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APPLICATION NUMBER(S)

21-371

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEWS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
DRAFT
(October 8, 2003)

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Generic Name: 17β-Estradiol

Brand Name: Estrasorb™

Formulations: [redacted]

Route of Administration: Topical

Indication: [redacted]

Sponsor: Novavax, Inc.
Rockville, MD

Type of Submission: Resubmission/New Topical Formulation (3S)

Reviewer: Sayed (Sam) Al Habet, RP.h., Ph.D.

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Synopsis:

This is a resubmission of the original NDA that was reviewed by OCPB in April of 2002 (see **Appendix III** for the original review).

ESTRASORB (estradiol) contains 17β-estradiol of micellar nanoparticle nanoemulsion size. Each gram of Estrasorb contains 2.5 mg estradiol hemihydrate USP. It is packaged in foil pouches containing either 1.15 grams or 1.74 grams of drug product. The product will be applied on each morning to the anterior thigh and calves as three 1.15 gram pouches. Each 1.15 gram pouch contains 2.875 mg estradiol and two of 1.74 grams foil pouches of Estrasorb contain a very similar amount of drug product and estradiol as three 1.15 gram pouches (3 X 2.875 mg = 8.625 mg). Each 1.74 gram pouch contains 4.35 mg of estradiol (2 X 4.35 mg = 8.7 mg). Therefore, the difference in the total estradiol amount between the packages is too small to be clinically significant (8.7 mg-8.625 mg = 0.075 mg).

In Phase III as well as all relevant PK studies, the packages containing 1.15 gram Estrasorb were used (lot # 0038). However, the to- be marketed packages containing 1.74 gram (lot # NS2) Estrasorb have never been used, except in the following studies that were included in this resubmission:

A. **Partner transfer study:** To determine if estradiol can be transferred to male partners via skin to skin contacts with female partners.
B. **Sunscreen study:** To determine the effect of sunscreen on the absorption of estradiol after application of Estrasorb.
C. ***In vitro* pouch expression study:** to determine the actual weight content in the clinical batch (Lot # 038, 3 X 1.15 gram pouch) and in the to-be-marketed batch (lot # NS2, 2 X 1.74 Gram Pouch). Additional batch was also tested in this study (Lot # NS1, 3 x 1.15 gram pouch). The formulation composition in all of these packages is the same as that of the clinical batch (i.e., lot # 0038), except in the packaging sizes.

I. Executive Summary

This is a resubmission of the original NDA that was reviewed by OCPB in April of 2002 (see **Appendix III** for the original review). The [redacted] The following three studies were included in this resubmission:

A. **Partner Transfer Study:** To determine if estradiol can be transferred to male partners via skin to skin contact with female partners. Briefly, in this study, 14 females applied two 1.74-gram pouches, daily for two days to their thighs and calves. At 2 and 8 hours after each application, each subject's male partner attempted to transfer estradiol to his forearms by vigorously rubbing them against his female partner's thighs for two minutes. Male partners serum estradiol, estrone, and estrone sulfate concentrations were compared to concentrations present 10 days before exposure to exogenous estradiol. After two and four such exposures, the AUC of estradiol increase by 14% and 25% compared to baseline (**Figure A and Table A**). A similar trend was followed for estrone and estrone sulfate.

Figure A.

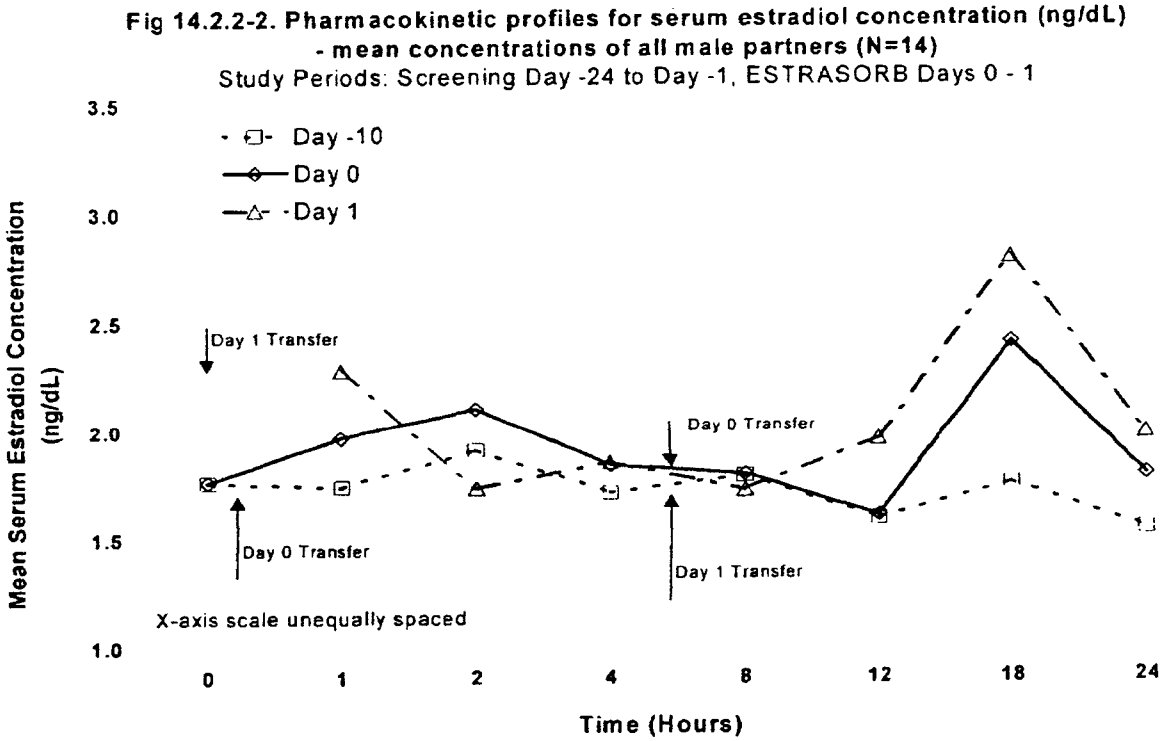


Table A.

Table 14.2.2-13. Descriptive statistics of pharmacokinetic parameters on profiling Days -10, 0 and 1 for all male partners (N=14)

Hormone	PK Parameter (Mean ± SD)	Profiling Day		
		Day -10	Day 0	Day 1
Estradiol	T_{max} (hr)	5.50 ± 7.28	10.00 ± 8.33	13.14 ± 7.97
	C_{max} (ng/dL)	2.17 ± 0.60	2.49 ± 0.90	2.83 ± 0.81
	C_{min} (ng/dL)	1.34 ± 0.27	1.46 ± 0.40	1.49 ± 0.41
	$C_{average}$ (ng/dL)	1.70 ± 0.43	1.93 ± 0.52	2.10 ± 0.44
	$AUC_{(0-24h)}$ (ng-h/dL)	40.73 ± 10.42	46.30 ± 12.46	50.46 ± 10.54
Estrone	T_{max} (hr)	8.79 ± 9.32	12.93 ± 8.64	11.50 ± 9.81
	C_{max} (ng/dL)	2.89 ± 0.87	3.34 ± 0.57	3.64 ± 0.79
	C_{min} (ng/dL)	1.53 ± 0.98	1.82 ± 0.70	1.88 ± 0.57
	$C_{average}$ (ng/dL)	2.14 ± 0.95	2.54 ± 0.58	2.69 ± 0.56
	$AUC_{(0-24h)}$ (ng-h/dL)	51.47 ± 22.69	61.02 ± 13.92	64.68 ± 13.56
Estrone Sulfate	T_{max} (hr)	6.21 ± 8.41	10.93 ± 7.19	8.00 ± 9.20
	C_{max} (ng/dL)	103.79 ± 50.31	121.43 ± 52.23	127.79 ± 44.85
	C_{min} (ng/dL)	72.93 ± 31.54	78.29 ± 32.59	76.71 ± 21.99
	$C_{average}$ (ng/dL)	86.93 ± 40.51	99.97 ± 43.26	95.66 ± 29.36
	$AUC_{(0-24h)}$ (ng-h/dL)	2086.4 ± 972.34	2399.3 ± 1038.2	2295.9 ± 704.56

B. Sunscreen study:

The main objective of this study is to determine the effect of sunscreen on the absorption of estradiol after application of Estrasorb. Briefly, two pouches of 1.74 gram each were used: one was applied to the right thigh and calf and the other to the left thigh and calf. Therefore, the total daily dose was 2 x 1.74 gram (i.e., 3.48 gram) of Estrasorb which translate to 2 x 4.35 mg (i.e., 8.7 mg) estradiol. Serum hormone levels of estradiol, estrone, estrone sulfate, and FSH were determined over 24 hours on Days 0, 7, 15, and 23. Upon completion of the PK studies a photosensitivity tests were performed on each subject.

On Days 8 through 15, sunscreen was applied to both thighs and calves, 10 minutes prior to Estrasorb application. On Days 16 through 23, sunscreen was applied to both thighs and calves, 25 minutes after the start of Estrasorb application. On Day 24, subjects applied Estrasorb to both thighs and calves. Subjects were then exposed to direct sunlight for 10 minutes at 10 AM. Subjects were observed for 2 hours for any photosensitivity reactions.

The application of sunscreen had some effect on serum levels of estradiol (**Figure B and Table B**). During trough day periods, there was 13% and 25% increase in Cmax on Days 8-15 and Days 16-23 when sunscreen was used compared to Days 0-7 when no sunscreen was used, respectively (**Table B**). For AUC, there was 38% and 46% increase in exposure as measured by AUC on Days 8-15 and Days 16-23 when sunscreen was used compared to Days 0-7 when no sunscreen was used, respectively. The observed increase in the exposure could not be completely associated with the use of sunscreen. The plasma level of estradiol may have not yet been completely at steady state, especially on Days 8-15. For instance, there was only 5% increase in exposure between Days 16-23 (AUC = 26.92 ng.h/ml), compared to Days 8-15 (AUC=25.52 ng.h/ml). Therefore, the steady state could have been achieved on Days 16-23, but not on Days 8-15. A similar pattern of increase in exposure was noted for etsrone and estrone sulfate.

The mean (± SD) estradiol Cmax was 2.5 ± 2.11, 5.54 ± 3.54, 9.72 ± 10.60, and 8.44 ± 6.07, on days 0, 7, 15, and 23, respectively (**Table C**). On the same days, the mean (± SD) estradiol AUC $_{(0\text{-}24\ h)}$, was 38.91 ± 32.27, 92.35 ± 57.63, 134.75 ± 107.06, and 115.22 ± 68.70 on days 0, 7, 15, and 23, respectively. It should be noted that there was a high variability in the data (**Table C**). A similar trend was also seen for estrone and estrone sulfate.

Overall, it can be concluded that sunscreen may have some effect on the absorption of estradiol in patients applying Estrasorb. However, considering the potential benefits of the sunscreen to females with sensitive skin and the prevention of sunburn, it is hard to justify that sunscreen should be avoided in patients applying Estrasorb. No evidence of photosensitivity reaction was noted after direct solar exposure (see Medical Officer's review).

Figure B.

Fig 14.2.1-5. Pharmacokinetic serum profile estradiol concentration (ng/dL) - mean concentrations of all subjects (N=14)

Study Periods Screening (Day -24), ESTRASORB only (Days 0-7), Sunscreen then ESTRASORB (Days 8-15), ESTRASORB then sunscreen (Days 16-23), ESTRASORB then sunlight exposure (Day 24)

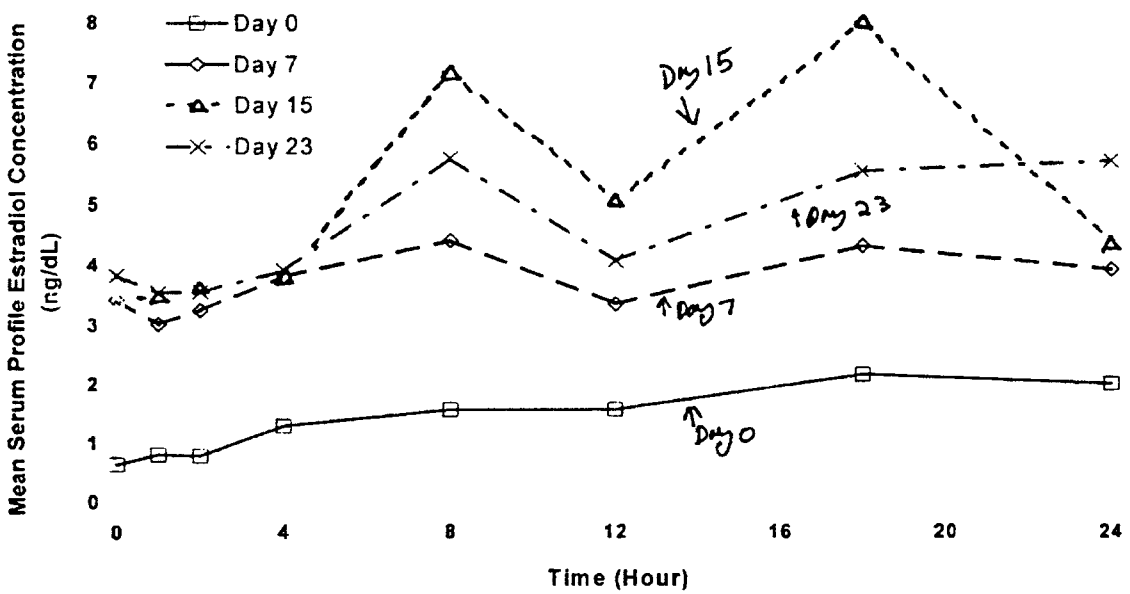


Table B.

Table 14.2.2-17. Summary of pharmacokinetic parameters on trough day periods for all subjects (N=14)

Hormone	PK Parameter (Mean ± SD)	Trough Day Periods		
		Days 0-7	Days 8-15	Days 16-23
Estradiol	T_{max} (hr)	5.57 ± 1.55	3.21 ± 2.46	3.00 ± 2.39
	C_{max} (ng/dL)	4.93 ± 3.54	5.61 ± 3.15	6.18 ± 3.89
	C_{min} (ng/dL)	0.61 ± 0.73	2.28 ± 1.56	2.41 ± 1.38
	$C_{average}$ (ng/dL)	2.63 ± 1.75	3.65 ± 2.27	3.85 ± 2.33
	AUC (ng-d/dL)*	18.43 ± 12.24	25.52 ± 15.88	26.92 ± 16.33
Estrone	T_{max} (hr)	5.36 ± 1.86	3.14 ± 2.88	2.86 ± 2.63
	C_{max} (ng/dL)	7.49 ± 4.61	9.42 ± 5.02	11.09 ± 7.15
	C_{min} (ng/dL)	1.91 ± 0.86	5.63 ± 3.89	5.75 ± 3.46
	$C_{average}$ (ng/dL)	5.12 ± 2.88	7.44 ± 4.41	7.99 ± 5.11
	AUC (ng-d/dL)	35.83 ± 20.18	52.08 ± 30.86	55.96 ± 35.74
Estrone Sulfate	T_{max} (hr)	5.36 ± 1.39	4.29 ± 2.09	3.36 ± 2.82
	C_{max} (ng/dL)	256.79 ± 192.17	325.57 ± 225.35	370.71 ± 307.66
	C_{min} (ng/dL)	46.07 ± 27.11	186.07 ± 133.28	189.07 ± 151.65
	$C_{average}$ (ng/dL)	166.66 ± 120.31	247.22 ± 175.21	255.52 ± 205.85
	AUC (ng-d/dL)	1166.6 ± 842.20	1730.6 ± 1226.5	1788.6 ± 1441.0
FSH	T_{max} (hr)	0.64 ± 1.39	2.57 ± 2.79	3.29 ± 1.98
	C_{max} (mIU/mL)	71.93 ± 20.38	57.36 ± 16.88	50.43 ± 15.65
	C_{min} (mIU/mL)	48.50 ± 12.85	41.57 ± 9.99	40.00 ± 13.00
	$C_{average}$ (mIU/mL)	57.58 ± 15.10	48.09 ± 12.77	45.49 ± 13.65
	AUC (mIU-d/mL)	403.04 ± 105.71	336.64 ± 89.41	318.46 ± 95.55

*Time unit in AUC is day.

Table C.

