharmacology and Biopharmaceutics Review of NDA 21-813/S-000 for discussion of the findings reported in Study EST008.

Medical Officer's Comments:

The proposed estradiol gel labeling should include the findings of Study EST008 regarding the concurrent application of sunscreen and estradiol gel.

7.4.3 Causality Determination

In Study EST005, one of the three reported serious adverse events was attributable to drug product. Subject 261 (2.6 gram per day estradiol gel, 54 year of age) experienced a worsening of a cervical cyst noted at study entry and an increase in endometrial thickness at end-of-study (4 mm at screening at baseline, 6 mm at end-of-study). She required hospitalization approximately three months after the last dose of study medication and underwent a transabdominal hysterectomy and bilateral salpingoophorectomy. The event was considered possibly related to study drug.

See Section 7.1.3 Dropouts and Other Significant Adverse Events for information regarding causality of endometrial hypertrophy and endometrial hyperplasia and estradiol gel use.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

For the treatment of moderate to severe vasomotor symptoms [redacted] the Applicant is requesting approval of [redacted] doses of estradiol gel: 0.87 gram per day, 1.7 gram per day[redacted]

8.2 Drug-Drug Interactions

In Study EST008, sunscreen applied 10 minutes before application of estradiol gel increased the absorption of estradiol by approximately 55%, but no [redacted] in estradiol absorption was observed when sunscreen was applied 25 minutes after estradiol gel application.

In Study EST008, there was a [redacted]-fold increase in estradiol AUC_{0-24} on day 37 relative to day 15. However, the mechanism for the increase remains unclear. The Agency's Clinical Pharmacology Reviewer agreed with the Applicant that sex hormone binding globulin (SHBG) could account for $\leq$ 15% of the observed 110% increase in estradiol AUC_{0-24} on day 37. These findings will be reflected in labeling.

See the Clinical Pharmacology and Biopharmaceutics Review of NDA 21-813/S-000 for discussion of the findings reported in Study EST006.

8.3 Special Populations

No pharmacokinetic studies were conducted in special populations, including subjects with renal or hepatic impairment.

Based on data from comparable estrogen therapy products, no formal studies in humans on the effect of estradiol gel on reproduction or pregnancy were performed. Similarly,[redacted] information on drug exposure in pregnant women, including any inadvertent exposure during drug development, was identified.

8.4 Pediatrics

Estradiol gel is not indicated for use in a pediatric population.

8.5 Advisory Committee Meeting

There was no advisory committee meeting in which estradiol gel was discussed.

8.6 Literature Review

Literature relevant to estrogen therapy has been referenced in this review as needed. There is no need for a separate comprehensive review of the literature.

8.7 Postmarketing Risk Management Plan

There is no need for a postmarketing risk management plan.

8.8 Other Relevant Materials

There are no relevant materials that are not included in other sections of this review. The results of a review of the product name from the Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety (ODS) is discussed in Section 2.1 of this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

9.2 Recommendation on Regulatory Action

This reviewer recommends approval of the 0.87 gram per day estradiol gel dose containing 0.52 mg of estradiol providing an estimated mean systemic delivery rate of 0.0125 mg of estradiol per day, and approval of the 1.7 gram per day estradiol gel dose containing 1.02 mg of estradiol providing an estimated mean systemic delivery of 0.0375 mg of estradiol per day for the treatment of moderate to severe vasomotor symptoms associated with the menopause. This recommendation is based upon the reported findings in 12-week, Phase 3 Study EST005 conducted to support the safety and efficacy of estradiol gel for this indication. The 0.87 gram per day estradiol gel dose achieved a statistically and clinically significant difference compared to placebo in reducing the frequency and severity of hot flushes at week 5 that was maintained through week 12. The 1.7 gram per day estradiol gel dose achieved a statistically and clinically significant difference compared to placebo in reducing the number and severity of hot flushes at week 4 that was maintained through week 12. Labeling will reflect that the 0.87 gram per day estradiol gel dose is not clinically and statistically different from placebo until week 5.

[redacted]

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No postmarketing risk management activities are recommended.

9.3.2 Required Phase 4 Commitments

No Phase 4 clinical study commitment is proposed.

9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests.

9.4 Labeling Review

The following are this reviewer's recommended changes for labeling.

Prescriber Labeling:

Boxed Warnings: The boxed warnings have been updated to include under CARDIOVASCULAR AND OTHER RISKS updated information regarding the Women's Health Initiative (WHI) estrogen alone and estrogen plus progestin substudies.

DESCRIPTION: Section modified to identify estradiol gel.

CLINICAL PARMACOLOGY:

A. Absorption: [redacted]
Figure 1 replaced with figure with error bars.
Caution statement added regarding seven days of application of sunscreen and estradiol gel.

CLINICAL STUDIES:

Effect on Vasomotor Symptoms:	Section modified to provide results of 12-week clinical trial for the 0.87 gram per day and the 1.7 gram per day estradiol gel doses.
[ ]	[ ]
Women's Health Initiative Studies:	Minor updates to text. Table 3 modified to incorporate updated information regarding the WHI estrogen alone substudy. Table 4 modified to incorporate update information regarding the WHI estrogen plus progestin substudy.
Women's Health Initiative Memory Study:	Minor updates to text.
INDICATIONS AND USAGE:	Section modified to indicate that the 0.87 gram per day estradiol gel dose is indicated for the treatment of VMS [ ] [ ] Section modified to indicate that the 1.7 gram per day estradiol gel dose is indicated for the treatment of VMS.
WARNINGS:	
1. Cardiovascular disorders a. Stroke:	Text updated to include updated WHI reported results. Coronary heart disease and stroke was separated into two subsections. Text modified to incorporate updated WHI estrogen alone and estrogen plus progestin reported results.
b. Coronary heart disease:	Text modified to incorporate updated WHI estrogen alone and estrogen plus progestin reported results.
c. Venous thrombosis (VTE):	Text modified to incorporate updated WHI estrogen alone and estrogen plus progestin reported results.
2. Malignant neoplasms a. Endometrial cancer:	Text modified to include one case of complex hyperplasia in clinical trial reported in 1.7 gram per day estradiol gel dose.
b. Breast cancer:	Text modified to update WHI estrogen alone reported results after an average of 7.1 years.
3. Dementia:	Text modified to incorporate WHI estrogen plus progestin substudy reported results. Information added regarding the pooled populations in the WHI estrogen alone and estrogen plus progestin substudies.
PRECAUTIONS A. General	

12. Sunscreen application:	Text modified to incorporate the reported findings of concomitant application of sunscreen and estradiol gel for seven or more days.
13. Miscellaneous:	Precaution added regarding the potentially flammable nature of alcohol gel.
I. Geriatric Use:	Text modified to include the absolute risk of developing probable dementia with estrogen alone from the WHI substudy; the increased risk of non-fatal stroke and invasive breast cancer in the estrogen plus progestin WHI estrogen plus progestin substudy in postmenopausal women greater than 75 years of age.
DOSAGE AND ADMINISTRATION:	Section modified to indicate that the 0.87 gram per day estradiol gel dose is indicated for the treatment of VMS[ ] Section modified to indicate that the 1.7 gram per day estradiol gel dose is indicated for the treatment of VMS.

Patient Information leaflet:

Boxed Warning:	Box added to: What is the Most Important Information I should know about[ ] (An Estrogen Hormone)?
What is[ ]?:	Minor edits added.
How should I use[ ]?:	[ ]
Important things to remember when using[ ]:	
Text modified to include:	Never apply[ ] in or around the vagina. Do not apply sunscreen to the area where the gel was applied for at least 25 minutes. Do no apply sunscreen to the area where the gel was applied for 7 or more consecutive days.
What can I do to lower my chances of a serious side effect with[ ]?:	Minor edits to text.
General information about safe and effective use of[ ]:	[ ]

9.5 Comments to Applicant

The following are this reviewer's recommended comments to the Applicant.

1. [redacted]

2. [redacted]

Per the Agency's 2003 draft Guidance for Industry entitled, "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation", we recommend that the treatment of moderate to severe symptoms of vulvar and vaginal atrophy[redacted] be granted on the basis of clinical trial data which establishes efficacy based on three co-primary endpoints:

1. Mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as being the most bothersome to her.
2. Mean change from baseline to week 12 in vaginal pH.
3. Mean change from baseline to week 12 in vaginal maturation index (parabasal and superficial cells).