Table 14.2.1-21. Summary of profile pharmacokinetic parameters on Days 0, 7, 15 and 23 for all subjects (N=14)

Hormone	PK Parameter (Mean ± SD)	Profiling Day			
		Day 0	Day 7	Day 15	Day 23
Estradiol	T_{max} (hr)	11.07 ± 9.19	9.29 ± 8.47	10.14 ± 7.16	11.71 ± 8.15
	C_{max} (ng/dL)	2.50 ± 2.11	5.54 ± 3.56	9.72 ± 10.60	8.44 ± 6.07
	C_{min} (ng/dL)	0.50 ± 0.51	2.44 ± 1.81	2.62 ± 1.83	2.73 ± 1.54
	$C_{average}$ (ng/dL)	1.62 ± 1.34	3.85 ± 2.40	5.61 ± 4.46	4.80 ± 2.86
	$AUC_{(0-24h)}$ (ng-h/dL)*	38.91 ± 32.27	92.35 ± 57.63	134.75 ± 107.06	115.22 ± 68.70
Estrone	T_{max} (hr)	17.57 ± 9.83	12.57 ± 10.00	9.79 ± 10.33	9.21 ± 9.63
	C_{max} (ng/dL)	3.82 ± 1.63	8.15 ± 4.20	9.60 ± 5.11	10.51 ± 8.34
	C_{min} (ng/dL)	1.16 ± 0.90	5.09 ± 3.30	5.86 ± 3.86	5.79 ± 3.30
	$C_{average}$ (ng/dL)	2.32 ± 1.16	6.41 ± 3.33	7.63 ± 4.10	7.44 ± 5.39
	$AUC_{(0-24h)}$ (ng-h/dL)	55.74 ± 27.78	153.84 ± 79.91	183.11 ± 98.47	178.57 ± 129.34
Estrone Sulfate	T_{max} (hr)	19.43 ± 9.26	8.00 ± 7.95	13.36 ± 9.68	9.86 ± 9.95
	C_{max} (ng/dL)	95.00 ± 48.40	263.57 ± 179.52	296.79 ± 188.50	358.14 ± 294.22
	C_{min} (ng/dL)	41.57 ± 24.40	141.50 ± 83.94	191.00 ± 131.18	163.64 ± 120.69
	$C_{average}$ (ng/dL)	62.56 ± 28.44	188.90 ± 117.50	237.01 ± 154.92	212.66 ± 143.29
	$AUC_{(0-24h)}$ (ng-h/dL)	1501.5 ± 682.52	4533.6 ± 2820.1	5688.3 ± 3718.1	5104.0 ± 3438.9
FSH	T_{max} (hr)	4.43 ± 7.75	12.29 ± 11.45	5.43 ± 7.54	9.64 ± 10.26
	C_{max} (mIU/mL)	73.57 ± 20.12	55.79 ± 16.19	51.79 ± 16.13	49.57 ± 17.79
	C_{min} (mIU/mL)	58.07 ± 14.48	45.43 ± 14.03	39.57 ± 12.02	38.21 ± 13.26
	$C_{average}$ (mIU/mL)	63.88 ± 16.62	49.99 ± 14.46	44.14 ± 13.12	43.14 ± 14.02
	$AUC_{(0-24h)}$ (mIU-h/mL)	1533.2 ± 398.87	1199.7 ± 347.11	1059.3 ± 314.82	1035.4 ± 336.56

*Time unit in AUC is hour.

B. *In vitro* pouch expression study:

The main objective of this study is to determine the actual weight content in the clinical batch (Lot # 038, 3 X 1.15 gram pouch) and in the to-be-marketed batch (lot # NS2, 2 X 1.74 Gram pouch). Additional batch was also tested in this study (Lot # NS1, 3 x 1.15 gram pouch). The formulation composition in all of these packages is the same as that of the clinical batch (i.e., lot # 0038), except in the packaging sizes. This was a simple study in which one analyst and 12 females were instructed to express the content of each package. The weight of each content was recorded for each package.

The data is summarized in **Figure D and Table D**. The mean (± SD) percent underweight was 8.84% ± 2.97%. The median was 8.80%, which range from 2.84% to 22.0%. Thus, on average, the amounts expressed from the foil pouches were 0.1 grams or 9% below the nominal weights of 1.15 or 1.74 grams. Pouches in lot NS2 were 4.5% and 3.8% were heavier than pouches in lots 038 and NSI, respectively. Underweight (differences between expressed and nominal weights) for the three lots (038, NSI and NS2) were 0.123, 0.120 and 0.108 grams, respectively. The mean percent underweight for the three lots, 038, NS I, and NS2, was 10.7%, 10.4%, and 6.2%, respectively. The difference between the analyst and an average subject was 0.018 grams (1.4%) greater than subjects.

Statistically, there was a difference between lots and rater (subject or analyst). However, quantitatively (i.e., in terms of weights), the difference may be considered small. There was a small differences in the amounts expressed from the two-pouch (2 X 1.74 grams) and three-pouch lots (3 x 1.15 grams).

The differences in the amount expressed in all packages may not be of clinical significance, for chronically administered topical products. However, the final call for the clinical significance of this difference should be expressed by the clinical Division (see also Medical Officer's Review).

Figure D.

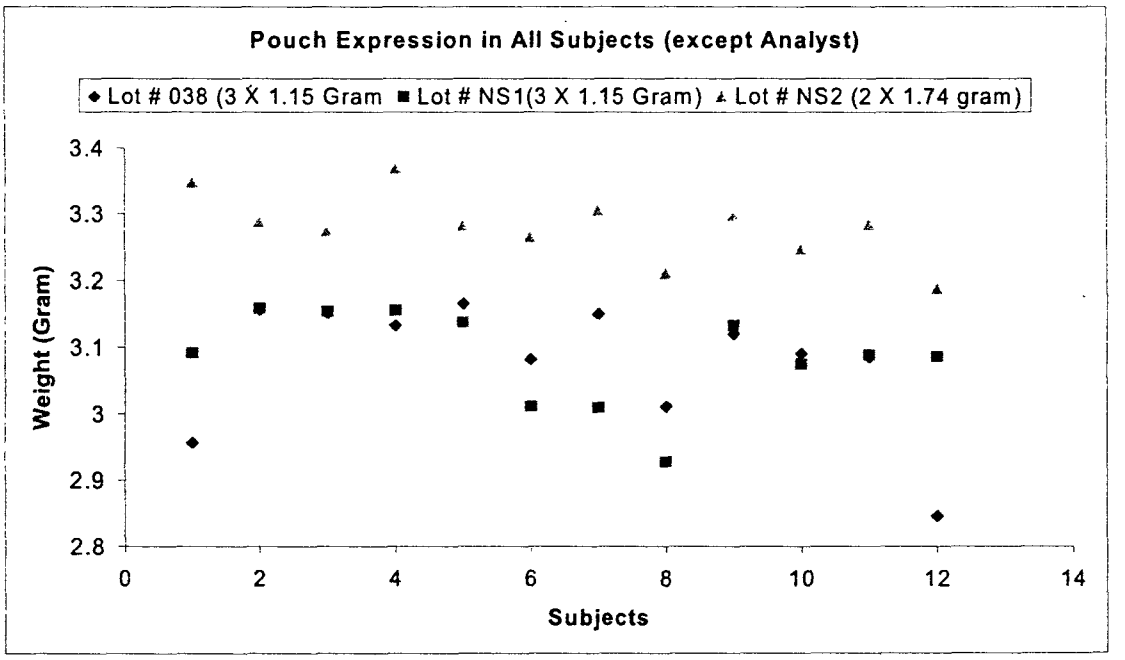


Table D.

Table 1: ESTRASORB pouch study, contrasts from two-way ANOVA using			
Contrast		Estimate ± SE (Grams)	p-value
No interaction of subject (or analyst) and lot			
NS1 vs. NS2		0.060 ± 0.0048	< 0.0001
038 vs. NS2		0.068 ± 0.0048	< 0.0001
038 and NS1 Combined vs. NS2		0.064 ± 0.0043	< 0.0001
With interaction of subject (or analyst) and lot			
NS1 vs. NS2	Subjects	0.065 ± 0.0068	< 0.0001
	Analyst	0.055 ± 0.0068	< 0.0001
038 vs. NS2	Subjects	0.067 ± 0.0068	< 0.0001
	Analyst	0.068 ± 0.0068	< 0.0001
038 and NS1 Combined vs. NS2	Subjects	0.066 ± 0.0061	< 0.0001
	Analyst	0.061 ± 0.0061	< 0.0001

General Comments:

- Transfer study showed some exposure to estradiol in male subjects. In real life, such exposure to male partner may not be of the same magnitude as was demonstrated in the study. Therefore, it may be advisable for male partners to use protective clothing to prevent Estrasorb transfer.
- The sunscreen study showed some increase in estradiol exposure. However, it is uncertain if the observed increase in estradiol level was directly associated with the effect of the sunscreen. The reason for this uncertainty is because estradiol steady-state level may not have been achieved at the time of the sunscreen application in this study (Days 8-15). Nevertheless, the patient should be advised to separate the use of sunscreen and Estrasorb by a period of at least 3-4 hours.
- Pouch expression study clearly showed that the to-be-marketed packages (lot # NS2) is consistently heavier than that of the clinical batch (Lot # 0038). Although this difference is statistically significant, but may not be clinically critical for chronically administered drug (please also see Medical Officer's review).
- The estradiol level from the to-be-marketed batch (Lot # NS2) in sunscreen study was within the range of that seen in the old PK study (study # E98-1, see **Appendix III)** using batch #0038. The analysis and the comparison between these two studies were performed because the new lot (NS2) was found to contain [redacted] (see chemistry review). Based on our analysis of the data from both studies, we cannot conclude that the two formulations are bio-equivalent. However, our conclusion is that the plasma levels from both studies are within the expected range, after dose normalization. In addition, the serum level (Cmax) on Day 8 in sunscreen and E98-1 studies is approximately 5.5 ng/dl which is slightly lower than the trough concentration at Week 2 (~8 ng/dl) in the pivotal Phase III study (#E99-1, see **Appendix III**).

Therefore, considering the several factors involved in the variability between the two studies, the presence of [redacted] may not affect the absorption of estradiol. It should be noted that we do not know if [redacted] are present in formulation #0038. Therefore, the data from lot # NS2 is acceptable, when compared to the data from lot #0038. Furthermore, the clinical significance of the observed difference between the two formulations should be assessed by the Clinical Division (please see medical Officer's Review).

1.1 RECOMMENDATION:

Based on the information submitted, this NDA was found is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics (OCPB).

1.2 LABELING RECOMMENDATIONS

A) For Partner Transfer Study:

The following general or similar statements in the label and patient's information sheet are

suggested:

-
-
-

B: For Sunscreen Study:

The following general or similar statements in the label and patient's information sheet are suggested:

A prolong use of sunscreen may potentially increase estradiol level

C: For Pouch Expression Study:

The following general or similar statement in the label and patient's information sheet is suggested:

Note: The above labeling comments were discussed with the Clinical Division Team Leader.

APPEARS THIS WAY
ON ORIGINAL

2.0

Clinical Pharmacology and Biopharmaceutics Review (Question Based Review)

2.1 Background

Estrasorb is an oil water base vehicle containing low concentrations of ethanol — that would deliver estradiol systemically and have a zero order pharmacokinetic profile. The final to-be-marketed formulation is packaged in foil-laminated pouches. Each pouch contains 1.74 gram of Estrasorb (4.35 gram estradiol).

2.2 What Studies are Submitted in this NDA?

The original NDA was reviewed by OCPB in April 2002 (**Appendix III**). Therefore, this is a resubmission of the original NDA. From the Clinical Pharmacology point of view, all studies and data from the original NDA were resubmitted. In addition, the following three new studies were submitted:

A. **Partner transfer study:** To determine if estradiol can be transferred to male partners via skin to skin contacts with female partners.
B. **Sunscreen study:** To determine the effect of sunscreen on the absorption of estradiol after application of Estrasorb.
C. ***In vitro* pouch expression study:** to determine the actual weight content in the clinical batch (Lot # 038, 3 X 1.15 gram pouh) and in the to-be-marketed batch (lot # NS2, 2 X 1.74 Gram Pouch). Additional batch that was also tested in this study (Lot # NS1, 3 x 1.15 gram pouch). The formulation composition in all of these packages is the same as that of the clinical batch (i.e., lot # 0038), except in the packaging sizes.

A. Partner Transfer Study:

Abstract:

The primary objective of this study was to determine the extent of the transfer potential of estradiol from females applying Estrasorb to her male partner after application to skin. In this study, 14 menopausal female subjects applied two 1.74-gram pouches of daily for two days to their thighs and calves. The total amount of estradiol contained in each administration was 8.7 mg. After 2 and 8 hours of Estrasorb application, each subject's male partner attempted to transfer estradiol to his forearms by vigorously rubbing them against his female partner's thighs for two minutes. Male partners serum estradiol, estrone, and estrone sulfate concentrations were compared to concentrations present 10 days before exposure to exogenous estradiol.

After two and four such exposures, male serum concentrations, as assessed by $AUC_{(0\text{-}24h)}$, increased by 14% and 25% for serum estradiol. Similarly, there was 26% and 34% increase in serum estrone and 17% and 16% for serum estrone sulfate.

In female subjects, comparing hormone concentrations after one and two day's of application, there were statistically significant increases in serum estradiol, estrone and estrone sulfate.

What are the Objectives of the Study?

The primary objective of this study was to determine the extent of systemic absorption of estradiol in a male partner after vigorous, serial intentional contact exposure over 48 hours with the primary Estrasorb application site of a post-menopausal female partner.

How was the Study designed?

This study was conducted in 14 female subjects. Estrasorb was applied as 2 X 1.74-gram pouches daily for two days to their thighs and calves (lot # NS2, to be marketed package size). On both days, 2 and 8 hours after application, each subject's male partner attempted to transfer estradiol to his forearms by vigorously rubbing them against his female partner's thighs for two minutes. Male partners had serial blood samples taken for measurement of serum estradiol, estrone, and estrone sulfate concentrations over a 48-hour period. These values were compared to baseline levels obtained 10 days prior to their first exposure to exogenous estradiol. **Table 1** summarizes the timing of study procedures and assessments. Also, **Tables 2 and 3** show the detail of PK sampling times (see below).

Table 1. Study Design Overview and Schedule of Events and Assessments

	Pre-Dosing				Dosing		Post Dosing
Study Day **Assessment**	Day -24	Day -11	Day -10	Day -9	Day 0	Day 1	Day 2
Signed informed consent	x						
Screening process	~ -Day 13						
Eligibility determined		x					
Eligibility Summary Form		x					
Medical history	x						
Vital signs (females)	x				x	x	
Weight (females)	x				x	x	
EKG	x						
Hematology	x						x (males)
Serum chemistries	x						x (males)
Urinalysis	x						
Pelvic exam, urinary HCG PAP smear, mammogram	x (females)						
Prostate exam	x (males)						
Serum estradiol	x		x (males)	x (males)	x	x	x (males)
Serum estrone	x		x (males)	x (males)	x	x	x (males)
Serum estrone sulfate	x		x (males)	x (males)	x	x	x (males)
FSH	x (females)				x (females)	x (females)	
Serum total testosterone	x						
Serum free testosterone	x						
Dihydrotestosterone	x						
PSA levels (males)	x						x
Concomitant medications	x				x	x (females)	
Adverse events	x				x	x	x (males)
Dermal assessment	x				x	x	x (males)

Baseline: On Day –24, blood samples were collected from female and male subjects for the determination of serum estradiol, estrone, estrone sulfate, FSH, total testosterone, free testosterone and dihydrotestosterone concentrations. In addition, male partners also had serum estradiol, estrone and estrone sulfate concentrations determined on Day -10, at time 0(10 AM) and then 1 (11 AM), 2 (12 noon), 4 (2 PM), 8 (6PM), 12 (10PM), 18 (4AM on Day -9) and 24 hours (10 AM on Day -9) after the initial blood draw.

Dosing (Day 0): The contents of two 1.74-gram Estrasorb (3.48 gm total) pouches were expressed and applied by the female subjects. After 2 hours of application, the male partner placed his left forearm on the anterior aspect of the left leg adjacent to the knee and rubbed his forearm vigorously back and forth across the skin. The rubbing was from the knee to the superior aspect of the left thigh for two minutes. The same procedure was repeated using the right forearm on the right thigh 8 hours after application.

When Were PK Blood Samples Collected?

Blood was collected from female and male subjects for the determination of serum estradiol, estrone, estrone sulfate (**Table 2 and 3**). For females, it was collected on Day 0 at 1, 2, and 8

hours after application of study medication. The blood was collected at 2 and 8 hours prior to the rubbing by the male partner. In male partners blood was also collected on Day 0 at time 0, 1, 2, 4, 8, 12, 18, and 24 hours after initial exposure to Estrasorb. The same procedure was repeated on the next day (Day 1) in which blood was collected from females and males.

Table 2. Overview of PK Samples for Hormone Assessments

	Pre Dosing		Dosing	
Study Day Assessment	Day -24	Day -10 (males only)	Day 0 (males only)	Day 1 (males only)
Serum estradiol	x	PK	PK	PK
Serum estrone	x	PK	PK	PK
Serum estrone sulfate	x	PK	PK	PK
Serum total testosterone	x			
Serum free testosterone	x			
Dihydrotestosterone	x			

Table 3. Timing of PK Samples

		Hours Following Initial Exposure to ESTRASORB™ Application Site for Pharmacokinetics Analysis									
Study day	ESTRASORB ™ dosing time	0 hrs	Exp[1]	1 hrs	2 hrs	4 hrs	Exp[2]	8 hrs	12 hrs	18 hrs	24 hrs
-10	NA	10 AM	NA	11 AM	12 PM	2 PM	NA	6 PM	10 PM	4 AM Day -9	10 AM Day -9
0	8 AM	9:45 AM	10 AM	11 AM	12 PM	2 PM	4 PM	6 PM	10 PM	4 AM Day 1	10 AM Day 1
1	9 AM	--	11 AM	12 PM	1 PM	3 PM	5 PM	7 PM	11 PM	5 AM Day 2	11 AM Day 2

[1] Exposure of the left arm to the application site on the left thigh and calf.
[2] Exposure of the right arm to the application site on the right thigh and calf.

What Assay Was Used in this Study?

Serum concentrations of estradiol, estrone, and estrone sulfate were determined by radioimmunoassay (RIA) as described in the original review (**Appendix III**).

Results:

Figures A1-**A16** and **Tables A4-A8** show the mean and individual data for estradiol, estrone, estrone sulfate, and FSH in both females and males. Individual data are in **Appendix I**.

Female Data:

- Mean serum estradiol levels on dosing days (Days 0 and 1) were much higher than on screening Day –24. This indicates that estradiol was absorbed after Estrasorb application (**Figures A1, A2 and Tables A4-A5**).
- There were two outliers in estradiol levels (patients #9F and #34F) throughout the two days of study (**Figure A1**) and one (patient # 34F) for estrone level (**Figure A3**).
- The similar patters for Cmax and AUC was also seen for estrone and estrone sulfate (**Figures A3-A6**).
- Overall, the systemic exposure to estradiol and its metabolites on the second day of application is about 2 folds higher than the first day.
- Accordingly and as expected, FSH level in Day 0 was higher than that of Day 1 (**Figures A7**). As expected, the reduction in FSH level on Day 1 compared to Day 0 indicates some relationship with estradiol serum level.

Male Partners:

- Estradiol and its metabolites were detected in the serum of the male partners. Again, hormone levels on the second day of treatment were higher than that of the first day (**Figures A8-A9 and Tables A6,A7**)
- Mean estradiol levels on exposure days (Days 0 and 1) were slightly higher than those on the pre-exposure day (Day -10).
- The means of $AUC_{(0\text{-}24h)}$ on Days -10, 0 and 1 were 40.73 ± 1.42, 46.30 ± 12.46 and 50.46 ± 10.54 ng-h/dL, respectively (**Table A6**).
- $AUC_{(0\text{-}24h)}$ values on Day 1 were statistically significantly higher than those on Day 0 (p-value=0.0005). The mean fold-ratios for $AUC_{(0\text{-}24h)}$ were 1.14 (Day -10 to Day 0), 1.25 (Day -10 to Day 1), and 1.10 (Day 0 to Day 1), with values above 1 indicating higher AUC at the later day (**Table A7**).
- After intentional transfer of Estrasorb, estradiol in male partners, as measured by mean fold ratios in $AUC_{(0\text{-}24h)}$, increased by about 14% after one day of exposure and 25% after two days of exposure (**Table A7**).
- Similarly, for Cmax, estradiol means fold ratios in male partners were increased about 13% after one day of exposure and 30% after two days of exposure (**Tables A7,A10 and Figures A8,A9**).

- It should be noted that there was one outlier (subject # 7M) which had a concentration of 5.10 ng/dl and 4.90 ng/dl at 18 hours in both Day 0 and Day 1, respectively. For this reason, estradil concentration was higher than usual at 18 hours (**Figure 8**).
- The same trend was also seen for estrone (**Figures A10-A13**) and estrone sulfate (**Figures A14-A15**).

Is there Consistency in Pouch Weight Expression?

The weight of the amount of applied Estrasorb was measured by comparing the weight of the combined foil pouches before and after each day's application. The pouch expression weight data are shown in **Figure A16 and Table A8**. The data consisting of two sets of fourteen numbers. The nominal weight of Estrasorb per pouch is 1.74 grams, or a total of 3.48 grams on each application day. The daily pouch weight means (± SD) were 3.204 ± 0.116 and 3.170 ± 0.120 grams, which are, respectively, 7.93% and 8.91% below the nominal weight. Ranges of pouch expression weight were 2.95-3.33 grams and 2.96-3.36 grams on Day 0 and 1, respectively.

The mean difference of pouch weight expression on the two days was –0.033 ± 0.133 grams (less expression on Day 1 than on Day 0). This difference was not statistically significant (p=0.36). Thus, there was no evidence of a significant change in pouch expression between the two days.

What is the Overall Summary?

- Based on fold-ratios in male $AUC_{(0\text{-}24h)}$, a mean increase of 14% in serum estradiol level in male partners was observed after the first day of two Estrasorb exposures, compared to the pre-exposure level.
- After two days, the overall serum estradiol concentration had increased by 25% compared to the pre-exposure concentration on Day -10. Similar results were seen for Cmax.
- In addition, similar results were observed for serum estrone and serum estrone sulfate among the 14 male partners. For serum estrone, based on fold-ratios in male $AUC_{(0\text{-}24h)}$, the mean increase of 26% in serum estrone level in male partners was observed after the first day of two Estrasorb exposures, compared to the pre-exposure level.
- After two days exposure, the serum estrone level had increased by 34% compared to the pre-exposure level on Day -10. Similar results were seen for C_{max} and most of these comparisons of serum estrone from screening Day -10 to Days 0 and 1 were statistically significant.
- For serum estrone sulfate, based on fold-ratios in male $AUC_{(0\text{-}24h)}$, the mean increase of 17% in serum estrone sulfate level in male partners was observed after the first day of two Estrasorb exposures, compared to the pre-exposure level. After two days exposur to estrasorb, the serum estrone sulfate level had increased by 16% compared to the pre-exposure level on Day -10. Similar results were seen for C_{max}.

Conclusions:

Estradiol was detected in male partners after vigorous skin-to-skin contact with the female

partner. Overall, there was about 25% increase in estradiol exposure compared to baseline in male partners. This level of estradiol may be of some clinical significance, but it may not be translated into real life situations.

What are the Labeling Recommendations?

Based on this study, it is recommended to include a general statement (s) in the label to reflect the following meanings:

- Male partners are advised to avoid vigorous skin-to-skin contact to the areas were Estrasorb is applied to female partners.
- It is advised that male partners wash or shower their skin immediately after vigorous skin-to-skin contact to the area where Estrasorb is applied in female partners.
- In terms of pouch expression, the following general or similar statement in the label and patient's information sheet is recommended: "To reduce day-to-day variability in estradiol exposure, the content of each pouch must be fully expressed in the same manner each time".

Estradiol Data (Females)

Figure A1

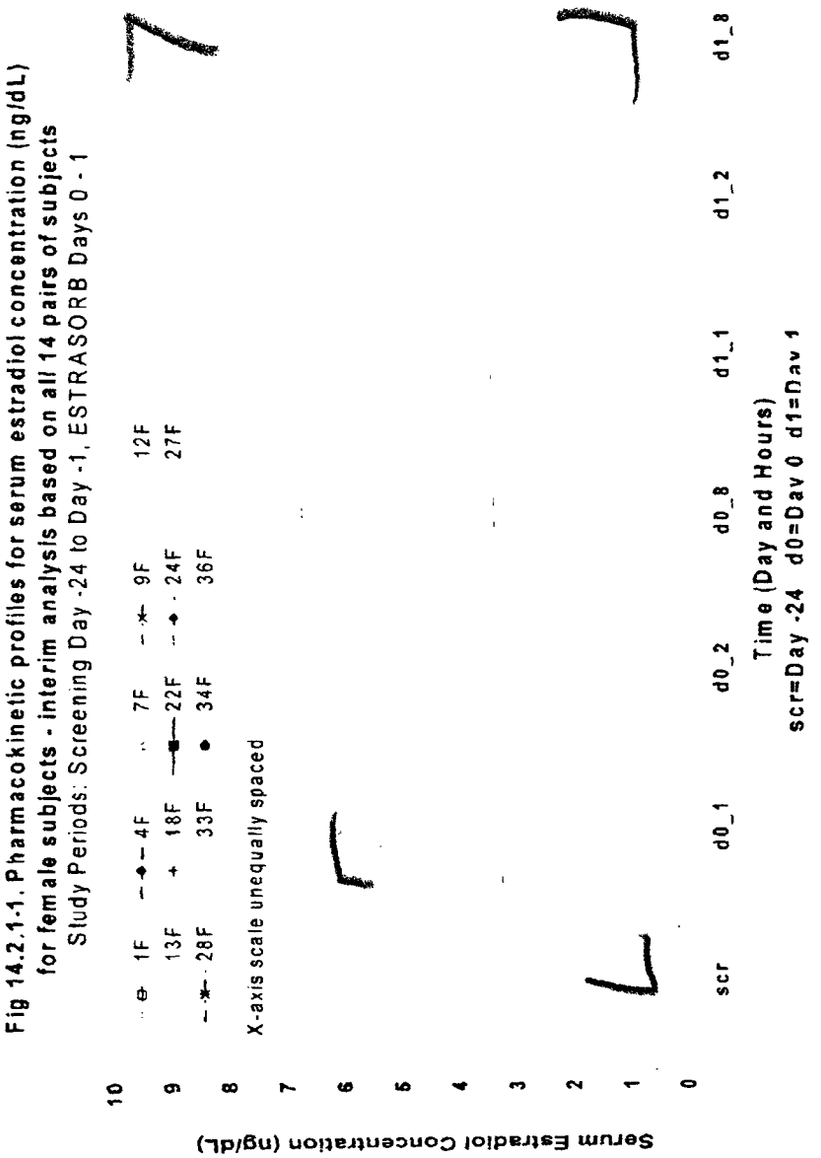


Figure A2

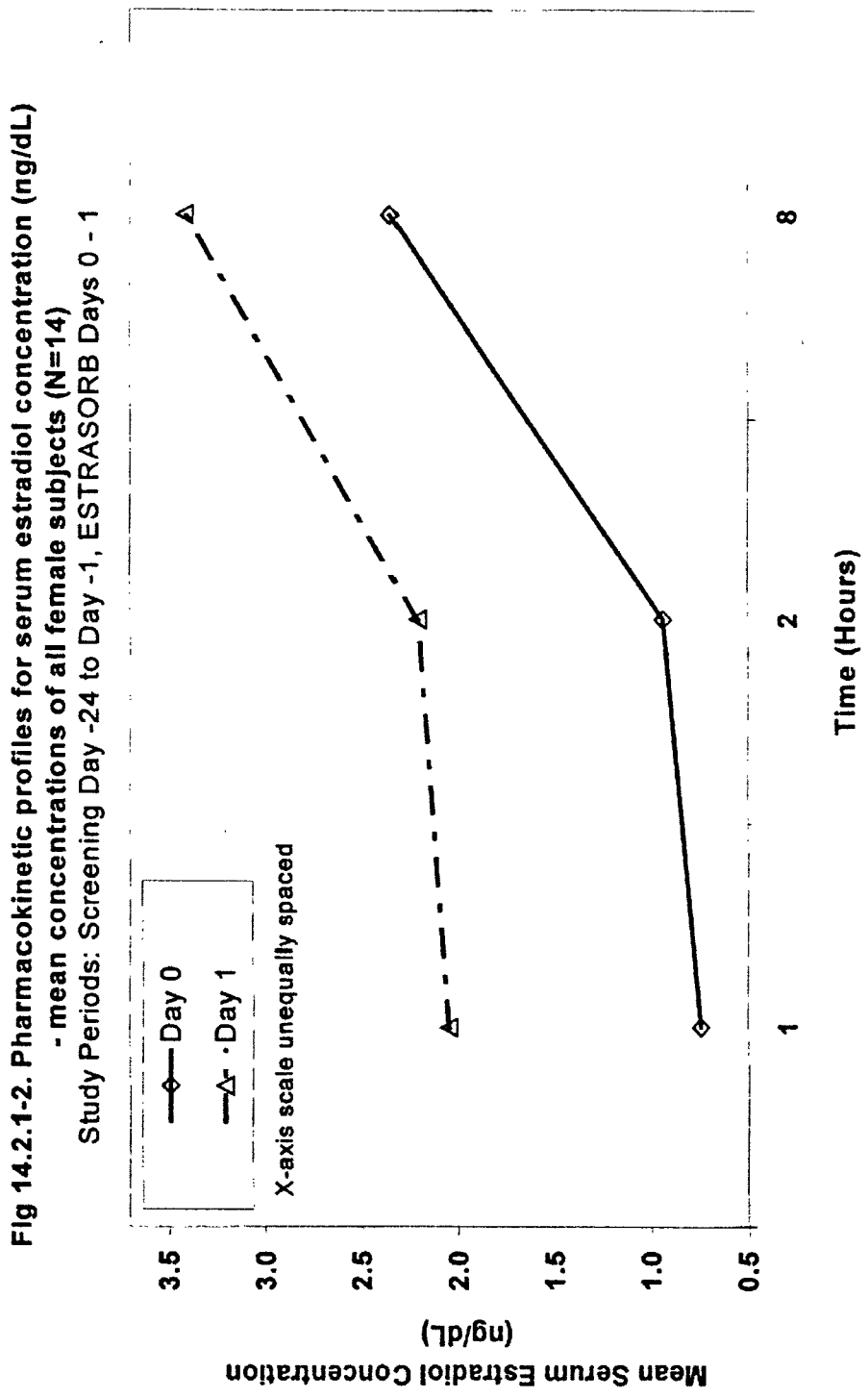


Fig 14.2.1-2. Pharmacokinetic profiles for serum estradiol concentration (ng/dL)
- mean concentrations of all female subjects (N=14)
Study Periods: Screening Day -24 to Day -1, ESTRASORB Days 0 - 1
Day 0
Day 1
X-axis scale unequally spaced
Mean Serum Estradiol Concentration
(ng/dL)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1
2
8
Time (Hours)

Table 14.2.1-13. Descriptive statistics of pharmacokinetic parameters on profiling Days 0 and 1 for all female subjects (N=14)

Hormone	PK Parameter (Mean ± SD)	Profiling Day	
		Day 0	Day 1
Estradiol	T_{max} (hr)	6.57 ± 2.85	6.07 ± 3.17
	C_{max} (ng/dL)	2.35 ± 2.11	3.54 ± 2.89
	C_{min} (ng/dL)	0.72 ± 1.19	1.87 ± 1.98
	$C_{average}$ (ng/dL)	1.53 ± 1.48	2.76 ± 2.27
	$AUC_{(1-8h)}$ (ng-h/dL)	10.70 ± 10.39	19.34 ± 15.91
Estrone	T_{max} (hr)	4.36 ± 3.30	4.71 ± 3.43
	C_{max} (ng/dL)	2.31 ± 1.28	4.85 ± 2.83
	C_{min} (ng/dL)	1.38 ± 1.25	3.47 ± 2.35
	$C_{average}$ (ng/dL)	1.79 ± 1.26	4.09 ± 2.53
	$AUC_{(1-8h)}$ (ng-h/dL)	12.50 ± 8.79	28.64 ± 17.73
Estrone Sulfate	T_{max} (hr)	7.57 ± 1.60	6.57 ± 2.85
	C_{max} (ng/dL)	62.93 ± 36.77	158.64 ± 94.47
	C_{min} (ng/dL)	36.64 ± 23.68	116.86 ± 68.67
	$C_{average}$ (ng/dL)	49.47 ± 28.94	138.50 ± 79.38
	$AUC_{(1-8h)}$ (ng-h/dL)	346.26 ± 202.57	969.48 ± 555.68
FSH	T_{max} (hr)	2.86 ± 2.82	2.93 ± 2.79
	C_{max} (mIU/mL)	70.14 ± 18.40	63.50 ± 15.45
	C_{min} (mIU/mL)	59.64 ± 15.84	56.14 ± 13.22
	$C_{average}$ (mIU/mL)	65.17 ± 17.87	59.46 ± 14.03
	$AUC_{(1-8h)}$ (mIU-h/mL)	456.17 ± 125.09	416.25 ± 98.24

Table 14.2.1-14. Geometric means, geometric mean fold ratios and paired t-test findings in $AUC_{(1\text{-}8h)}$ and C_{max} for hormones on profiling Days 0 and 1 for all female subjects (N=14)

PK Parameter			Serum Hormone			
			Estradiol (ng/dL)	Estrone (ng/dL)	Estrone Sulfate (ng/dL)	FSH (mIU/mL)
$AUC_{(1\text{-}8h)}$						
Geometric Mean	$AUC_{(1\text{-}8h)}$	Day 0	7.30	10.10	297.68	442.30
		Day 1	15.02	25.15	834.32	405.83
	Fold Ratio in $AUC_{(1\text{-}8h)}$ from Day 0 to Day 1		2.06	2.49	2.80	0.92
Pair-wise comparison p-value*	$AUC_{(1\text{-}8h)}$: Day 0 vs. Day 1		0.0011	0.0005	< 0.0001	0.0072
	Fold Ratio in $AUC_{(1\text{-}8h)}$: Day 0 vs. Day 1		0.0006	< 0.0001	< 0.0001	0.0038
C_{max}						
Geometric Mean	C_{max}	Day 0	1.50	1.98	54.27	68.09
		Day 1	2.73	4.29	134.13	61.76
	Fold Ratio in C_{max} from Day 0 to Day 1		1.82	2.16	2.47	0.91
Pair-wise Comparison p-value*	C_{max}: Day 0 vs. Day 1		0.0057	0.0013	< 0.0001	0.0086
	Fold Ratio in C_{max}: Day -10 vs. Day 0		0.0052	0.0004	< 0.0001	0.0047

*Paired t-test

Estrone Data (Females)