[redacted]

10 APPENDICES

10.1 Review of Individual Study Reports

The results of supportive, four-week, Phase 2 Study EST004 entitled "A Phase II/III, Multicenter, Double-Blind Study of the Safety and Efficacy of Bio-E-Gel (Topical Estradiol Gel) Versus Placebo for Treatment of Vasomotor Symptoms in Postmenopausal Females" have been incorporated throughout sections of this review. No individual study report of Study EST004 is prepared.

10.2 Line-by-Line Labeling Review

See final agreed upon labeling.

REFERENCES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Theresa Van Der Vlugt
11/21/2006 12:05:59 PM
MEDICAL OFFICER

Shelley Slaughter
12/14/2006 01:09:42 PM
MEDICAL OFFICER
I concur with the MO recommendations to approve the 0.87 and 1.7 g/day dose for VMS [redacted]

See TL review.

Tradename (estradiol gel)
Team Leader Review

NDA:	**21-813** [ ]
Drug:	**Tradename (estradiol gel)**
Indications:	**1. Treatment of moderate-to-severe vasomotor symptoms associated with the menopause** [ ]
Dosage/Form/Route:	**0.87 g per day (estimated mean systemic delivery rate 0.0125 mg per day).** **1.7 g per day (estimated mean systemic delivery rate of 0.0375 mg per day)** [ ]
Applicant:	**Biosante Pharmaceuticals, Inc.**
Original Submission Stamp Date:	**February 16, 2006**
Primary Review Completion date:	**October 16, 2006**
Date of Final Memorandum:	**December 13, 2006**

Executive Summary:

A single Phase 3 study, EST005, was submitted in support of efficacy of the estradiol gel for the treatment of moderate to severe vasomotor symptoms [ ] [ ] The safety base was composed of Phase 3 Study EST005, Phase2 Study EST 004 and [ ] Phase 1 studies. Results of Study EST005 demonstrated that the 1.7 and 2.6 g/day dose of estradiol gel demonstrated both clinically and statistically significant reductions in frequency and statistically significant reductions in severity of vasomotor symptoms at Week 4 which was maintained through Week 12 and, thus, met the criteria for efficacy as stated in the January 2003 Draft Guidance for Industry, entitled "Estrogen and Estrogen/Progestin Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation" (to be referred to in this review as the Draft HT Clinical Trial Guidance). In Study EST005, the 0.87 g/day dose did not demonstrate either a statistically or clinically significant reduction in frequency or a statistically significant reduction in severity of vasomotor symptoms at Week 4. A clinically and statistically significant reduction in frequency and a statistically significant reduction in severity were achieved at Week 5 with this dose and the clinically and statistically significant reduction achieved at Week 5 was maintained to Week 12.

The Draft HT Clinical Trial Guidance recommends that women who are experiencing moderate to severe symptoms of vulvar and vaginal atrophy should be evaluated in a placebo-controlled clinical trial and that efficacy should be demonstrated with statistically significant improvements when compared to placebo in each of the three co-primary endpoints of vaginal pH, vaginal maturation (increase in superficial cells and decrease in parabasal cells) and the moderate-to-severe symptom of vaginal atrophy self-identified by the subject as being most bothersome to her. Study EST005 enrolled subjects experiencing mild symptoms of vulvar and vaginal atrophy as well as moderate to severe symptoms at baseline. Therefore, a subset analysis was necessary to include subjects experiencing moderate to severe symptoms as well as those meeting the entrance criteria for vaginal pH and vaginal superficial cells. The data was subjected to a sub-subset analysis to evaluate the individual symptoms of vulvar and vaginal atrophy. [ ]

The 2.6 gm per day dose was found to have an unacceptably high rate of endometrial hyperplasia at Week 12. No other significant safety issues were identified.

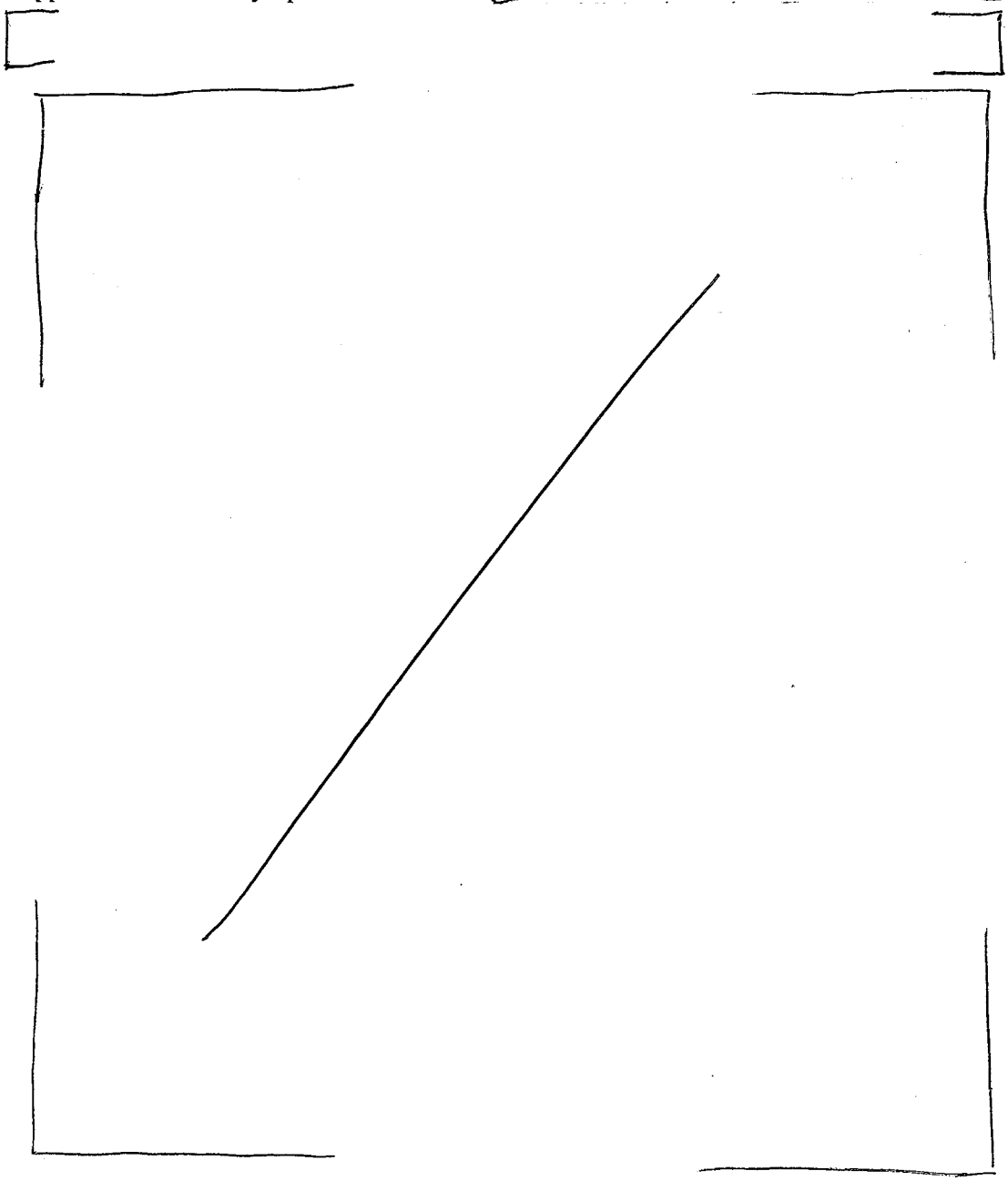
Based on the totality of the efficacy and safety findings, this reviewer recommends that both the 0.87 g/ day and 1.7 g/day dose of estradiol gel be approved for the indication of treatment of the moderate to severe vasomotor symptoms. The labeling must clearly reflect that when compared to placebo, clinically and statistically significant reductions in vasomotor symptoms were not obtained for the 0.87 g per day dose until Week 5.