Figure A3

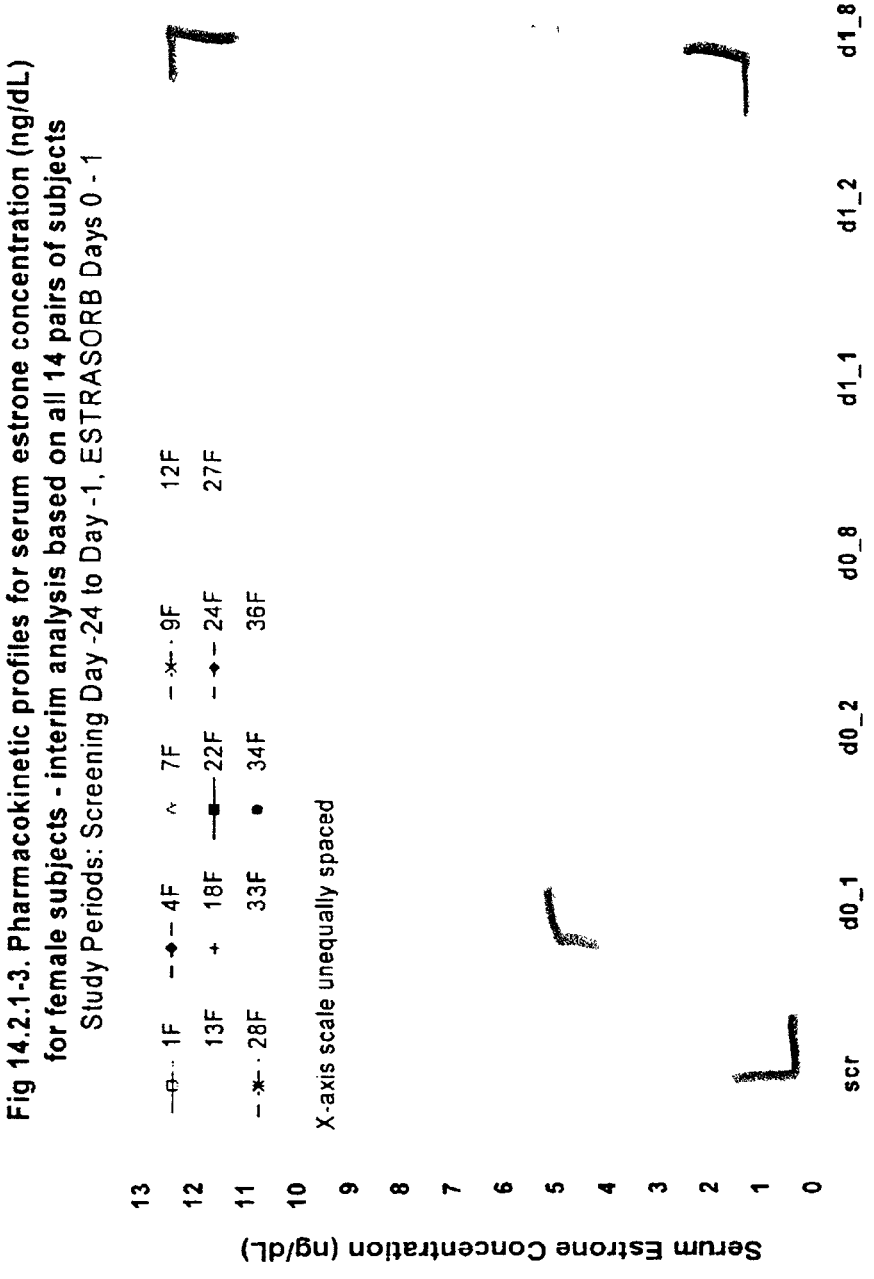


Figure A4

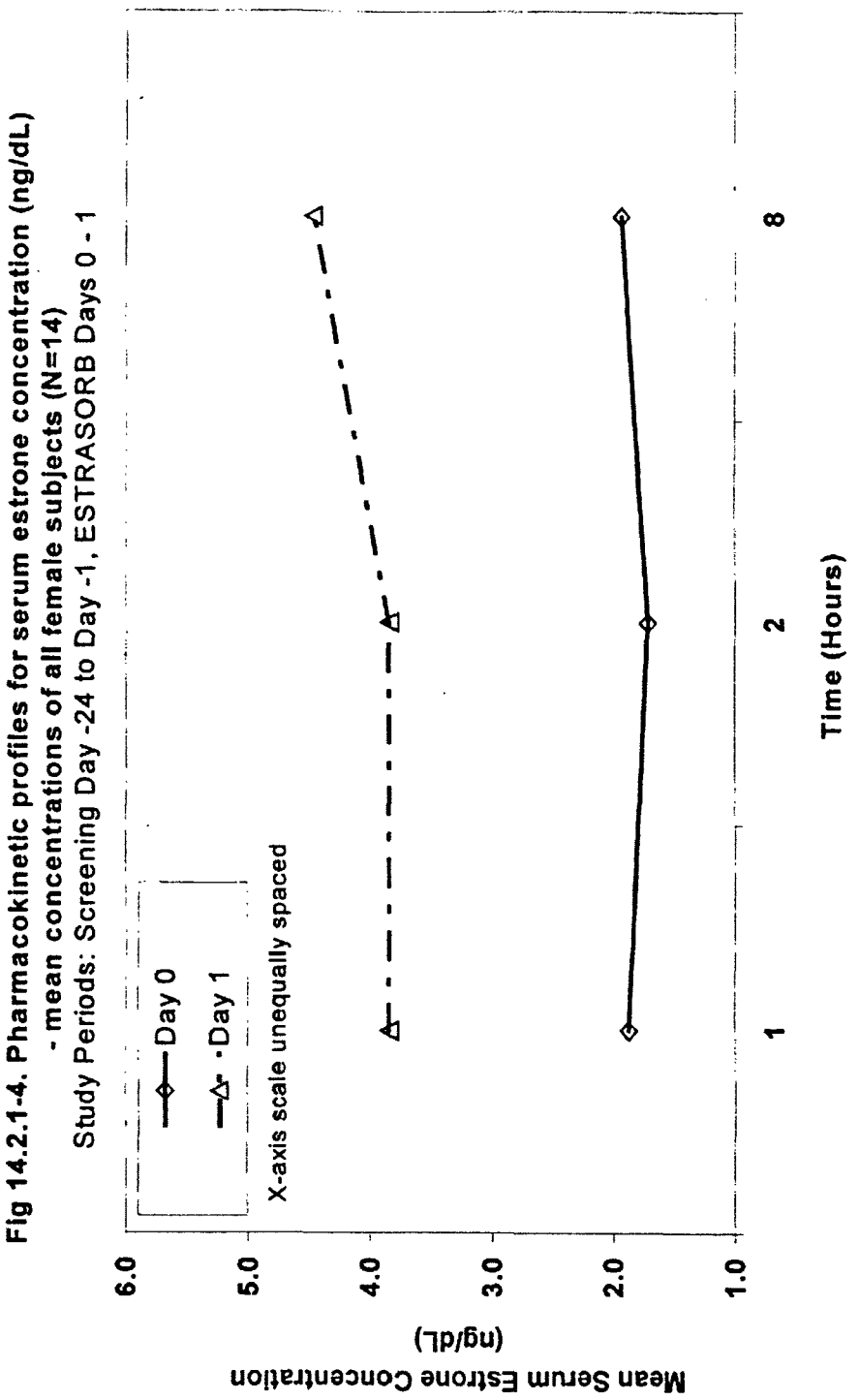


Fig 14.2.1-4. Pharmacokinetic profiles for serum estrone concentration (ng/dL)
- mean concentrations of all female subjects (N=14)
Study Periods: Screening Day -24 to Day -1, ESTRASORB Days 0 - 1
Day 0
Day 1
X-axis scale unequally spaced
Mean Serum Estrone Concentration
(ng/dL)
6.0
5.0
4.0
3.0
2.0
1.0
1
2
8
Time (Hours)

Estrone Sulfate Data (Females)

Figure A5

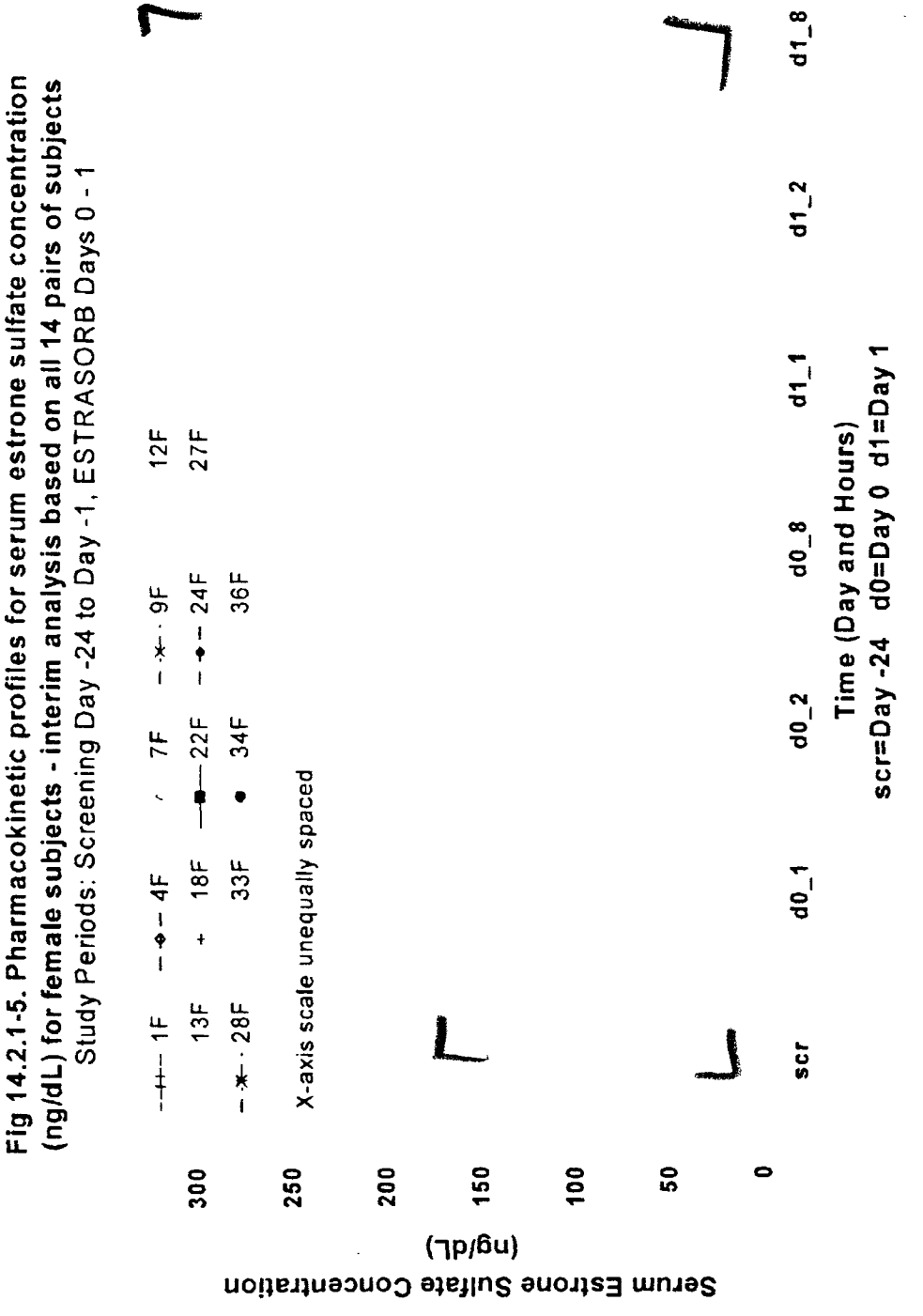


Figure A6

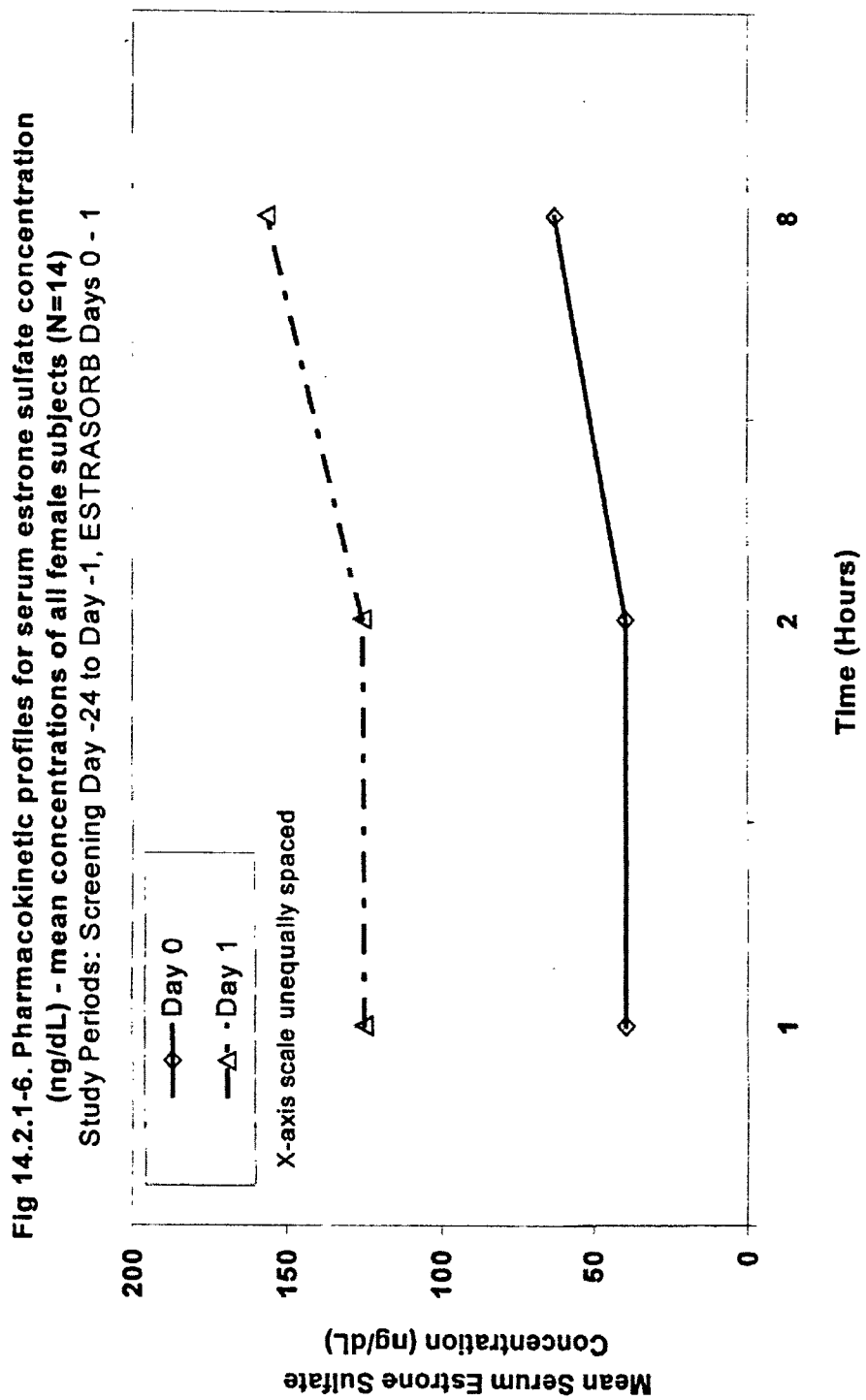
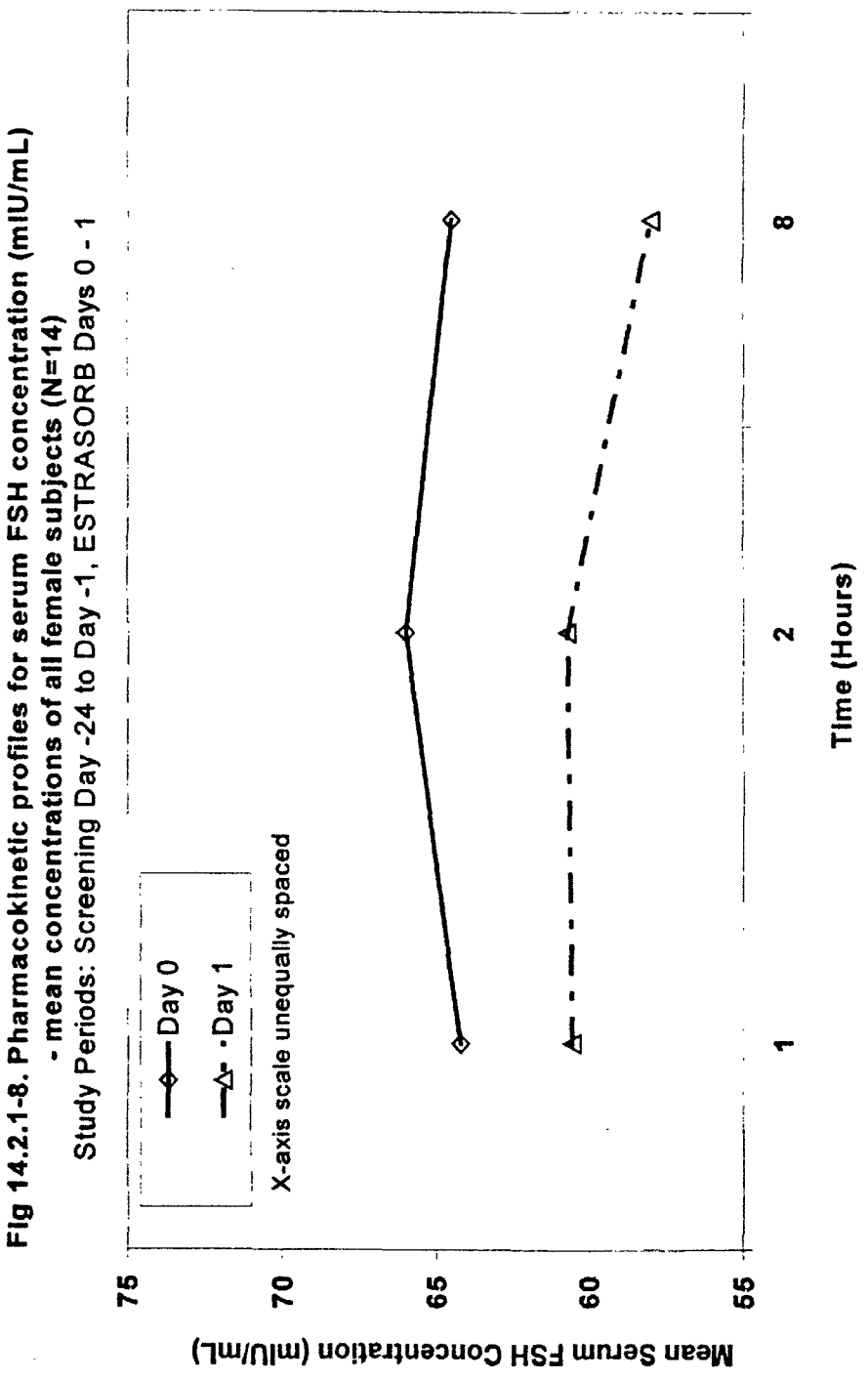