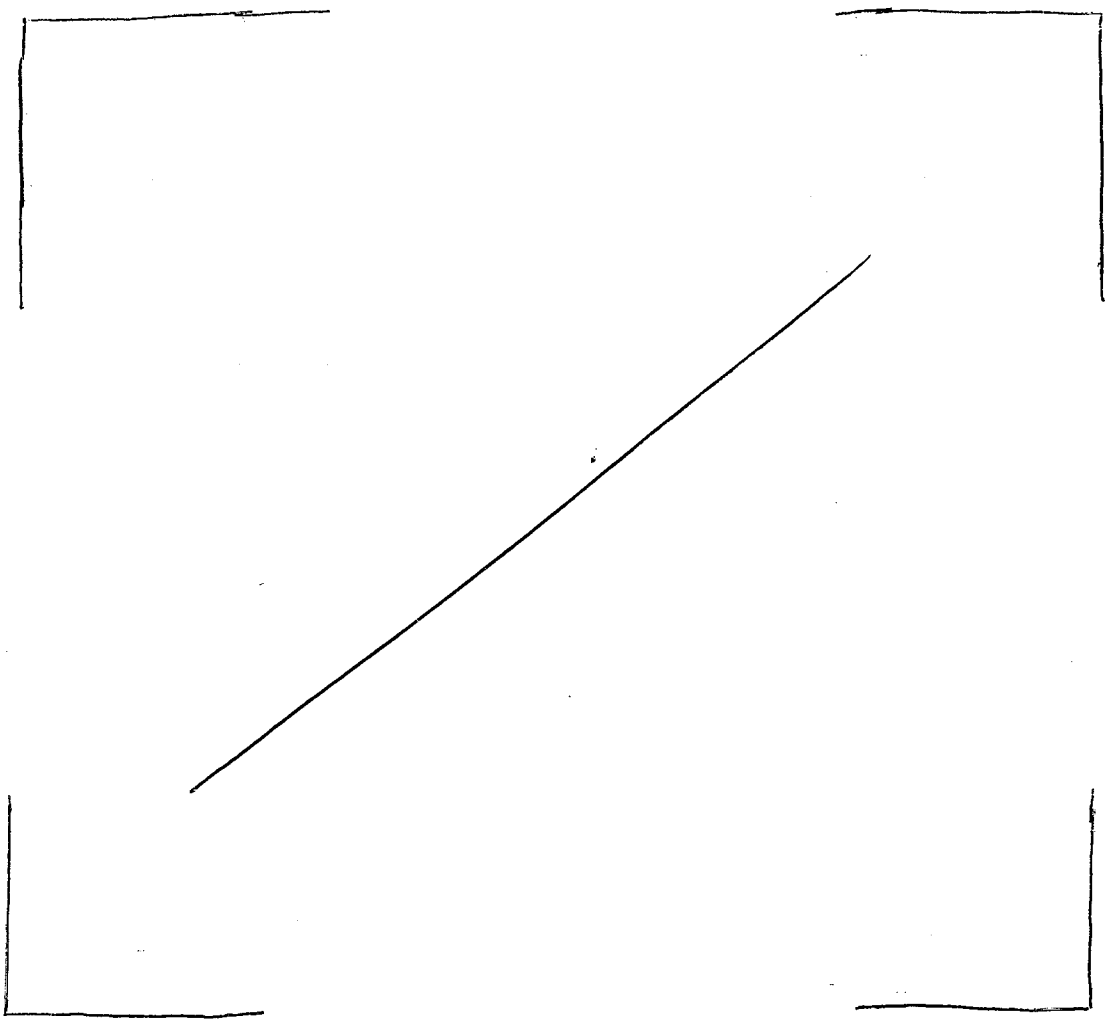
[ ]

Background and Regulatory History

The Sponsor submitted briefing documents and a pre-IND (IND 51229) request for a meeting on June 11 and 13, 2001. The briefing document included a [ ] In the pre-IND teleconference, August 15, 2001 between the Sponsor and the Division of Reproductive and Urologic Products (DRUP), DRUP recommended that prior to proceeding to Phase 3 clinical trials, the Applicant conduct a Phase 2 dose-finding, placebo-controlled clinical trial of four weeks duration to determine the lowest effective dose of estradiol gel for the treatment of moderate to severe vasomotor symptoms associated with the menopause. Alternatively, DRUP stated that a Phase 3 trial could be conducted provided the study identifies the lowest effective dose and addresses all pharmacokinetic issues. DRUP further clarified that the primary efficacy endpoint should

be a change from baseline at Week 4 for both frequency and severity of vasomotor symptoms. Finally, DRUP agreed that one robust, well-controlled, double-blind, placebo-controlled clinical trial is sufficient to demonstrate the efficacy and safety of a drug product for the relief of moderate-to-severe vasomotor symptoms associated with the menopause; the study should be at least 12-weeks in duration, should evaluate dosage levels that include the lowest effective dose, and should be conducted under double-blind conditions. DRUP advised that the Sponsor could proceed with the Phase 3 trials as proposed, however, the Sponsor was cautioned regarding the risk in proceeding to Phase 3 trials without having identified the lowest effective dose, a criterion for a pivotal trial to support a vasomotor symptom indication...[





On February15, 2002 the Agency received submission 002 to the IND which included the protocol for Study EST004, a Phase 2/3 multi-center double-blind, placebo-controlled parallel 4-week group study to determine the change from baseline in the frequency of moderate to severe vasomotor symptoms at week 4. The protocol was reviewed by the Division with a single clinical comment relayed to the Sponsor stating that responders during the 7-day placebo period prior to treatment should not be dropped from the study.

An end-of-Phase 2 (EOP2) meeting was held between DRUP and the Sponsor on April 24, 2003. The Sponsor presented data from its Phase 2 dose-ranging study of the 0.625 g/day (delivering 37.5 µg estradiol/day), 1.25 g/day (delivering 75 µg estradiol per day) and 2.5 g/day (delivering 150 µg estradiol per day) doses. DRUP noted concern that the lowest effective dose may not have been identified in Phase 2 and recommended that one or more lower doses be included in their Phase 3 study. The Sponsor was also advised to conduct "Partner Transfer", "Effect of Sunscreen" and "Effect of Washing Studies".

A new Phase 3 protocol for Study EST005 was sent on June 13, 2003 and Amendments were sent in submissions dated September 17, 2003, September 30, 2003 and October 2, 2003. The following clinical advice was sent to the Sponsor on November 12, 2003:

- Should both [redacted] doses, 1.7 g/day and 2.6 g/ day, demonstrate effectiveness, an ineffective lower dose would not be demonstrated in Study EST 005. Reference could be made to dose-finding Study EST004 to demonstrate an ineffective dose provided a relative link between the different packaging systems could be established.
- Please be advised that a mean change from baseline to Week 12 in the moderate to severe symptom identified by the patient as being most bothersome to her is the efficacy endpoint of interest for a treatment of moderate to severe symptoms of vulvar and vaginal atrophy [redacted]
- We recommend that the Subject Vaginal Health Self-Assessment Questionnaire be revised as follows:
  - Number five (vaginal bleeding with sexual activity) should be reported as no sexual activity, none, a little (mild), quite a bit (moderate), and extremely (severe) to bring the reporting of this question into compliance with the first 4 questions.
  - The questionnaire should be revised to allow the subject, independent of the "site coordinator" to record the one moderate (quite a bit) to severe (extremely) response reported that is most bothersome to her.
- You have proposed a plan to not randomize any subject who has a $\geq$ 50% placebo response during the placebo lead-in period. We recommend that no responder during the 7-day placebo period prior to treatment be dropped from the study. This would artificially enhance the patient population to exclude placebo responders.
- We recommend that the following inclusion criteria be added to Study EST005:
  - The subject self-identifies at least one moderate to severe symptom of vulvar and vaginal atrophy on the Vaginal Atrophy Questionnaire that is most bothersome to her.
  - The subject has a baseline vaginal pH that is greater than 5.0.
  - The subject has $\leq$ 5% superficial cells at baseline on the vaginal cytology smear (maturation index)
- We recommend that age subgroup analyses (< 50, 50 to 59, 60 years of age and older) also be performed to demonstrate the mean change from baseline in the daily moderate to severe hot flush frequency and severity at weeks 4 and 12 of treatment.