Fig 14.2.1-6. Pharmacokinetic profiles for serum estrone sulfate concentration (ng/dL) - mean concentrations of all female subjects (N=14)
Study Periods: Screening Day -24 to Day -1, ESTRASORB Days 0 - 1
Day 0
Day 1
X-axis scale unequally spaced
Mean Serum Estrone Sulfate Concentration (ng/dL)
200
150
100
50
0
1
2
8
Time (Hours)

FSH Data (Female)

Figure A7



Estradiol Data (Male)

Figure A8

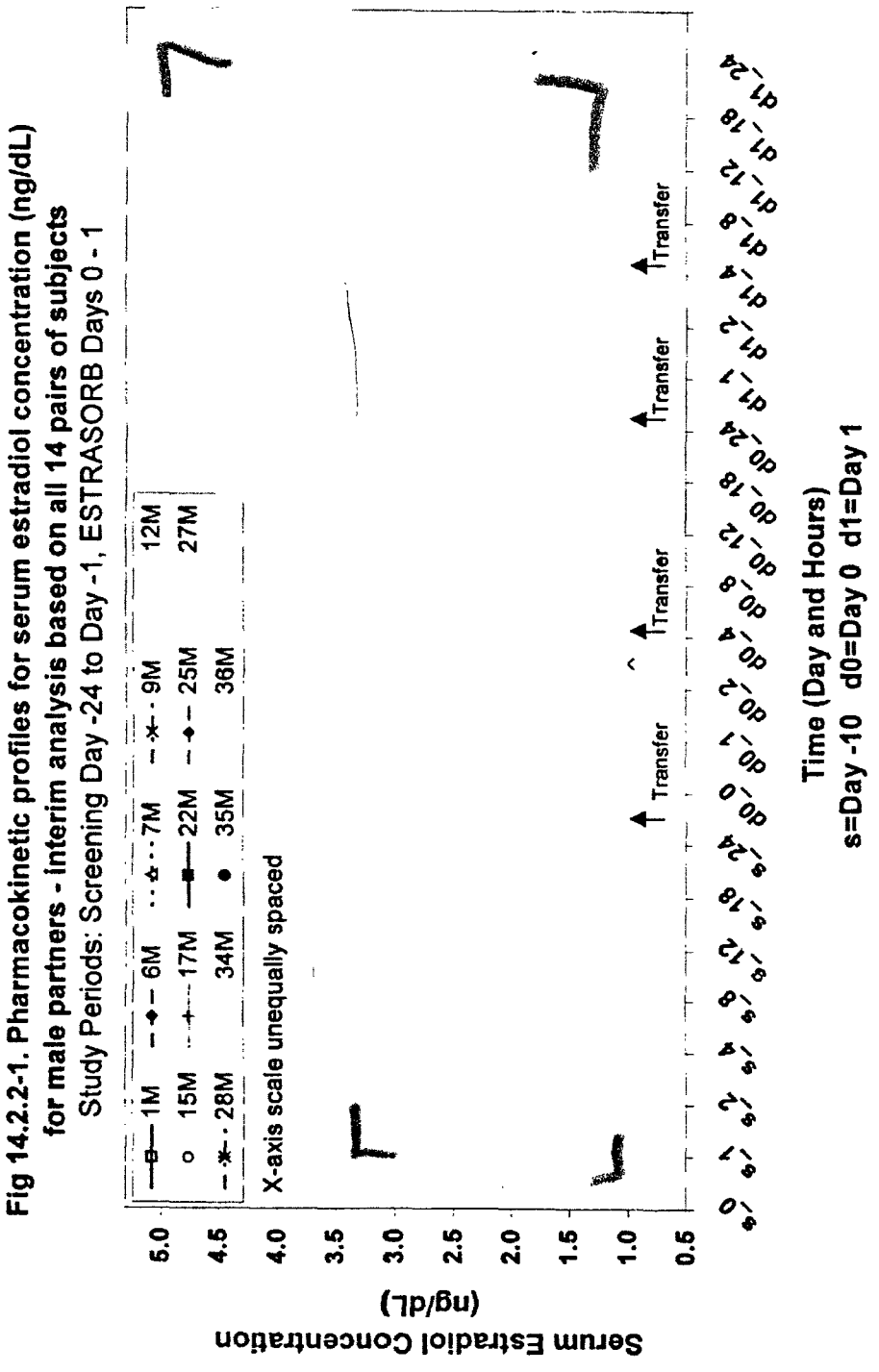


Figure A9

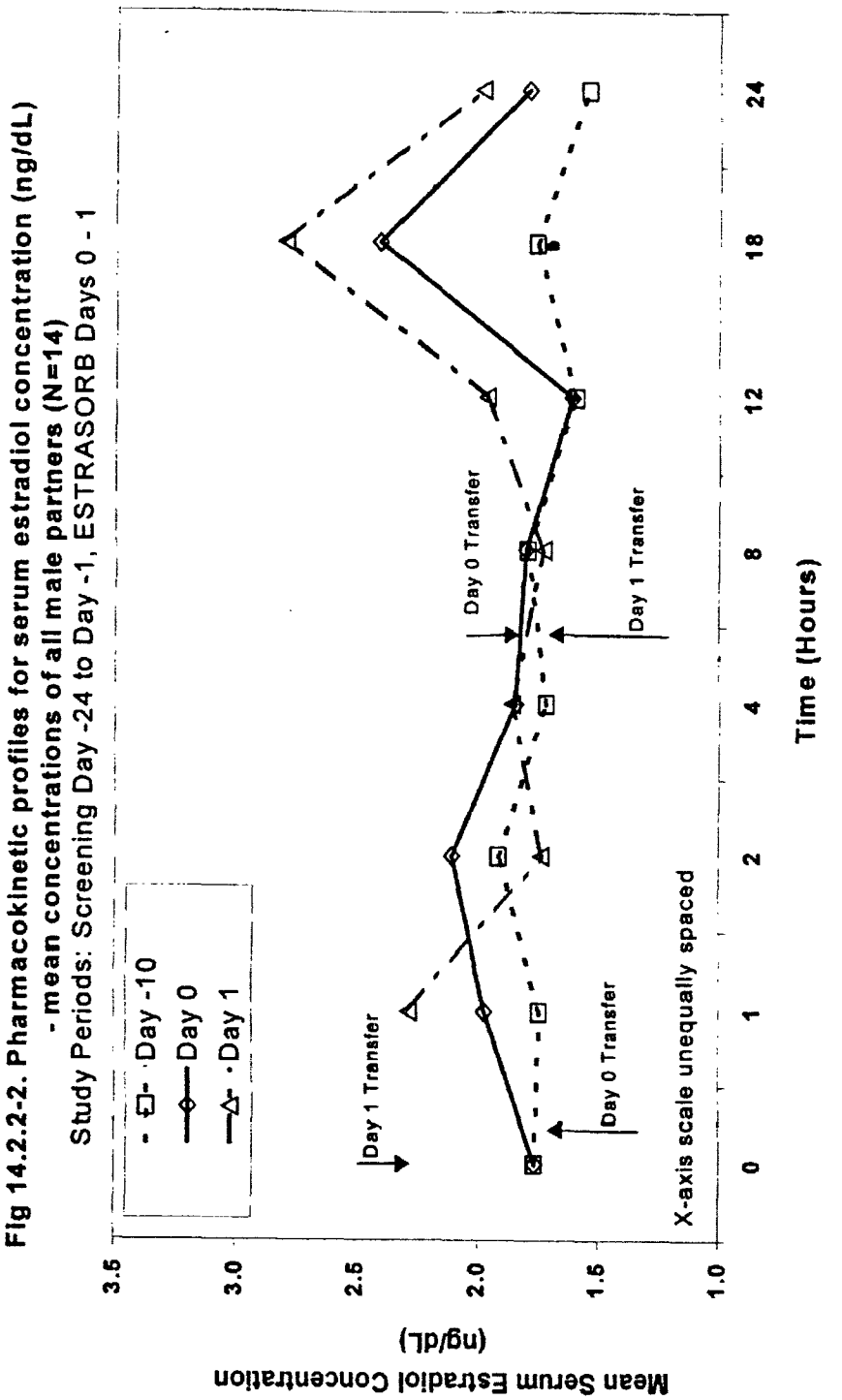


Fig 14.2.2-2. Pharmacokinetic profiles for serum estradiol concentration (ng/dL)
- mean concentrations of all male partners (N=14)
Study Periods: Screening Day -24 to Day -1, ESTRASORB Days 0 - 1
Day -10
Day 0
Day 1
Day 1 Transfer
Day 0 Transfer
Day 0 Transfer
Day 1 Transfer
X-axis scale unequally spaced
Mean Serum Estradiol Concentration (ng/dL)
Time (Hours)
3.5
3.0
2.5
2.0
1.5
1.0
0
1
2
4
8
12
18
24

Table 14.2.2-13. Descriptive statistics of pharmacokinetic parameters on profiling Days -10, 0 and 1 for all male partners (N=14)

Hormone	PK Parameter (Mean ± SD)	Profiling Day		
		Day -10	Day 0	Day 1
Estradiol	T_{max} (hr)	5.50 ± 7.28	10.00 ± 8.33	13.14 ± 7.97
	C_{max} (ng/dL)	2.17 ± 0.60	2.49 ± 0.90	2.83 ± 0.81
	C_{min} (ng/dL)	1.34 ± 0.27	1.46 ± 0.40	1.49 ± 0.41
	$C_{average}$ (ng/dL)	1.70 ± 0.43	1.93 ± 0.52	2.10 ± 0.44
	$AUC_{(0-24h)}$ (ng-h/dL)	40.73 ± 10.42	46.30 ± 12.46	50.46 ± 10.54
Estrone	T_{max} (hr)	8.79 ± 9.32	12.93 ± 8.64	11.50 ± 9.81
	C_{max} (ng/dL)	2.89 ± 0.87	3.34 ± 0.57	3.64 ± 0.79
	C_{min} (ng/dL)	1.53 ± 0.98	1.82 ± 0.70	1.88 ± 0.57
	$C_{average}$ (ng/dL)	2.14 ± 0.95	2.54 ± 0.58	2.69 ± 0.56
	$AUC_{(0-24h)}$ (ng-h/dL)	51.47 ± 22.69	61.02 ± 13.92	64.68 ± 13.56
Estrone Sulfate	T_{max} (hr)	6.21 ± 8.41	10.93 ± 7.19	8.00 ± 9.20
	C_{max} (ng/dL)	103.79 ± 50.31	121.43 ± 52.23	127.79 ± 44.85
	C_{min} (ng/dL)	72.93 ± 31.54	78.29 ± 32.59	76.71 ± 21.99
	$C_{average}$ (ng/dL)	86.93 ± 40.51	99.97 ± 43.26	95.66 ± 29.36
	$AUC_{(0-24h)}$ (ng-h/dL)	2086.4 ± 972.34	2399.3 ± 1038.2	2295.9 ± 704.56

Table 14.2.2-14. Geometric means, geometric mean fold ratios and paired t-test findings in $AUC_{(0\text{-}24h)}$ and C_{max} for hormones on profiling Days -10, 0 and 1 for all male partners (N=14)

PK Parameter				Serum Hormone (ng-h/dL)		
				Estradiol	Estrone	Estrone Sulfate
$AUC_{(0\text{-}24h)}$	Geometric Mean	$AUC_{(0\text{-}24h)}$	Day -10	39.56	47.16	1909.28
			Day 0	44.95	59.29	2231.86
			Day 1	49.51	63.26	2210.47
		Fold Ratio in $AUC_{(0\text{-}24h)}$ from	Day -10 to Day 0	1.14	1.26	1.17
			Day -10 to Day 1	1.25	1.34	1.16
			Day 0 to Day 1	1.10	1.07	0.99
	Pair-wise comparison p-value*	$AUC_{(0\text{-}24h)}$	Day -10 vs. Day 0	0.017	0.097	0.051
			Day -10 vs. Day 1	< 0.0001	0.032	0.070
			Day 0 vs. Day 1	0.0005	0.20	0.40
		Fold Ratio in $AUC_{(0\text{-}24h)}$	Day -10 vs. Day 0	0.011	0.059	0.021
			Day -10 vs. Day 1	< 0.0001	0.018	0.021
			Day 0 vs. Day 1	0.0003	0.11	0.82
C_{max}	Geometric Mean	C_{max}	Day -10	2.09	2.78	94.20
			Day 0	2.37	3.30	112.93
			Day 1	2.73	3.55	121.41
		Fold Ratio in C_{max} from	Day -10 to Day 0	1.13	1.19	1.20
			Day -10 to Day 1	1.30	1.28	1.29
			Day 0 to Day 1	1.15	1.08	1.08
	Pair-wise Comparison p-value*	C_{max}	Day -10 vs. Day 0	0.099	0.041	0.063
			Day -10 vs. Day 1	0.0005	0.0074	0.0009
			Day 0 vs. Day 1	0.042	0.022	0.39
		Fold Ratio in C_{max}	Day -10 vs. Day 0	0.087	0.025	0.024
			Day -10 vs. Day 1	0.0002	0.0065	0.0007
			Day 0 vs. Day 1	0.035	0.021	0.15

*Paired t-test

Figure A10

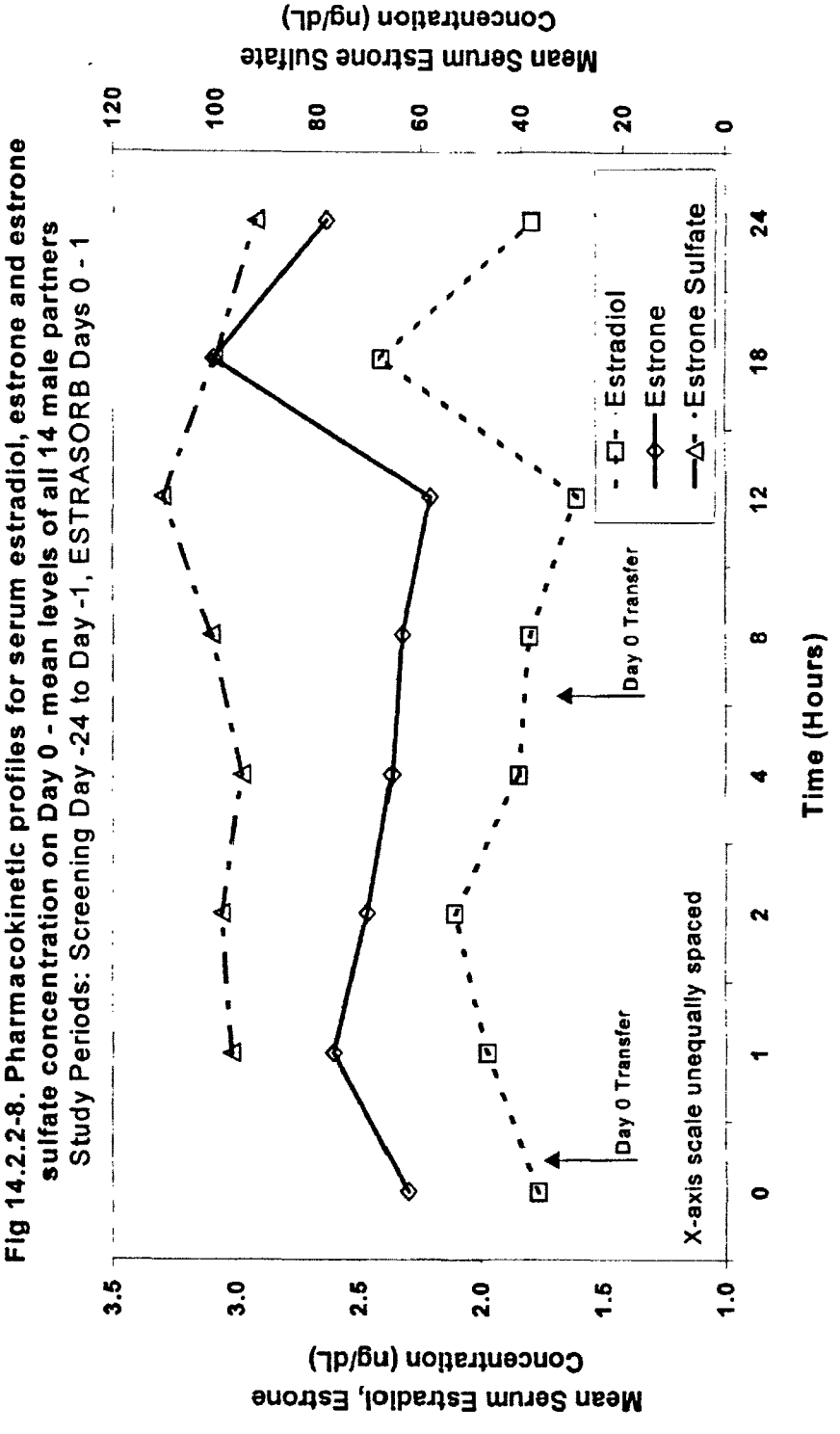


Fig 14.2.2-8. Pharmacokinetic profiles for serum estradiol, estrone and estrone sulfate concentration on Day 0 - mean levels of all 14 male partners
Study Periods: Screening Day -24 to Day -1, ESTRASORB Days 0 - 1
Mean Serum Estradiol, Estrone Concentration (ng/dL)
Mean Serum Estrone Sulfate Concentration (ng/dL)
Time (Hours)
X-axis scale unequally spaced
Day 0 Transfer
Day 0 Transfer
Estradiol
Estrone
Estrone Sulfate
3.5
3.0
2.5
2.0
1.5
1.0
120
100
80
60
40
20
0
0
1
2
4
8
12
18
24