[redacted]

Study EST005 was conducted from September 9, 2003 to April 1, 2005. NDA 21-813 was received on February 16, 2006 and it was administratively filed on April 17, 2006.

Clinical

Efficacy

Study EST005

A single Phase 3 Study, EST005, was conducted in support of [ ] indications:

1. Treatment of moderate-to-severe vasomotor symptoms associated with the menopause.

[ ]

Study EST005 was a Phase 3 multicenter (32 sites), randomized, double-blind, parallel group, and placebo-controlled trial. Subjects were screened to those who had ≥ 60 moderate-to-severe hot flushes per week at baseline consistent with the HT Clinical Trial Guidance. Despite guidance from the Division on multiple occasions to enroll subjects who at baseline met Draft HT Clinical Trial Guidance recommendations for trials of vulvar and vaginal atrophy, the Sponsor did not require the enrollment of subjects with the minimal criteria of at least one moderate-to-severe symptom of vulvar and vaginal atrophy which the subject self-identified as most bothersome to her and a pH > 5 and ≤ 5% superficial cells on a vaginal smear. Other than the preceding discrepancy, enrollment criteria were consistent with the Draft HT Clinical Trial Guidance.

Four Hundred Eight Four (484) subjects were randomized to receive treatment in an unbalance fashion. Subjects received estrogen gel 1.7 g/ day, estrogen gel 2.6 g/ day, or placebo according to a 1:1:1 randomization scheme until approximately 50 subjects per treatment group were enrolled. Once approximately 50 subjects were enrolled in the estrogen gel 2.6 g/day arm, eligible subjects were then randomized according to a 4:2:2 scheme to receive estradiol gel 0.87 g/ day, estradiol 1.7 g/ day and placebo until approximately 127 subjects were enrolled in these groups. The daily dose of study drug was applied topically by the subject at the same time of day each morning. Subjects were instructed not to wash the application sites for at least six hours (and preferably not until the next morning). Subjects were instructed to allow the gel to dry three to five minutes before covering the application sites with clothing or before coming into contact with another person. Subjects were also cautioned against applying lotions, ointments, gels, sunscreen or other skin care products to the skin areas used for gel application during the study and to wash their hands after gel application. Subjects were instructed not to apply the gel to the breast or intra-vaginally.

Subjects maintained a daily diary of hot flush frequency and severity. Severity was scored as: mild, moderate and severe.

Vulvar and vaginal atrophy symptoms were evaluated based on a subject vaginal health self-assessment. Subjects completed a Vaginal Health Self-Assessment Questionnaire by checking the selected response using a four-point scale ("None", "A little (mild)", "Quite a bit (moderate)", "Extremely (severe)", or "No sexual activity" for the following questions:

1. "Do you experience vaginal dryness (decreased vaginal lubrication, secretions, fluid, or mucus)?"
2. "Do you experience vaginal (or vaginal area) irritation or itching?"
3. "Do you experience pain or difficulty passing urine?"
4. "Do you experience vaginal pain with sexual activity?"
5. "Do you experience vaginal bleeding with sexual activity?"

The subject determined which symptom rated moderate or severe was the most bothersome to her. The Vaginal Health Self-Assessment Questionnaire was completed at visit one (day-21), at visit two (day-7) and weekly (based on her experience the previous week) for the remainder of the 12-week study. A specimen was obtained from the vaginal wall during visit one (day-21) and visit 6 (day-85) or last visit for subjects who discontinued prematurely.

Demographics

The mean age (± SD) per treatment group was 54.4 ± 6.3, 53.9 ± 6.2, 55.3 ± 8.5 and 54.4 ± 5.8, in the 0.87 g/day estradiol gel, the 1.7 g/day estradiol gel, the 2.6 g/day estradiol gel and the placebo treatment groups, respectively. Caucasian women made up 82.5 % - 88.2 % of the study drug treatment groups, with minority groups making up the difference (Black women constituted approximately 7-13% of the treatment groups, Hispanics 3.7-7% and American Indians 0-0.7%). There were no substantial differences in BMI and weight between the treatment groups.

VMS

The primary efficacy analyses for frequency of vasomotor symptoms are shown in Table 1 [adapted from Medical Officer Review (MOR) Table 7 and Statistical Review (SR) Table 3.2.3]. The daily moderate-to-severe hot flush frequency was calculated as the total number of moderate-to-severe hot flushes recorded in the daily diary during the seven days immediately preceding and including the weekly study date, divided by the number of those seven days with diary entries completed. Severity was calculated as the sum of the average daily hot flush severity rating divided by the number of those seven days with diary entry completed.

Table 1 - Mean Daily Number of Moderate-to-Severe Hot Flushes and Change from Baseline in Mean Daily Number of Moderate-to-Severe Hot Flushed during Therapy in All Subjects with > 60 Moderate-to-Severe Hot Flushes Per Week at Baseline, Intent-to-Treat Population with LOCF.

Week	Hot Flush Frequency and Mean Change[a,b]			
	0.87 g/day (N = 136)	1.7 g/day (N = 142)	2.6 g/day (N = 69)	Placebo (N = 137)
Baseline Mean Number (±SD)	13.30 ± 4.6	13.10 ± 6.5	12.87 ± 6.5	13.47 ± 4.5
Week 1				
Mean Number	9.63	10.59	9.94	9.23
Mean Change	-3.45	-2.38	-2.92	-3.98
p-value vs. placebo[c]	ns	<0.01	ns	
Week 2				
Mean Number	8.43	8.26	7.17	8.57
Mean Change	-4.58	-4.60	-5.68	-4.53
p-value vs. placebo[c]	ns	ns	ns	
Week 3				
Mean Number	7.47	6.16	4.74	8.14
Mean Change	-5.61	-6.75	-8.30	-4.95
p-value vs. placebo[c]	ns	<0.01	<0.0001	
Week 4				
Mean Number	6.55	4.87	3.69	7.91
Mean Change	-6.5	-8.00	-9.32	-5.14
p-value vs. placebo[c]	ns	<0.0001	<0.0001	
Week 5				
Mean Number	5.50	4.03	3.19	7.83
Mean Change	-7.47	-8.81	-9.83	-5.14
p-value vs. placebo[c]	<0.001	<0.0001	<0.0001	
Week 6				
Mean Number	5.2	3.54	2.80	7.60
Mean Change	-7.70	-9.30	-10.19	-5.37
p-value vs. placebo[c]	<0.001	<0.0001	<0.0001	
Week 7				
Mean Number	4.67	3.21	2.30	7.31
Mean Change	-8.25	-9.69	-10.79	-5.75
p-value vs. placebo[c]	<0.0001	<0.0001	<0.0001	
Week 8				
Mean Number	4.55	3.04	2.25	7.32
Mean Change	-8.33	-9.79	-10.77	-5.67
p-value vs. placebo[c]	<0.0001	<0.0001	<0.0001	
Week 9				
Mean Number	4.46	2.82	1.90	7.40
Mean Change	-8.43	-10.04	-11.14	-5.61
p-value vs. placebo[c]	<0.0001	<0.0001	<0.0001	

Week	Hot Flush Frequency and Mean Change[a,b]			
	0.87 g/day (N = 136)	1.7 g/day (N = 142)	2.6 g/day (N = 69)	Placebo (N = 137)
Week 10				
Mean Number	4.22	2.68	2.00	7.4
Mean Change	-8.61	-10.16	-11.04	-5.57
p-value vs. placebo[c]	<0.0001	<0.0001		
Week 11				
Mean Number	4.15	2.61	2.0	7.23
Mean Change	-8.63	-10.16	-10.96	-5.67
p-value vs. placebo[c]	<0.0001	<0.0001	<0.0001	
Week 12				
Mean Number	4.00	2.50	2.05	7.30
Mean Change	-8.50	-10.02	-10.66	-5.35
p-value vs. placebo[c]	<0.0001	<0.0001	<0.0001	<0.0001

[a]Difference from baseline to each week based on LS mean derived from the ANCOVA model with factors for baseline, treatment site and treatment by baseline interaction

[b]Unadjusted means and standard deviation. Baseline based on the first 14 days of the screening period.

[c]Dunnett's adjustments for multiple dose comparisons

The primary efficacy analyses for severity of vasomotor symptoms are shown in Table 2 (adapted from MOR Table 8 and SR Table 3.2.3).

Table 2 - Mean Daily Severity of Moderate-to-Severe Hot Flushes and Change from Baseline in Mean Daily Severity of Moderate-to-Severe Hot Flushed during Therapy in All Subjects with > 60 Moderate-to-Severe Hot Flushes Per Week at Baseline, Intent-to-Treat Population with LOCF.

Week	Hot Flush Severity and Mean Change[a,b]			
	0.87 g/day (N = 136)	1.7 g/day (N = 142)	2.6 g/day (N = 69)	Placebo (N = 137)
Baseline[c] Mean Severity (±SD)	2.42±0.32	2.4±0.27	2.41±0.32	2.41±0.32
Week 1				
Mean Severity	2.27	2.31	2.32	2.26
Mean Change	-0.15	-0.09	-0.10	-0.16
p-value vs. placebo[d]	ns	<0.01	ns	
Week 2				
Mean Severity	2.18	2.15	2.02	2.20
Mean Change	-0.22	-0.25	-0.40	-0.19
p-value vs. placebo[d]	ns		<0.05	
Week 3				
Mean Severity	2.08	1.88	1.71	2.14
Mean Change	-0.34	-0.52	-0.71	-0.25
p-value vs. placebo[d]	ns	<0.01	<0.0001	
Week 4				
Mean Severity	1.93	1.70	1.45	2.12
Mean Change	-0.45	-0.67	-0.96	-0.24
p-value vs. placebo[d]	ns	<0.0001	<0.0001	
Week 5				
Mean Severity	1.85	1.59	1.34	2.12
Mean Change	-0.50	-0.77	-1.05	-0.22
p-value vs. placebo[d]	<0.01	<0.0001	<0.0001	
Week 6				
Mean Severity	1.77	1.46	1.26	2.07
Mean Change	-0.57	-0.90	-1.14	-0..27
p-value vs. placebo[d]	<0.01	<0.0001	<0.0001	
Week 7				
Mean Severity	1.70	1.34	1.10	2.04
Mean Change	-0.64	-1.01	-1.31	-0.30
p-value vs. placebo[d]	<0.01	<0.001	<0.0001	
Week 8				
Mean Severity	1.65	1.27	1.02	2.06
Mean Change	-0.67	-1.07	-1.39	-0.27
p-value vs. placebo[d]	<0. 01	<0.0001	<0.0001	
Week 9				
Mean Severity	1.64	1.28	0.93	2.06
Mean Change	-0.67	-1.08	-1.47	-0..27
p-value vs. placebo[d]	<0. 01	<0.0001	<0.0001	

Week	Hot Flush Severity and Mean Change[a,b]			
	0.87 g/day (N = 136)	1.7 g/day (N = 142)	2.6 g/day (N = 69)	Placebo (N = 137)
Week 10				
Mean Severity	1.60	1.18	0.87	2.10
Mean Change	-0.70	-1.16	-1.52	-0.22
p-value vs. placebo[d]	<0. 01	<0.0001	<0.0001	
Week 11				
Mean Severity	1.55	1.19	0.92	2.06
Mean Change	-0.76	-1.14	-1.47	-0..25
p-value vs. placebo[d]	<0.0001	<0.0001	<0.0001	
Week 12				
Mean Severity	1.52	1.15	0.86	2.05
Mean Change	-0.77	-1.17	-1.51	-0.26
p-value vs. placebo[c]	<0.0001	<0.0001	<0.0001	<0.0001

[a]Difference from baseline to each week based on LS mean derived from the ANCOVA model with factors for baseline, treatment site and treatment by baseline interaction

[b]Severity score 0=none; 1=mild; 2=moderate; 3=severe

[c]Unadjusted means and standard deviation. Baseline based on the first 14 days of the screening period.

[d]Dunnett's adjustment for multiple dose comparisons

The Draft HT Clinical Trial Guidance recommends that clinical trials for drug products seeking to demonstrate efficacy for the treatment of moderate-to-severe vasomotor symptoms show both a statistically and clinically significant reduction from baseline vs. placebo in frequency and a statistically significant reduction from baseline vs. placebo in severity of hot flushes beginning at Week 4 and persisting through Week 12. A clinically significant reduction in frequency is defined as at least two more than placebo per day or at least 14 more than placebo per week. The endpoints for efficacy for VMS (hot flushes) are:

- Mean change in frequency of moderate to severe vasomotor symptoms from baseline to week 4.
- Mean change in severity of moderate to severe vasomotor symptoms from baseline to week 4.
- Mean change in frequency of moderate to severe vasomotor symptoms from baseline to week 12.
- Mean change in severity of moderate to severe vasomotor symptoms from baseline to week 12.

Consistent with the Draft HT Clinical Trial Guidance recommendation, the 1.7 g/day dosage strength and the 2.6 g/day dosage strength of estradiol gel were shown to be efficacious. The 0.87 g/day dosage strength did not demonstrate a clinically and statistically significant reduction from baseline when compared to placebo at Week 4. This dosage strength reached both clinical (frequency) and statistical (frequency and severity) significance at Week 5 and maintained significance through Week 12.

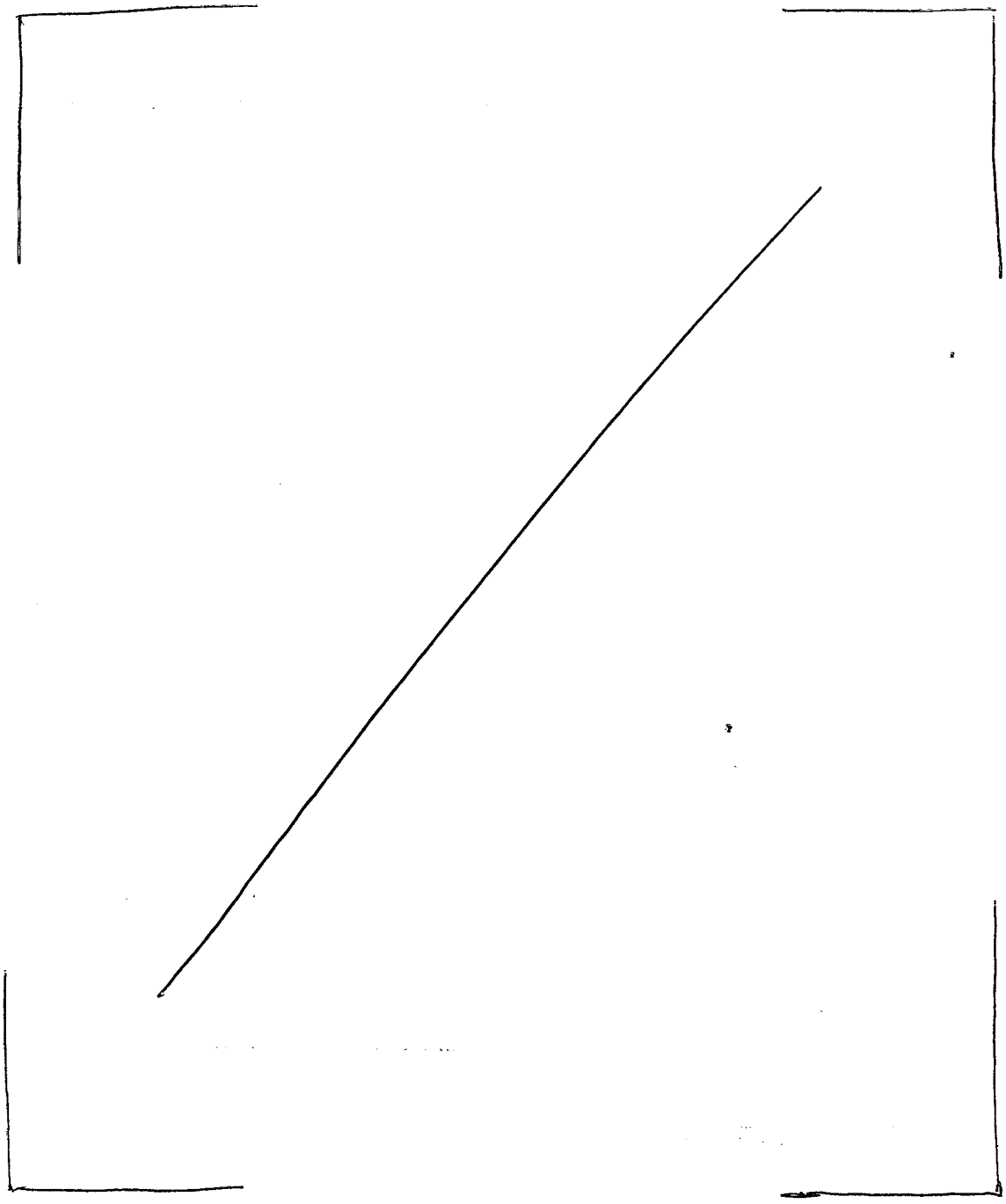
Redacted 5 page(s)

of trade secret and/or

confidential commercial

information from

Medical Reviews -
Team Leader Review (12/14/06)