Figure A11

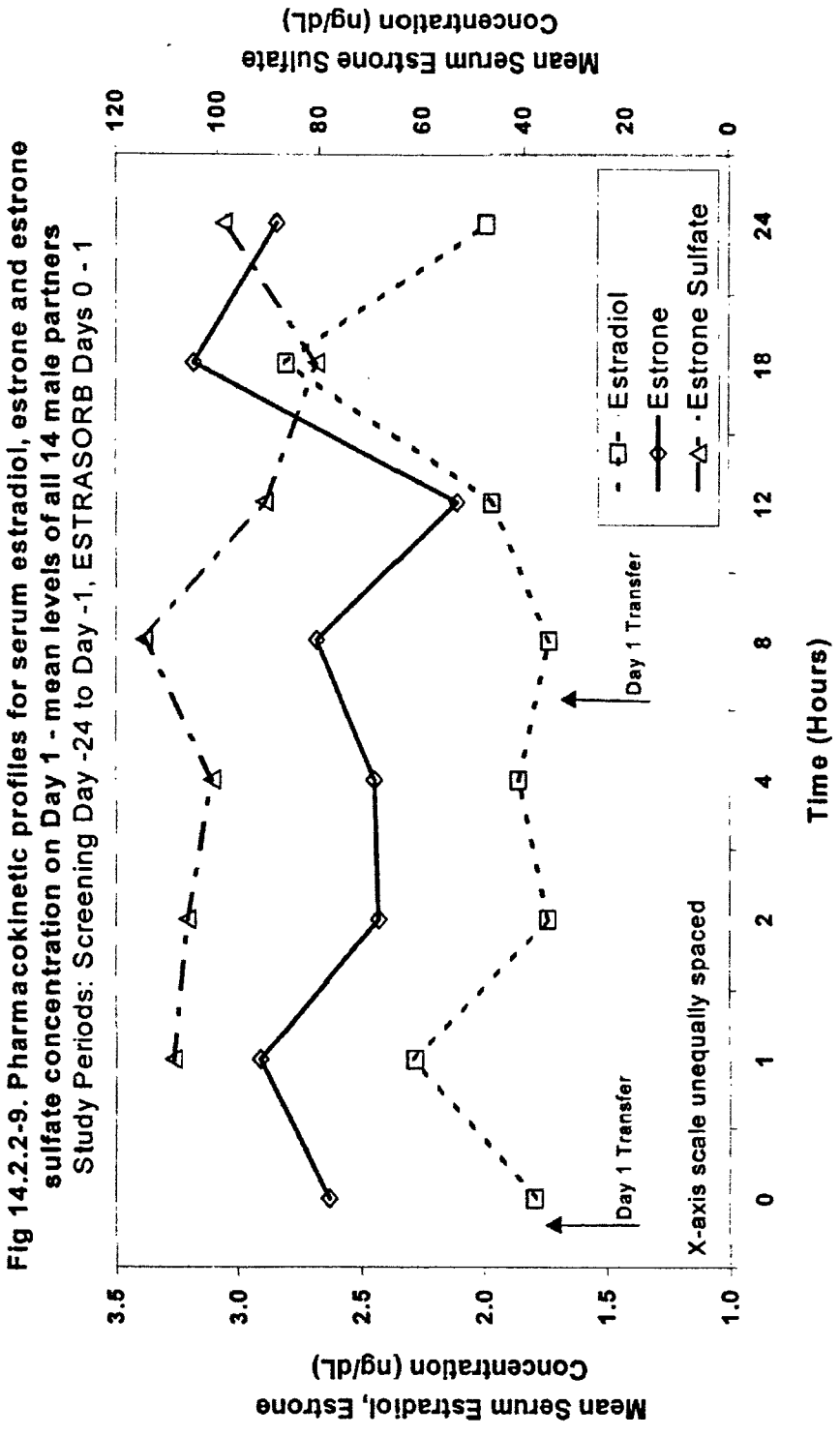


Fig 14.2.2-9. Pharmacokinetic profiles for serum estradiol, estrone and estrone sulfate concentration on Day 1 - mean levels of all 14 male partners
Study Periods: Screening Day -24 to Day -1, ESTRASORB Days 0 - 1
Mean Serum Estradiol, Estrone Concentration (ng/dL)
Mean Serum Estrone Sulfate Concentration (ng/dL)
Time (Hours)
Estradiol
Estrone
Estrone Sulfate
Day 1 Transfer
Day 1 Transfer
X-axis scale unequally spaced

Estrone Data (Males)

Figure A12

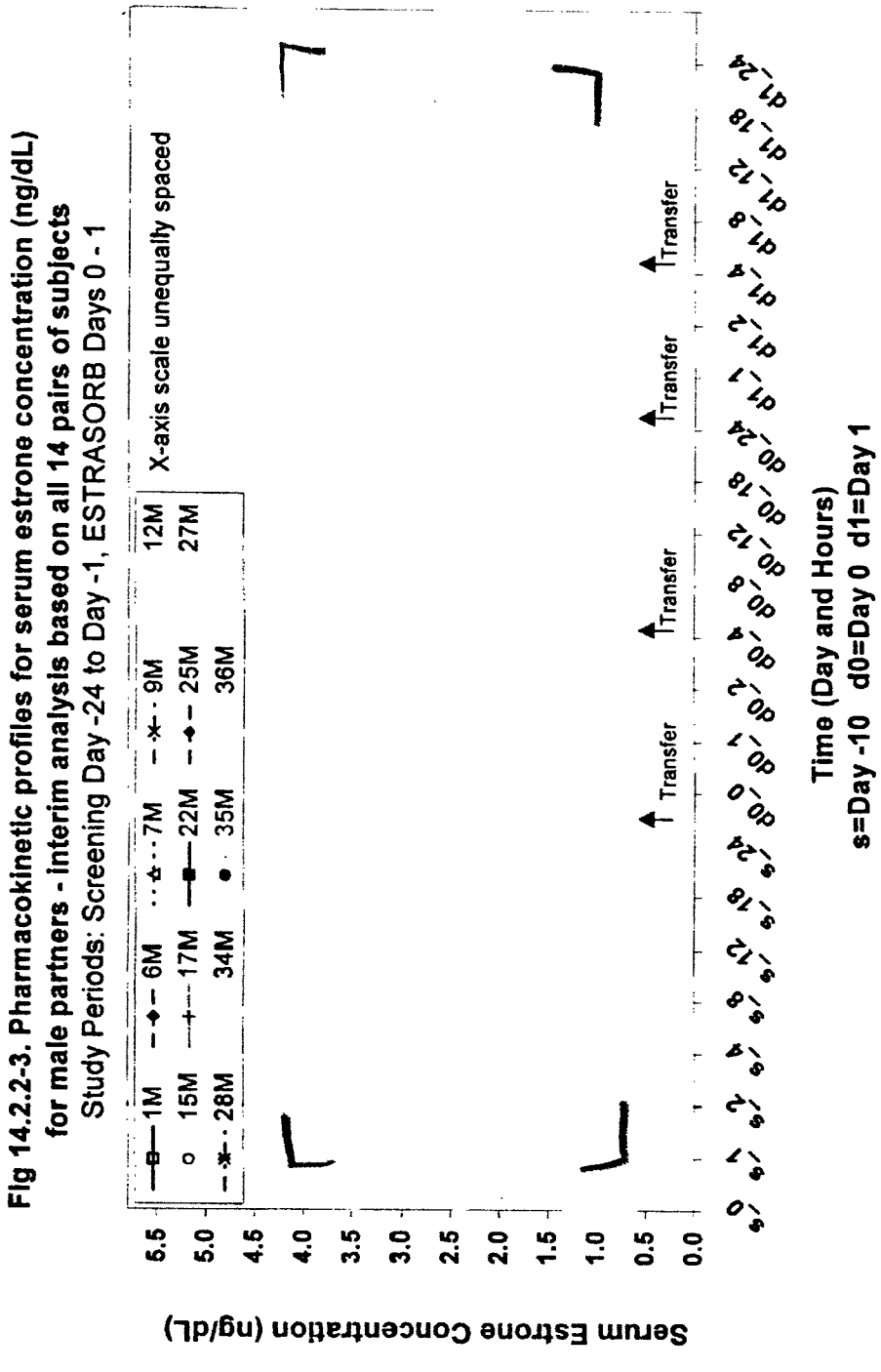


Figure A13

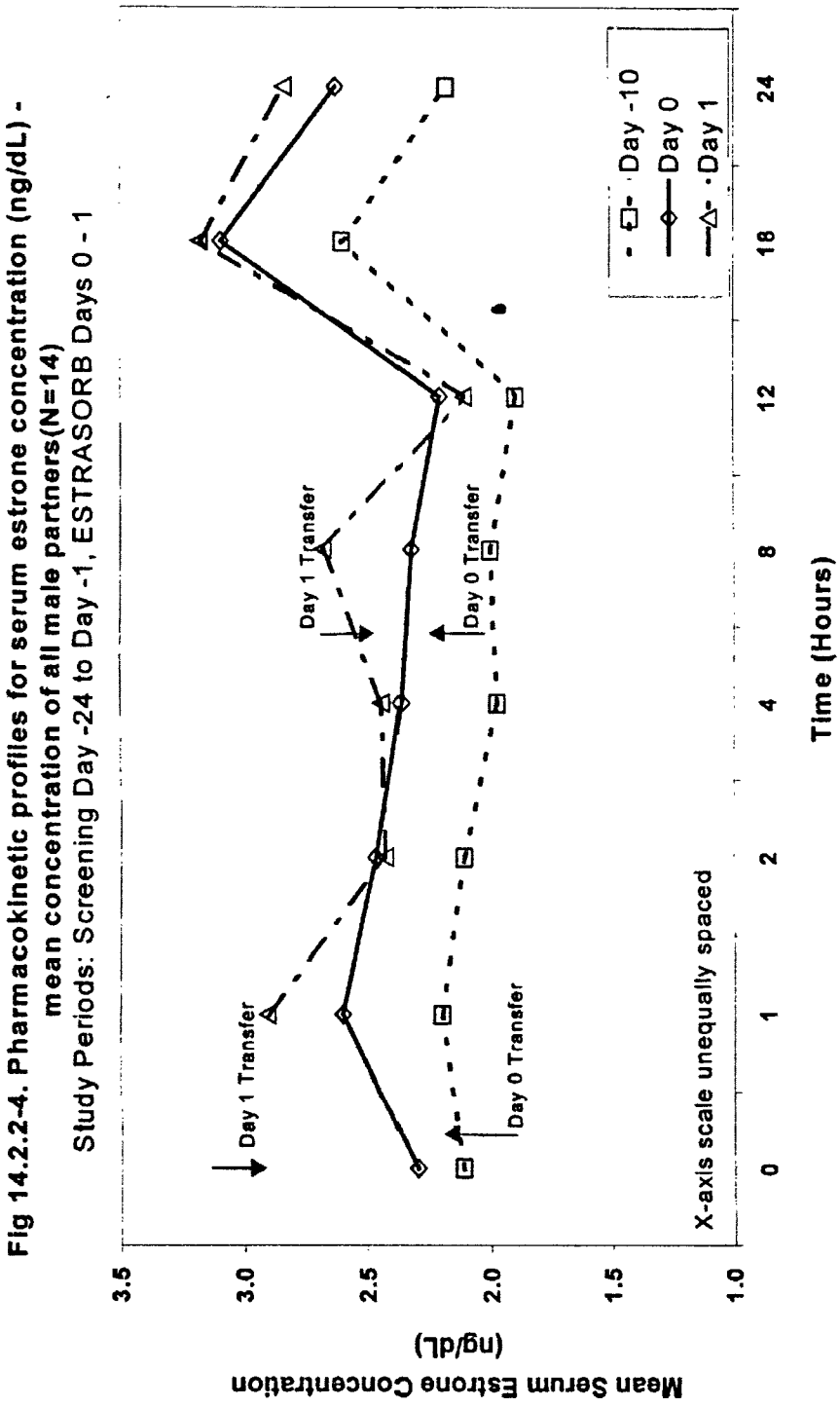
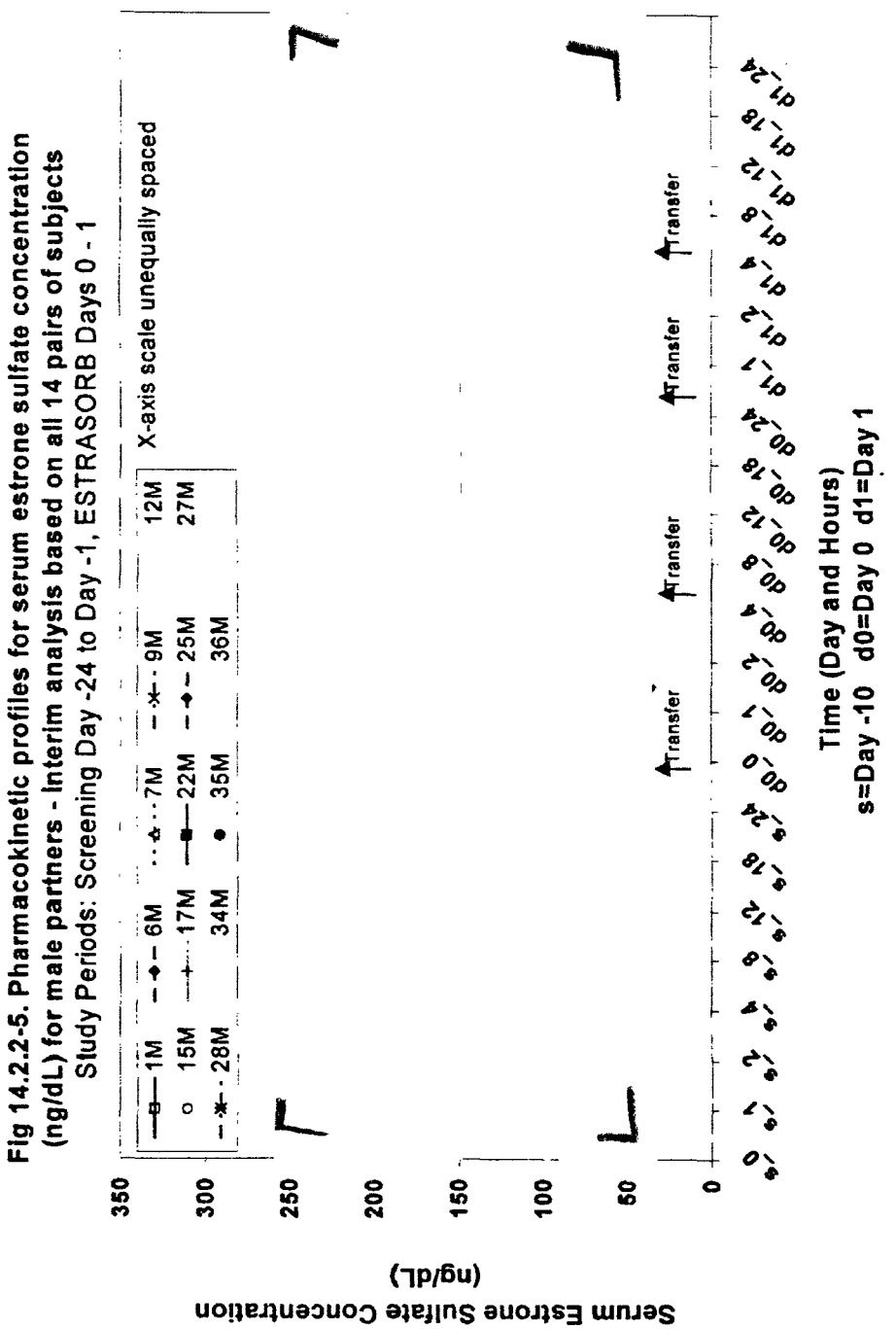


Fig 14.2.2-4. Pharmacokinetic profiles for serum estrone concentration (ng/dL) - mean concentration of all male partners(N=14)
Study Periods: Screening Day -24 to Day -1, ESTRASORB Days 0 - 1
Mean Serum Estrone Concentration (ng/dL)
Time (Hours)
X-axis scale unequally spaced
Day -10
Day 0
Day 1
Day 1 Transfer
Day 0 Transfer
Day 1 Transfer
Day 0 Transfer
3.5
3.0
2.5
2.0
1.5
1.0
0
1
2
4
8
12
18
24

Estrone Sulfate Data (Males)

Figure A14



Estrone Sulfate Data (Males)