Safety

Data from the two placebo-controlled clinical studies, EST004 (4 weeks) and EST 005 (12 weeks) were combined with [ ] Phase 1 studies for the Integrated Summary of Safety. The ISS summarizes data on a total of 756 subjects (645 from EST004 and EST005 and 111 subjects from Studies [ ] EST003, EST006, EST007 and EST008)

Endometrial hyperplasia

One of the most concerning adverse events most commonly associated with use of unopposed estrogens in women with a uterus is endometrial hyperplasia. Consistent with the Draft HT Clinical Trial Guidance recommendation for 12 week trials for VMS and VVA, subjects with a uterus had an endometrial biopsy (EMB) at baseline and at end-of-study. Subjects also had transvaginal ultrasounds (TVU) when the EMB yielded insufficient tissue. A total of 304 subjects with a uterus received EMB, TVU or both. At baseline, 87.5% of the 304 subjects with a uterus received an EMB, while 83.9% received an EMB at the end of the study. The following Table 7 replicated from MOR Table 24 summarizes the occurrence of endometrial hyperplasia in 12 week Study EST005.

Table 7: Subjects With Abnormal Endometrial Biopsy at Final Visit (Study EST005) (ISS Safety Population)

Study Drug	Subject Number (Study day)	Age (year) Race	Biopsy Description[a]		Trough Estradiol (pg/mL)	Comments
			Baseline	End-of-Study		
1.7 g/day	313 (day 90)	54 White	Strips of benign surface	Atypical hyperplasia (10)	Baseline:<10 Week 4: 15 Week 8: 18 Week 12: 13	Biopsy showed complex hyperplasia with atypia. Fractional dilatation and curettage pathology: focal squamous metaplasia, benign endometrial polyps with focal hyperplasia, simple and complex, without atypia. Follow-up: 3-months progestin treatment followed by dilatation and curettage. Subject discontinued progestin after < 1 month. No further treatment (as of Jan. 2005)
2.6 g/day	129 (day 92)	62 White	Inactive/ atrophic	Simple hyperplasia without atypia (8)	Baseline:<10 Week 4: 21 Week 8: 69 Week 12:<10	Subject received Provera. Repeat biopsy approximately 3 months later showed inactive/ atrophic endometrium
	173 (day 86)	60 White	Strips of benign surface	Simple hyperplasia without atypia (8)	Baseline:<10 Week 4: 39 Week 8: 47 Week 12:<10	Subject received Provera. Repeat biopsy approximately 3 months later showed inactive/ atrophic endometrium
	271 (day 86)	69 White	Inactive/ atrophic	Simple hyperplasia without atypia (8)	Baseline:<10 Week 4: <10 Week 8: 20 Week 12: 47	Subject received progestin and had bleeding. No other follow-up
	302 (day 93)	56 White	Inactive/ atrophic	Simple hyperplasia without atypia (8)	Baseline:<10 Week 4: 39 Week 8: 52 Week 12: 41	Subject received Novo-Medtrone (3 days light bleeding). Repeat biopsy showed no evidence of malignancy or hyperplasia.

Study Drug	Subject Number (Study day)	Age (year) Race	Biopsy Description[a]	Trough Estradiol (pg/mL)	Comments	Study Drug
	375 Day 89)	54 White	Inactive/ atrophic	Simple hyperplasia without atypia (8)	Baseline:<10 Week 4: 37 Week 25: 25 Week 12: 17	Subject received Prometrium (no bleeding). No other follow-up

Source: Adapted from NDA 21-813/S-000, Section 8, Volume 62, Table 8.8.6-5, page 131 of 277 and Table 2.3 in submission dated June 13, 2006, page 1247, and Appendix 16.2.7.2: Adverse Events, Volume 44, pages 1-114.

a. Endometrial biopsy results were classified into 1 of 11 categories of which 1-6 were normal and 7-11 were abnormal: 1=strips of benign surface and glandular lining epithelium; 2=inactive/atrophic endometrium; 3=proliferative endometrium; 4=progestational secretory endometrium; 5=menstrual type endometrium; 6=polyp; 7=polyp; 8=simple hyperplasia without atypia; 9=complex hyperplasia without atypia; 10=atypical hyperplasia; 11=cancer.

No subject in the estrogen gel 0.87 g/day treatment group was diagnosed with endometrial hyperplasia. One subject in the 1.7 g/day treatment group was diagnosed with complex hyperplasia with atypia based on an EMB at 90 days of study participation. This subject subsequently received a fractional dilatation and curettage with findings of: "endometrial curettings and polyps; benign endometrial polyps with focal hyperplasia, simple and complex, without atypia". The subject subsequently was prescribed three months of progestin therapy which she discontinued after one month. Complex atypical hyperplasia is a concerning pathological diagnosis. However, it would be difficult to determine that the endometrial safety profile was unacceptable based on a single case. In contrast, there were five cases of endometrial hyperplasia seen in the 45 subjects with a uterus who were treated with 2.6 g/day estradiol gel dose. These 5 cases were all simple hyperplasia without atypia, but the 11.1% incidence rate in a 12 week study is concerning and should not be discounted

Other Serious Adverse Events

No deaths occurred during the conduct of primary, Phase 3 Study EST005, Phase 2 Study EST004, or any of the [redacted] PK studies conducted under the estradiol gel clinical development program.

Three subjects in Study EST005 had serious adverse events, one during the single-blind placebo lead-in period and two during the double-blind treatment period. Subject 913 experienced chest pain which required hospitalization during the single-blind placebo lead-in period. Placebo medication was discontinued. The event was not considered related to study drug. Subject 106 (1.7 g/day, 50 years of age) experienced a severe staphylococcal infection in her left thumb at a site where she had a previous surgery with pin insertion which required hospitalization (study day 76). Medication was discontinued. The event was not considered related to study drug. Subject 261 (2.6 g/day, 54 year of age) experienced a worsening of a cervical cyst noted at study entry and an increase in endometrial thickness at end-of-study (4 mm at baseline, 6 mm at end-of-study). She required hospitalization approximately three months after the last dose of study medication and underwent a transabdominal hysterectomy and bilateral salpingoophorectomy. The event was considered possibly related to study drug.

Seventeen subjects of the 484 randomized to Study EST005, discontinued the study due to an adverse event. The discontinuations exhibited dose proportionality with a greater number of subjects discontinuing in the 2.6 g/day dose of estradiol gel compared to the those discontinuing the 1.7 g/day dose of estradiol gel (9 of 142, 6.3%) or the 0.87 g/day of estradiol gel (4 of 136; 2.9%).

As might be expected, the reproductive disorders class of adverse events was observed in the ISS to be most affected by estradiol gel treatment, and the incidence in this class overall and individually (breast tenderness, metrorrhagia, vaginal discharge, endometrial hyperplasia, nipple pain) increased in a time and dose-dependent manner. There was a higher incidence of treatment-emergent adverse events (TEAEs) of this class in the estrogen gel treatment arms across all doses group than in the placebo groups. The adverse events were generally similar to adverse events known to occur during treatment with estrogens.

Treatment emergent adverse events were experienced by between 56% and 68% of all randomized subjects across the four treatment groups in Study EST005, and between 47.7% and 50.0% across the four treatment groups in Study EST004. Per the Sponsor, most treatment-emergent adverse events were considered to be mild or moderate intensity, with severe intensity being reported among 6% to 9% of all randomized subjects across treatment groups

DSI

DSI audits were requested and conducted on three clinical study sites for EST005. These were:

1. Center 24, Northern California Research Corp
   Carmichael, CA
   Dr. Douglas Young - Principal Investigator

2. Center 21, Women's Clinic of Lincoln, PC
   Lincoln, NE
   Dr. Stephen Swanson – Principal Investigator

3. Center 10, Montreal Clinical Study Center, Inc
   Montreal, Quebec
   Dr. Michele Moreau – Principal Investigator

DSI has conducted and reporting the findings on all centers. There were no limitations to inspection at these sites. Except for some minor deficiencies related to record keeping at one of the sites, all of the sites were found to be compliant with regulations governing the conduct of clinical investigations and the protection of human subjects. The recommendation was made that data from the three sites could be used in support of the application.

Clinical Pharmacology

Four supporting Phase 1 studies, EST003, EST006, EST 007 and EST008, and Phase 2 Study EST004 were submitted in the NDA. [ ] additional Phase 1 studies [ ] and [ ] were submitted, but these studies were conducted with a different formulation and were not reviewed as supportive of the current NDA. For the [ ] doses, estradiol exposure increases linearly with dose but at a higher than proportional rate. Exposures to the [ ] doses are within the range of currently approved products. The 0.87 g/day dose would deliver a rate lower than any other approved product.

Estradiol metabolites estrone and estrone sulfate concentrations also increased with estradiol gel application. However, the baseline-unadjusted estradiol:estrone ratio also increased with dose. The estradiol:estrone ratios were 0.53, 0.98, and 1.3 for 0.87, 1.7, and 2.6 g/day doses, respectively.

Examination of the responses due to estradiol gel suggested that the reduction in frequency and severity of vasomotor symptoms was dose dependent. [ ] [ ] In term of safety, dose dependent rate of common adverse effects in the reproductive and breast class was observed as would be anticipated. There was also a high rate of the significant adverse effect endometrial hyperplasia (11.1%) in the 2.6 g/day dose group.

There was no observed change in estradiol concentration in male partner following direct contact at 2 and 8 hours post estradiol gel application. Less than 10% of applied estradiol was recovered on application site at 2 and 8 hours post application. Washing the area with soap and water reduced residual skin estradiol to about [ ]% of applied dose.

A finding of significance in this review is that application of sunscreen 10 minutes before application of estradiol gel increased the exposure to estradiol by approximately 55%. No significant change in estradiol exposure was observed when sunscreen was applied 25 minutes after application of estradiol gel. In the same study, prolonged (7 days) concomitant application of sunscreen to the site of estradiol gel application increased exposure to estradiol by about 2-fold, regardless of whether it was applied before or after application of estradiol gel. About 15% of the increase may be attributed to the increase in SHBG concentration. The cause of the remaining increase is not known.

Pre-Clinical Pharmacology and Toxicology

Three studies were reviewed for this submission: [ ], an *in vitro* human skin permeation and skin layer distribution study comparing this formulation of estradiol gel and a comparator marketed in Europe; [ ], an *in vitro* skin permeation time- and dose- proportionality study with guinea pig skin; and [ ], a rabbit skin irritation study with topical application of estradiol gel. The *in vitro* skin permeability studies demonstrate no significant difference between estradiol gel and a comparator product with respect to the cumulative amount of permeated estradiol at any time point

throughout the 24 hours of study drug application with human cadaver skin. In the dose-proportionality study using guinea pig skin, the in-vitro flux rate of estradiol was shown to be dose-related. The flux rate for the current formulation estrogen gel containing [ ] was greater than an estrogen gel formulation without [ ] and a comparator product (also not containing [ ] [ ]). The current formulation of estradiol gel demonstrate no apparent toxicity in the primary rabbit skin irritation study, The safety of the excipient, [ ], was established with subchronic toxicology, genotoxicology and reproductive toxicology studies provided in DMF [ ] and oral and transdermal carcinogenicity studies provided in NDA 21-794.

Based on the known pharmacology, pharmacokinetics and toxicology of transdermal and orally administered estradiol as well as the information provided in the preclinical studies submitted to the NDA, the Pharmacology reviewer has recommended approval from a Pharmacology/Toxicology perspective.

Chemistry, Manufacturing and Controls (CMC):

The Sponsor cross referenced DMF [ ] for CMC information on the drug substance, Estradiol. This DMF was previously reviewed and found to be adequate on January 27, 2006. No updated information to the DMF was submitted in this application. The Sponsor has provided adequate acceptance specifications and Certification of Analysis for the drug substance. The manufacturing facility received an acceptable recommendation from the Office of Compliance.

The drug product is a topically applied estradiol gel with a concentration of 0.06% w/w. The inactive ingredients include ethanol, propylene glycol (PG), diethylene glycol monoethylether (DGME), [ ], triethanolamine, purified water, edetate disodium. All excipients are either USP or NF. The drug product is packaged in a [ ] metered dose pump.

Assay specification of the solvents [ ] were adjusted by the Sponsor based on the recommendation of the Agency and are acceptable. The Sponsor also accepted the Agency's recommendation for the specifications of impurities and physical appearance. The Agency finds that the drug product specifications are acceptable. Based on the long term stability data, the Sponsor's proposal of a 24 month expiration date is acceptable

The Sponsor proposed to use the established name, "transdermal estradiol gel." CMC felt that the use of the term "transdermal" was not consistent with the established name for previously approved estradiol gel drug products which are intended to be used on the skin surface. The established name "estradiol gel" was conveyed to the Sponsor.

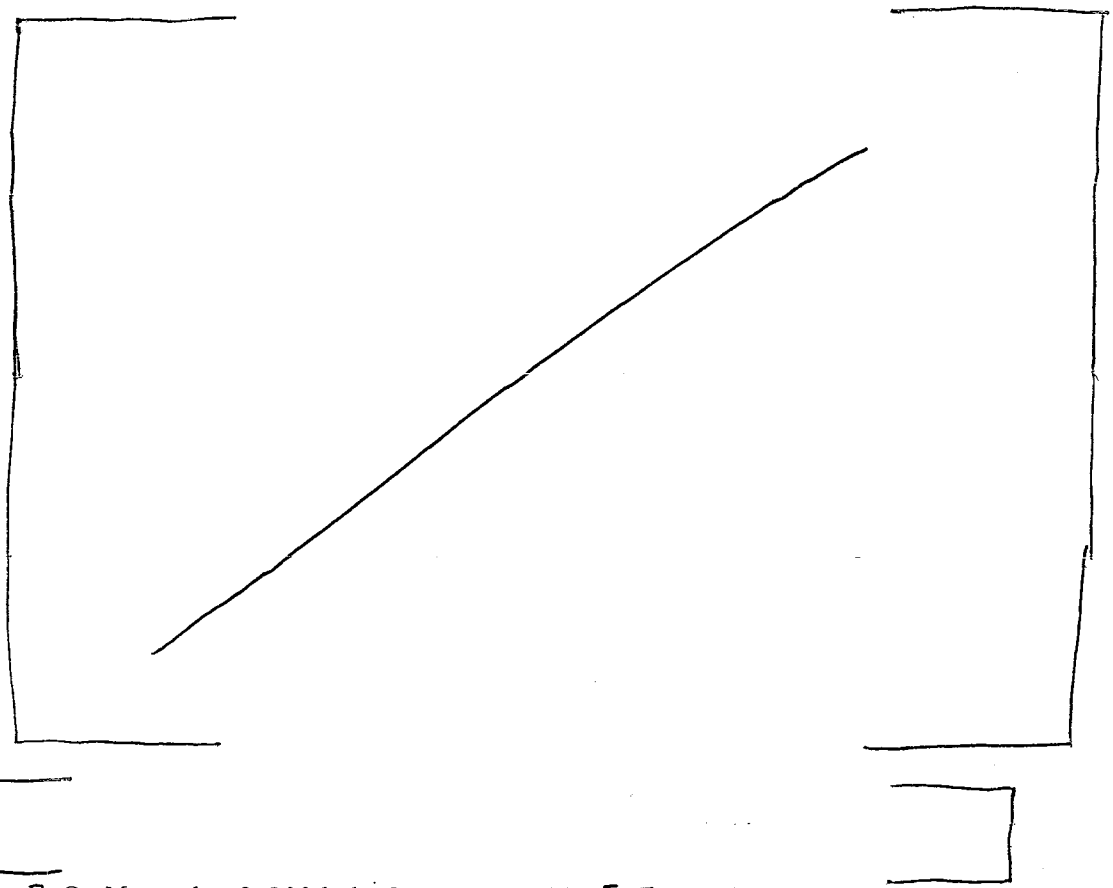
From a CMC perspective the application can be approved provided that the Sponsor agrees to the use of "estradiol gel" as the established name and accepts the minor changes to the CMC section of the label.