Figure A15

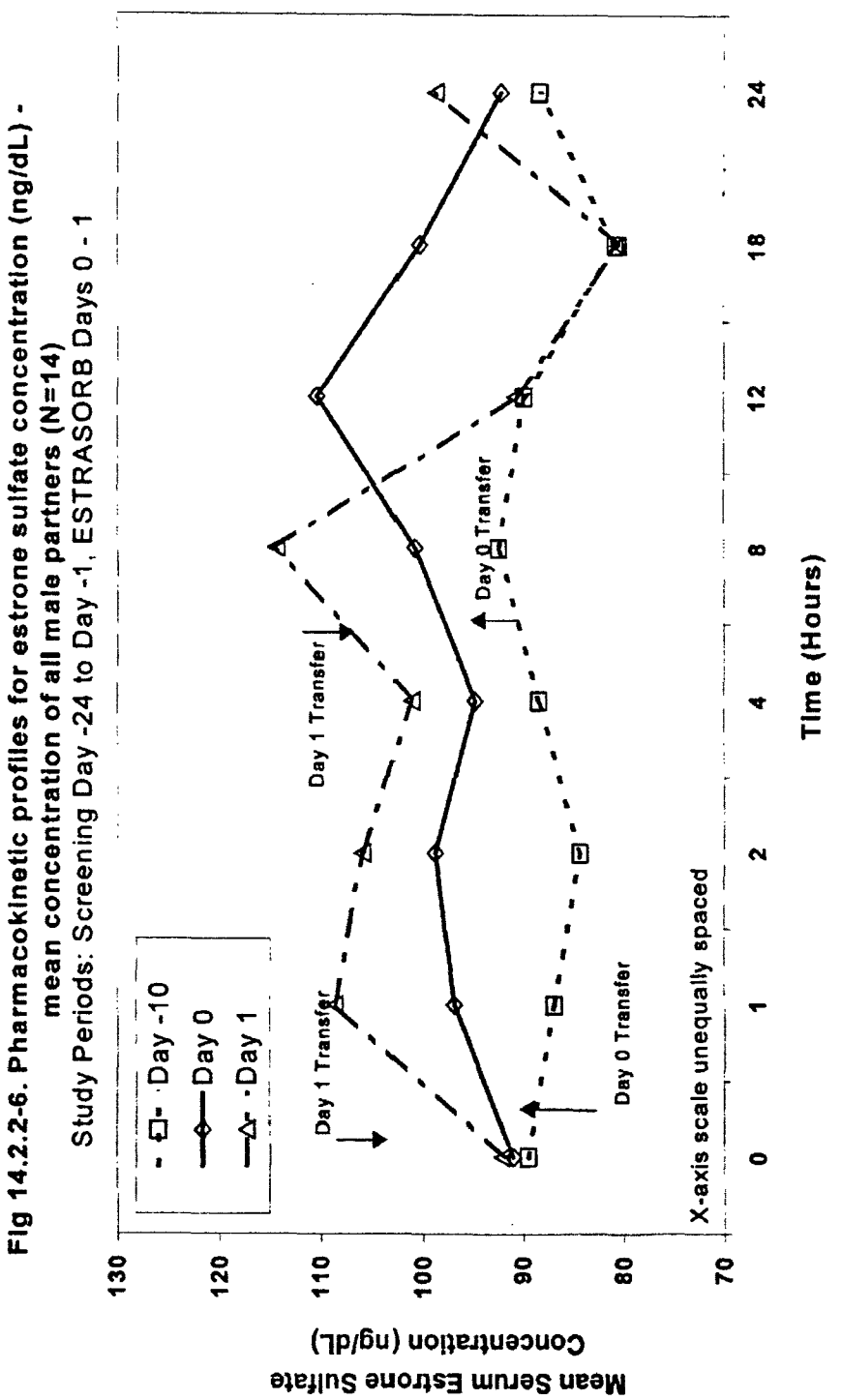
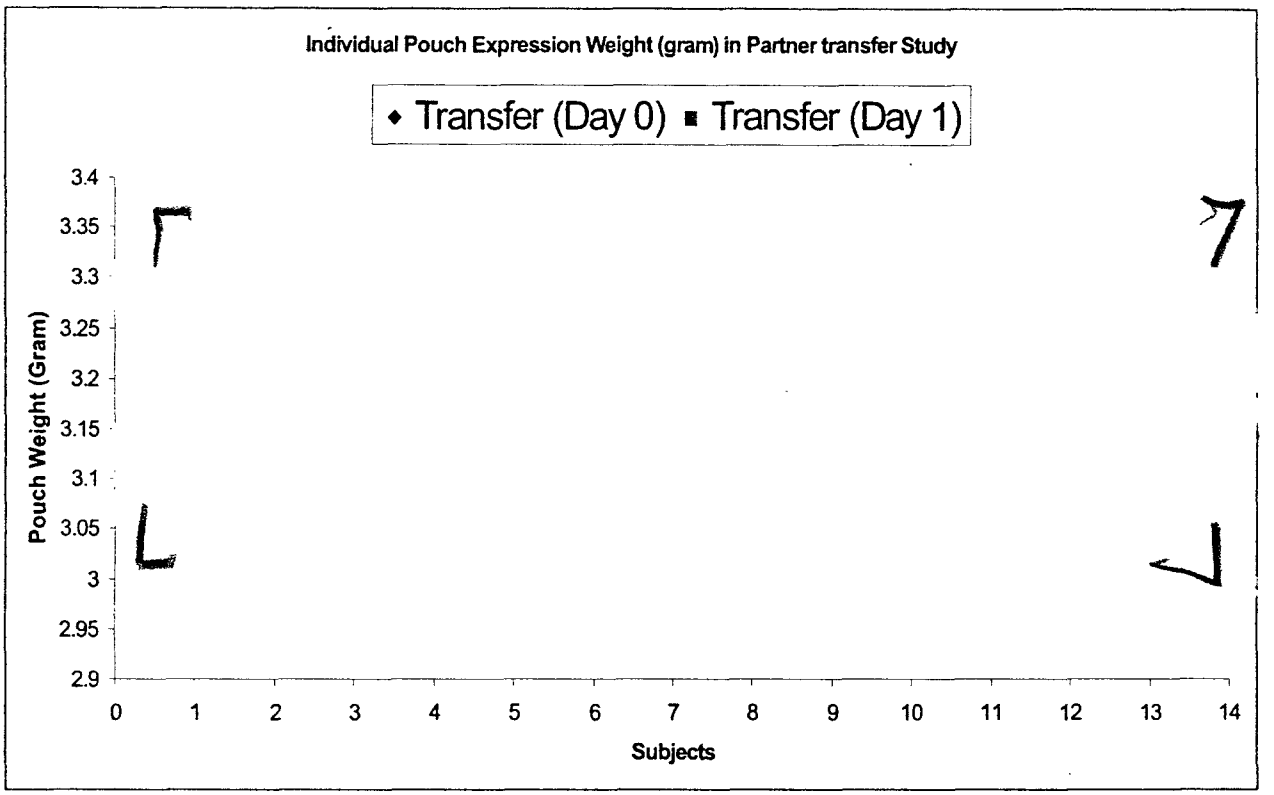


Figure A16.



APPEARS THIS WAY
ON ORIGINAL

14.2.3 Pouch Expression Weight Analysis

Table 14.2.3-1. Descriptive statistics of total pouch expression weights per day for all 14 female subjects

Subject/ID	---- Pouch Expression Weights (g) ---- Day 0	Day 1	Change From Day 0 to Day 1
01F			
04F			
07F			
09F			
12F			
13F			
18F			
22F			
24F			
27F			
28F			
33F			
34F			
36F			
Mean	3.204	3.170	-0.033
SD	0.116	0.120	0.133
%CV	3.606	3.798	-397.752
Median	3.254	3.182	-0.050
Minimum			
Maximum			

Safety and Efficacy Assessment:

There were no major safety and efficacy issues in this study. Please see the Medical Officer's review for details.

B) Sunscreen Study:

What Are the Objectives of this Study?

- To determine the effect of sunscreen on the systemic absorption of estradiol from Estrasorb.
- To determine if Estrasorb exposure causes photosensitivity reactions.
- To determine the actual amount of Estrasorb expressed from the packaging solution. A secondary analysis concerns between-subject and within-subject variability in pouch expression.

How Was the Study Designed?

This was a 49-day study in 14 postmenopausal women to assess the effect of sunscreen on the systemic absorption of estradiol from Estrasorb. Estradiol dose was 4.35 mg per 1.74 gram of estrasorb pouch applied daily for 25 days. Two pouches were used: one was applied to the right thigh and calf and the other to the left thigh and calf. Therefore, the total daily dose was 2 x 1.74 gram (i.e., 3.48 gram) of Estrasorb which translate to 2 x 4.35 mg (i.e., 8.7 mg) estradiol. Serum hormone levels of estradiol, estrone, estrone sulfate, and FSH were determined at 15 minutes post dosing and at 1, 2, 4, 8, 12, 18, and 24 hours on Days 0, 7, 15, and 23. Upon completion of the PK studies a photosensitivity tests were performed on each subject. In addition, information on pouch content was obtained for each subject by weighing the pouches before and after expression. **Tables B1-B4** summarize the study schedule and sampling times.

When Was the Sunscreen Applied?

On Days 8 through 15, SPF15 sunscreen was applied to both thighs and calves by the subjects 10 minutes prior to Estrasorb application. On Days 16 through 23, SPF15 sunscreen was applied to both thighs and calves by the subjects 25 minutes after the start of Estrasorb application. On Day 24, subjects applied Estrasorb to both thighs and calves. Subjects were then exposed to direct sunlight for 10 minutes at 10 AM. Subjects were observed for 2 hours for any photosensitivity reactions. If weather conditions did not permit sun exposure on Day 24 at 10:00 AM then subjects would report to the study site daily for blood draw and dosing until such time as weather conditions permitted sun exposure at 10:00 AM.

Results:

- The data are shown in **Figure B1-14** and **Tables B5-B12**.
- Sunscreen had some effect on serum levels of estradiol, estrone, or estrone sulfate (**Figures B1-B3, and Tables B5-B8**).
- During trough day periods, the mean Cmax (± SD) for estradiol was 4.93 (± 3.54), 5.61 (± 3.15), and 6.18 (± 3.89) ng/ml on Days 0-7, 8-15, and 16-23, respectively. There was 13% and 25% increase in Cmax on Days 8-15 and Days 16-23 when sunscreen was used compared to Days 0-7 when no sunscreen was used, respectively (**Table B5**).
- For AUC, the mean (± SD) for estradiol was 18.43 (± 12.24), 25.52 (± 15.88), and 26.92 (± 16.33) ng.h/ml on Days 0-7, 8-15, and 16-23, respectively. There was 38% and 46% increase

in exposure as measured by AUC on Days 8-15 and Days 16-23 when sunscreen was used compared to Days 0-7 when no sunscreen was used, respectively (**Table B5**)

- The observed increase in the exposure could not be completely associated with the use of sunscreen. The plasma level of estrasorb may have not yet been completely at steady state especially on Days 8-15. There was only 5% increase in exposure between Days 16-23 (AUC = 26.92 ng.h/ml) compared to Days 8-15 (AUC=25.52 ng.h/ml) (**Table B5**). Therefore, the steady state could have been achieved on Days 16-23, but not on Days 8-15.
- The mean (± SD) estradiol Cmax was 2.5 ± 2.11, 5.54 ± 3.54, 9.72 ± 10.60, and 8.44 ± 6.07, on days 0, 7, 15, and 23, respectively (**Table B6**). On the same days, the mean (± SD) estradiol AUC $_{(0\text{-}24\ h)}$, was 38.91 ± 32.27, 92.35 ± 57.63, 134.75 ± 107.06, and 115.22 ± 68.70 on days 0, 7, 15, and 23, respectively. It should be noted that there was a high variability in the data (**Table B**). A similar trend for estrone and estrone sulfate.
- As expected, there was a reduction in FSH level as a result of increase in estradiol level (**Figure B4 and Table B9**).
- A similar pattern of increase in exposure was noted for etsrone and estrone sulfate.
- Overall, it can be concluded that sunscreen may have some effect o the absorption of estradiol in patients applying Estrasorb. Considering the potential benefits of the sunscreen to sensitive skin females and the prevention of sunburn, it is hard to justify that sunscreen should be avoided in patients applying Estrasorb.
- No evidence of photosensitivity reaction was noted after direct solar exposure (see Medical Officer's review).
- No evidence of safety related issues (see Medical Officer's Review).
- In terms of pouch expression weight analysis, there was a remarkably consistent data throughout (**Figure B5 and Table B9**). The daily mean pouch weight was between 3.25 and 3.31 grams with SD between 0.05 and 0.11 grams. These daily means weights were 4.89% and 6.61% below the nominal weight, respectively. The data were similar to that seen in the transfer study. For comparison, **Figure B6** shows pouch wights from the three studies, sunscreen, partner transfer, and pouch expression study for lot # NS2.

What is the Effect of [redacted]

Does the Presence of [redacted] in Estrasorb Affect the Absorption of Estradiol?

What is the Rational?

The formulation used in sunscreen study was found to contain [redacted] (Lot # NS2, see chemistry review). However, the formulation used in study E98-1 (lot # 0038) is assumed to be free from [redacted] Since no materials are available for the formulation used in study E98-1, not formal bioequivalence study can be conducted. Study E98-1 has been reviewed in the original NDA (see **Appendix III**).

Briefly, study E98-1 was a small (n=10) preliminary parallel arms PK study after a single dose of 7.5 mg estradiol applied to one thigh or split to both thighs. The study was two groups, each consists of five females: four subjects received active drug and one subject received placebo. In one group, the dose was applied once daily for 8 days to a single site (anterior thigh) as 3 gram (3.2 ml) Estrasorb equivalent to 7.5 mg estradiol. In the other group the same dose was split as 1.5 g (1.6 ml) to each of the anterior thighs (four subjects active and one subject placebo). For PK studies blood samples were collected on Days 1 and 8 for estradiol, estrone, and estrone sulfate levels at the following time points: 0 (predose), 0.5, 1, 2, 4, 6, 8, 12, 18, and 24 hours post dose.

Data Analysis and Interpretation:

- For comparison, Day 1 data was used from both studies.
- The comparative data for Cmax and AUC for the estradiol estrone, and estrone sulfate were summarized by the sponsor (**Tables B10-B12**). The focus will be on estradiol levels and on Day 1 data only. The individual data and estradiol plasma profiles from study E98-1 and sunscreen are shown in **Figures B7-B14.** Although, there was a high variability in estradiol profiles between subjects and studies, overall the data is comparable after the 1st dose and the 8th dose for sunscreen and E98-1 studies (**Figures B11-B14**). This indicates that there is no obvious effect of [redacted] on the absorption of estradiol.
- The mean (± SD) of estradiol Cmax on Day 1 was 3.45 ng/dl (± 2.66) and 2.5 ng/dl (± 2.11) for study E98-1 and sunscreen (study # E2002-2), respectively. For exposure, however, the mean (± SD) of estradiol AUC on Day 1 was 37.3 ng.h/dl (± 25.1) and 38.91 ng.h/dl (± 32.27) for study E98-1 and sunscreen (study # E2002-2), respectively (**Table B10**).
- The residual plots, however, for the two sites application from studies E98-1 and sunscreen shows some trend that estradiol plasma level from study E98-1 is slightly higher than that found in sunscreen study (**Figures B7-B9**). Therefore, these data are inconclusive, but it provides some indications for the comparability between the two formulations. In other word, we may be able to conclude that the data from both formulations are within the acceptable range and variability. However, we can not conclude that the two formulations are bioequivalent. In addition, we cannot utilize this data set to perform a standard tests and analysis to establish the bioequivalency between the two formulations for reasons, including but not limited to the following:

1. Unequal number of subjects in each study: n= 4 for E98-1 and n=14 for sunscreen
2. Both studies were conducted at different times separated by years.
3. Both studies used different subject population.
4. The design of each study is different.
5. Both studies were conducted at different conditions.
6. The plasma samples were analyzed at different analytical conditions.

Therefore, the reported data and analysis only provide a rough or crude way to indicate that estradiol plasma level from the two formulations falls within the same range.

Furthermore, the serum level (Cmax) on Day 8 in sunscreen and E98-1 (**Table B10**) studies is approximately 5.5 ng/dl which is slightly lower than the trough concentration at Week 2 (~8 ng/dl) in the pivotal Phase III study (#E99-1, **Table B10**, see also **Appendix II, individual data**).

Summary:

- Sunscreen may exhibit some effect on the absorption of estradiol from Estrasorb. The observed in increase estradiol Cmax (13% to 25%) and the AUC (38% to 46%) during Days 8-23 could be attributed to the following:
  a) The effect of sunscreen or
  b) Or estradiol level did not reached the steady state. This is evidenced by the fact that the overall exposure on Days 16-23 was increased by only 5%-10% from Days 8-15.
  c) Or Both
- Whatever the reason or reasons may be, such an increase in estradiol level may only be a transit for a short period of time. In real life situations, patients would be using sunscreen for a short period of time during the summer. Therefore, the risk/benefit ratio for the use of sunscreen to prevent sunburn and the risk of transit increase in estradiol level should be considered (see also Medical Officer's review).
- The study shows no evidence of photosensitivity reactions (see also Medical Officer's review).
- The formulations used in E98-1 study and in the current sunscreen study produce estradiol levels within the acceptable range of variability. However, it should be noted that the levels reported from study E98-1 tends to be higher than that reported in the sunscreen study. The set of data cannot be utilized to establish bioequivalency between the two formulations. Therefore, it can be concluded that [redacted] may have some or no effect on the absorption of estradiol from Estrasorb. The answer to this question will remains inconclusive, unless the sponsor performs a standard BE study using two formulations with and without [redacted] The rational for such a study has to be justified based on the available clinical data.

Conclusions:

- The sponsor provided adequate study to investigate the effect of sunscreen on the absorption

of estradiol from Estrasorb.

- The sunscreen appears to have some effect on the absorption of estradiol. However, the observed small increase in estradiol exposure could be attributed to the fact that the steady state level has not been achieved during this study.
- It is recommended to consider the potential use of sunscreen to prevent sunburns in sensitive skin patients and the possible transit increase in estradiol level.
- In terms of skin reaction, the study did not show any evidence (see also Medical Officer's review).