Microbiology:

The review notes no deficiencies in the preservatives effectiveness testing and microbial limits specifications provided in the application and recommends approval from the standpoint of product quality microbiology.

Product Name

On February 16, 2006, a consultation for evaluation of the trade name "Bio-E-Gel" was sent to the Division of Medication Errors and Technical Support (DMETS). DMETS provided the following comments on September 13, 2006.



[ ] On November 9, 2006, the Sponsor provided [ ] alternative trade names. Per DMETS decision to review only [ ] of the alternatives, the Sponsor's first choice of alternative names [ ] were forwarded to DMETS on November 15, 2006. Late in the review cycle on December 7, 2006, DMETS accepted the tradename. Elestrin™. This reviewer concurs in the acceptance of this tradename.

Conclusions and Recommendations

This reviewer concurs with the primary Clinical Reviewer and recommends that both the 0.87 g/day and 1.7 g/day receive approval for the indication of treatment of moderate-to-severe vasomotor symptoms. However, the label should clearly delineate that the 0.87 g/day dose when compared to placebo did not demonstrate a clinically and statistically significant reduction of hot flushes until Week 5.

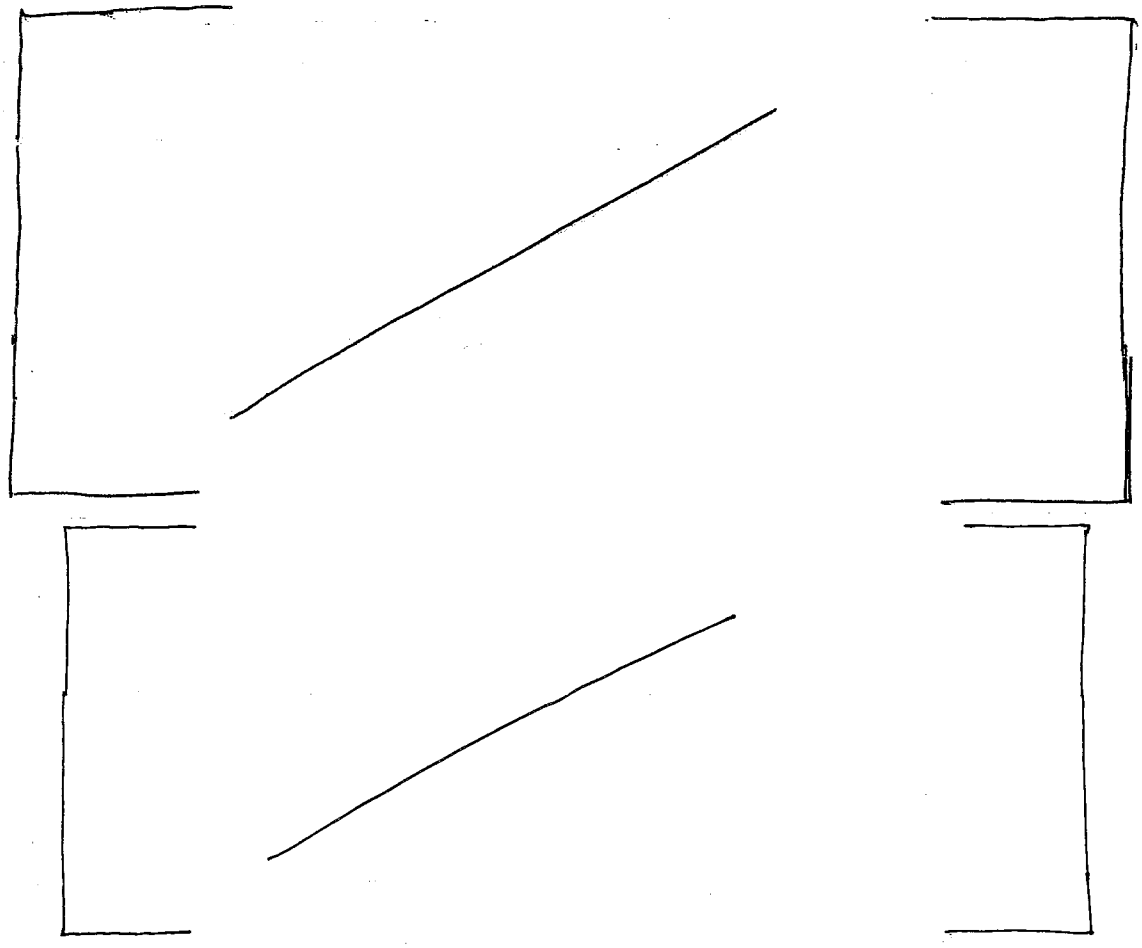
As a response to the concerns for systemic HT heightened by the results of the WHI, the Agency published the January 2003 Draft Guidance for Industry, entitled "Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms-Prescribing Information for Health Care Providers and Patient Labeling", which among other efforts to improve the safe use of this class of drug products, changed the language for the vulvar and vaginal atrophy [ ] from the "treatment of vulvar and vaginal atrophy" to "treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause". "When prescribing solely for the treatment of symptoms of vulvar and vaginal, topical vaginal products should be considered." The emphasis was that women to be treated for vulvar and vaginal atrophy should be symptomatic (and not just demonstrate physical signs of vulvar and vaginal atrophy) and when vulvar and vaginal atrophy symptoms are the only menopausal symptoms experienced, topical as opposed to systemic therapies should be first considered. Consistent with this, the Draft HT Clinical Trial Guidance recommends that to be considered [ ], a drug product should be studied in a trial where subjects display at least one moderate to severe symptom of vulvar and vaginal atrophy at baseline as well as the physical findings consistent with vulvar and vaginal atrophy (pH≥ 5.0 and vaginal smear superficial cells < 5%).

During drug development and study, the Sponsor was twice notified (Advice letter dated January 7, 2001 and November 12, 2003) of the requirement for subjects to have at least one moderate-to-severe symptom of vulvar and vaginal atrophy as well as the above physical signs at baseline. The Sponsor did not follow the Agency's advice in their enrollment and thus subset analyses of subjects meeting requirements had to be performed. The subset of subjects who met only the criteria for at least one moderate-to-severe most bothersome symptom constituted approximately one-half of the subjects in each original treatment group. [ ]

The intent of the Draft HT Clinical Trial Guidance was not that studies evaluate improvement in a composite of all most bothersome symptoms relative to placebo but rather that the study demonstrate improvement in at least one symptom of VVA that a woman has identified is most bothersome to her on entry into the study. To that end studies will have to be appropriately powered to assess for this individual symptoms change.

A sub (each individual symptom)-subset of the already limited subset with at least one most bothersome symptom had to be considered in order to evaluate the individual symptoms.

When the individual symptoms were considered for subjects meeting all three recommended enrollment criteria (symptoms, vaginal pH and superficial cells) at baseline,



Labeling negotiations have been completed and the final negotiated label is to be made part of the final decisional package.

Shelley R. Slaughter, MD., PhD
Medical Officer Team Leader and
Group Leader for NDA 21-813

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Shelley Slaughter
12/14/2006 12:55:56 PM
MEDICAL OFFICER