Comments to Labeling:

The label should include a statement or statements to indicate the following:

A prolong use of sunscreen may potentially increase estradiol level

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Table B1. Study design Overview

	Pre-Dosing		Dosing							
Study Day **Assessment**	Day -24	Day -11	Day 0	Days 1-6	Day 7	Days 8-14	Day 15	Days 16-22	Day 23	Day 24
Signed informed consent	x									
Eligibility determined		x								
Eligibility Summary Form		x								
Medical history	x									
Vital signs	x		x	x	x	x	x	x	x	x
Weight	x		x		x		x		x	
EKG	x									
Hematology	x									x
Serum chemistries	x									x
Urinalysis	x									
Pelvic exam, PAP smear, mammogram	x									
Urinary HCG	x									x
Serum estradiol	x		x	x	x	x	x	x	x	x
Serum estrone	x		x	x	x	x	x	x	x	x
Serum estrone sulfate	x		x	x	x	x	x	x	x	x
FSH	x		x	x	x	x	x	x	x	x
Serum total testosterone	x									
Serum free testosterone	x									
Dihydrotestosterone	x									
Concomitant medications	x		x	x	x	x	x	x	x	x
Adverse events	x		x	x	x	x	x	x	x	x
Dermal assessment			x		x		x		x	x

Day -24 = Screening Visit 1

Table B2. Schedule of Effectiveness and Safety Assessment

	Pre-dosing	Dosing							
Study Day **Assessment**	Day -24	Day 0	Days 1-6	Day 7	Days 8-14	Day 15	Days 16-22	Day 23	Day 24
SAFETY:									
Physical exam	x								
Vital signs	x	x	x	x	x	x	x	x	x
Weight	x	x		x		x		x	
Clinical laboratory	x								x
Concomitant medications	x	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x
Dermal assessment		x		x		x		x	x
EFFECTIVENESS:									
Serum estradiol	x	x	x	x	x	x	x	x	x
Serum estrone	x	x	x	x	x	x	x	x	x
Serum estrone sulfate	x	x	x	x	x	x	x	x	x
FSH	x	x	x	x	x	x	x	x	x
Serum total testosterone	x								
Serum free testosterone	x								
Dihydrotestosterone	x								

Screening Visit 1 = Day -24

Table B3. Overview of PK and Hormone Assessments

	Pre-dosing	Dosing							
Study Day **Assessment**	Day -24	Day 0	Days 1-6	Day 7	Days 8-14	Day 15	Days 16-22	Day 23	Day 24
Serum estradiol	x	PK	x	PK	x	PK	x	PK	x
Serum estrone	x	PK	x	PK	x	PK	x	PK	x
Serum estrone sulfate	x	PK	x	PK	x	PK	x	PK	x
FSH	x	PK	x	PK	x	PK	x	PK	x
Serum total testosterone	x								
Serum free testosterone	x								
Dihydrotestosterone	x								

Screening Visit = Day -24

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Table B4. Overview of PK and Hormone Assessments

		Hours Following Initial Exposure to ESTRASORB™ Application Site for Pharmacokinetics Analysis							
Study day	ESTRASORB ™ dosing time	0 hrs	1 hrs	2 hrs	4 hrs	8 hrs	12 hrs	18 hrs	24 hrs
0	7:45 AM	8:00 AM	9:00 AM	10:00 AM	12 noon	4:00 PM	8:00 PM	2 AM Day 1	8:00 AM Day 1
7	7:45 AM	8:00 AM	9:00 AM	10:00 AM	12 noon	4:00 PM	8:00 PM	2 AM Day 8	8:00 AM Day 8
15	7:45 AM [7:35 AM sunscreen]	8:00 AM	9:00 AM	10:00 AM	12 noon	4:00 PM	8:00 PM	2 AM Day 16	8:00 AM Day 16
23	7:45 AM [8:10 AM sunscreen]	8:00 AM	9:00 AM	10:00 AM	12 noon	4:00 PM	8:00 PM	2 AM Day 24	8:00 AM Day 24

Figure B1

Fig 14.2.1-5. Pharmacokinetic serum profile estradiol concentration (ng/dL) - mean concentrations of all subjects (N=14)

Study Periods: Screening (Day -24), ESTRASORB only (Days 0-7), Sunscreen then ESTRASORB (Days 8-15), ESTRASORB then sunscreen (Days 16-23), ESTRASORB then sunlight exposure (Day 24)

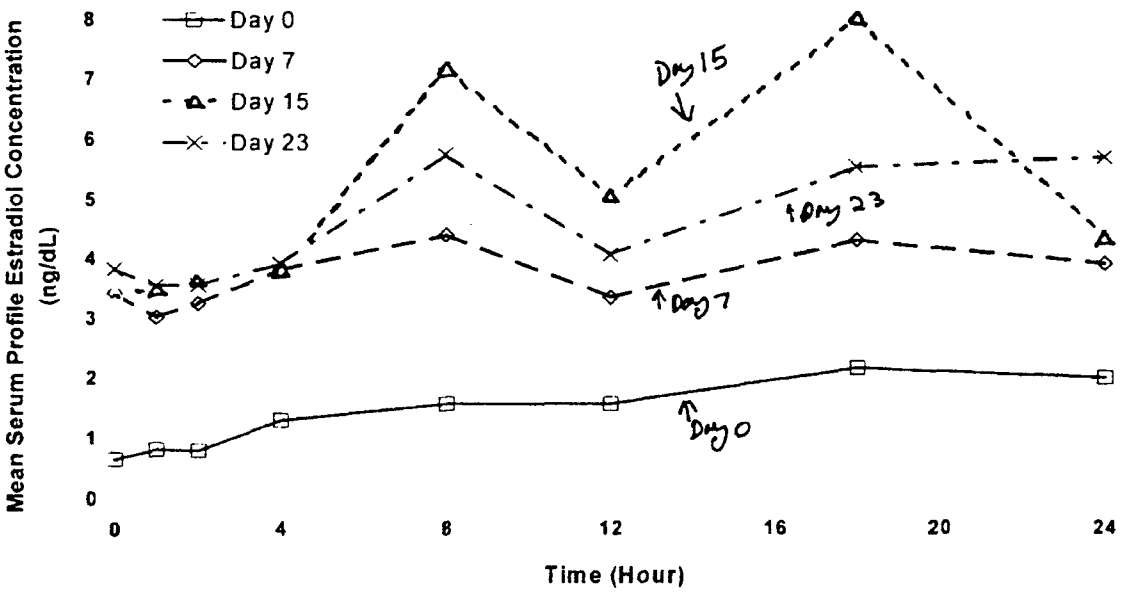

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Figure B2

Fig 14.2.1-10. Pharmacokinetic serum profile estrone concentration (ng/dL) - mean concentrations of all subjects (N=14)

Study Periods: Screening (Day -24), ESTRASORB only (Days 0-7), Sunscreen then ESTRASORB (Days 8-15), ESTRASORB then sunscreen (Days 16-23), ESTRASORB then sunlight exposure (Day 24)

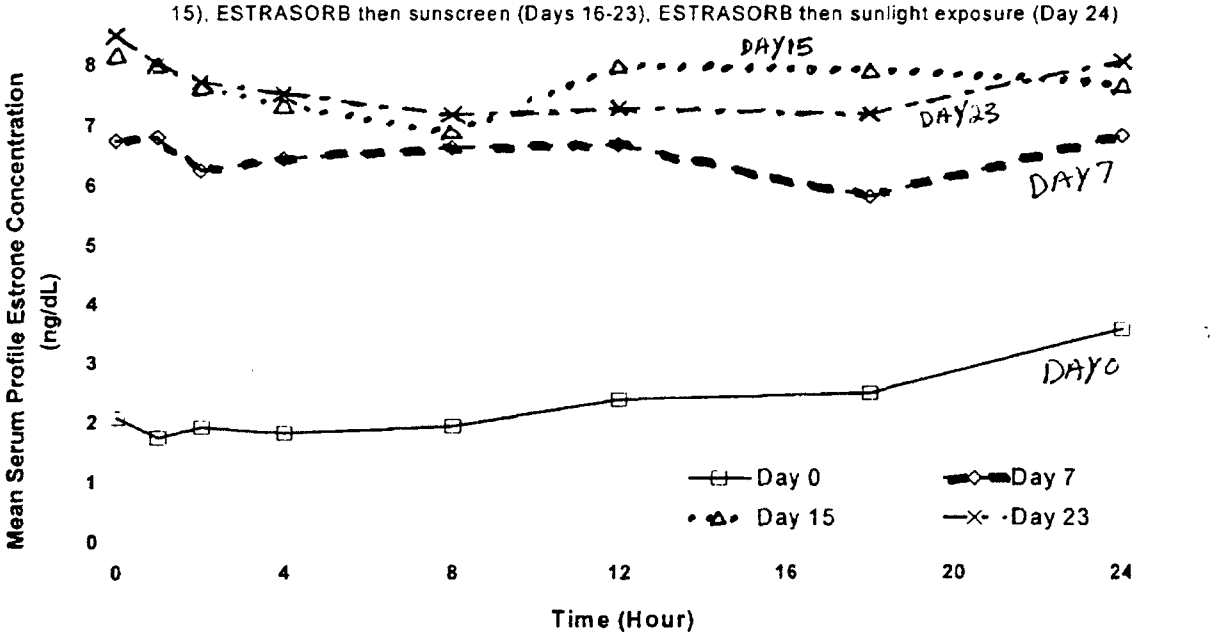

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Figure B3

Fig 14.2.1-15. Pharmacokinetic serum profile estrone sulfate concentration (ng/dL) - mean concentrations of all subjects (N=14)

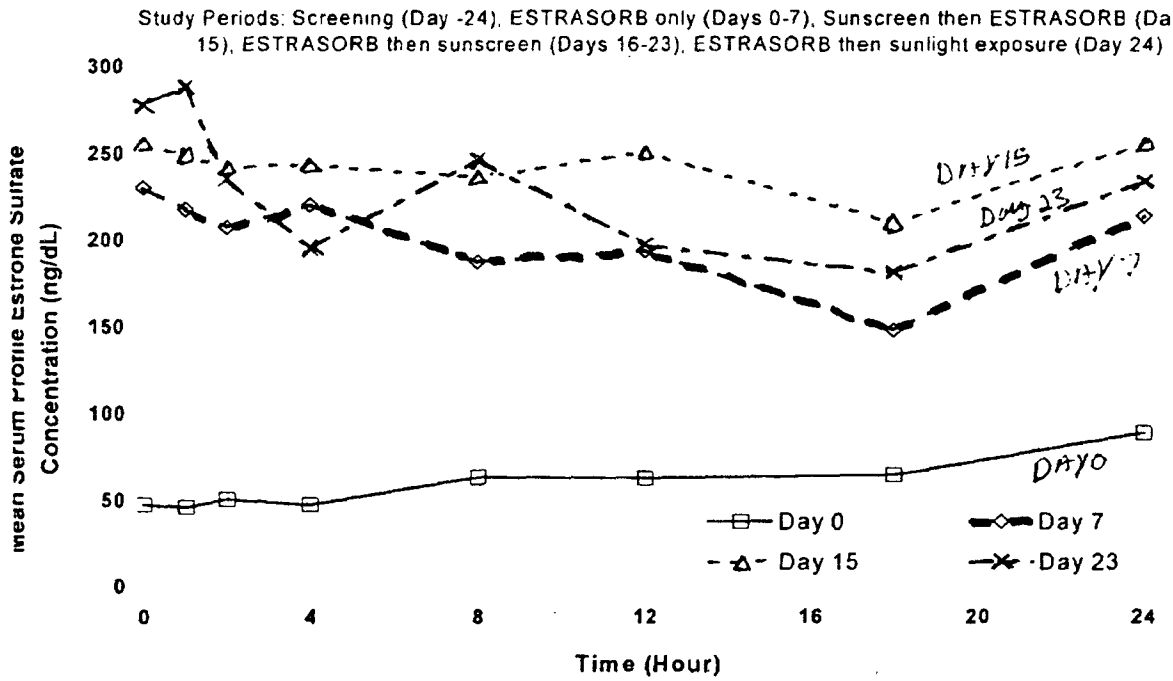

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Figure B4

Fig 14.2.1-20. Pharmacokinetic serum profile FSH concentration (mIU/mL) - mean concentrations of all subjects (N=14)

Study Periods: Screening (Day -24), ESTRASORB only (Days 0-7), Sunscreen then ESTRASORB (Days 8-15), ESTRASORB then sunscreen (Days 16-23), ESTRASORB then sunlight exposure (Day 24)

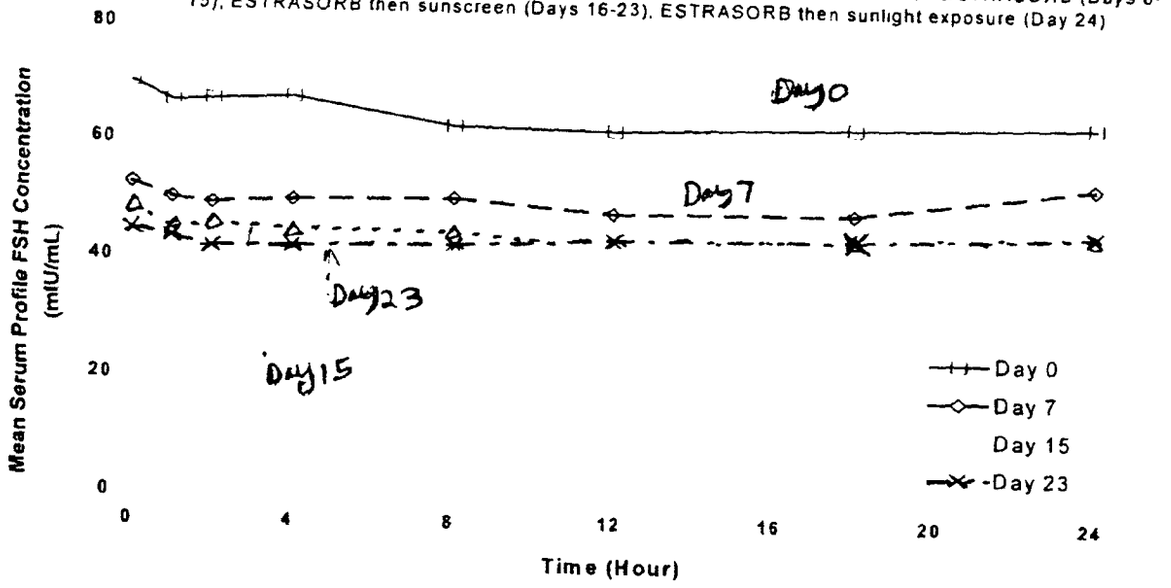

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Table B5

Table 14.2.2-17. Summary of pharmacokinetic parameters on trough day periods for all subjects (N=14)

Hormone	PK Parameter (Mean ± SD)	Trough Day Periods		
		Days 0-7	Days 8-15	Days 16-23
Estradiol	T_{max} (hr)	5.57 ± 1.55	3.21 ± 2.46	3.00 ± 2.39
	C_{max} (ng/dL)	4.93 ± 3.54	5.61 ± 3.15	6.18 ± 3.89
	C_{min} (ng/dL)	0.61 ± 0.73	2.28 ± 1.56	2.41 ± 1.38
	$C_{average}$ (ng/dL)	2.63 ± 1.75	3.65 ± 2.27	3.85 ± 2.33
	AUC (ng-d/dL)*	18.43 ± 12.24	25.52 ± 15.88	26.92 ± 16.33
Estrone	T_{max} (hr)	5.36 ± 1.86	3.14 ± 2.88	2.86 ± 2.63
	C_{max} (ng/dL)	7.49 ± 4.61	9.42 ± 5.02	11.09 ± 7.15
	C_{min} (ng/dL)	1.91 ± 0.86	5.63 ± 3.89	5.75 ± 3.46
	$C_{average}$ (ng/dL)	5.12 ± 2.88	7.44 ± 4.41	7.99 ± 5.11
	AUC (ng-d/dL)	35.83 ± 20.18	52.08 ± 30.86	55.96 ± 35.74
Estrone Sulfate	T_{max} (hr)	5.36 ± 1.39	4.29 ± 2.09	3.36 ± 2.82
	C_{max} (ng/dL)	256.79 ± 192.17	325.57 ± 225.35	370.71 ± 307.66
	C_{min} (ng/dL)	46.07 ± 27.11	186.07 ± 133.28	189.07 ± 151.65
	$C_{average}$ (ng/dL)	166.66 ± 120.31	247.22 ± 175.21	255.52 ± 205.85
	AUC (ng-d/dL)	1166.6 ± 842.20	1730.6 ± 1226.5	1788.6 ± 1441.0
FSH	T_{max} (hr)	0.64 ± 1.39	2.57 ± 2.79	3.29 ± 1.98
	C_{max} (mIU/mL)	71.93 ± 20.38	57.36 ± 16.88	50.43 ± 15.65
	C_{min} (mIU/mL)	48.50 ± 12.85	41.57 ± 9.99	40.00 ± 13.00
	$C_{average}$ (mIU/mL)	57.58 ± 15.10	48.09 ± 12.77	45.49 ± 13.65
	AUC (mIU-d/mL)	403.04 ± 105.71	336.64 ± 89.41	318.46 ± 95.55

*Time unit in AUC is day.

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Table 6.

Table 14.2.1-21. Summary of profile pharmacokinetic parameters on Days 0, 7, 15 and 23 for all subjects (N=14)

Hormone	PK Parameter (Mean ± SD)	Profiling Day			
		Day 0	Day 7	Day 15	Day 23
Estradiol	T_{max} (hr)	11.07 ± 9.19	9.29 ± 8.47	10.14 ± 7.16	11.71 ± 8.15
	C_{max} (ng/dL)	2.50 ± 2.11	5.54 ± 3.56	9.72 ± 10.60	8.44 ± 6.07
	C_{min} (ng/dL)	0.50 ± 0.51	2.44 ± 1.81	2.62 ± 1.83	2.73 ± 1.54
	$C_{average}$ (ng/dL)	1.62 ± 1.34	3.85 ± 2.40	5.61 ± 4.46	4.80 ± 2.86
	$AUC_{(0-24h)}$ (ng-h/dL)*	38.91 ± 32.27	92.35 ± 57.63	134.75 ± 107.06	115.22 ± 68.70
Estrone	T_{max} (hr)	17.57 ± 9.83	12.57 ± 10.00	9.79 ± 10.33	9.21 ± 9.63
	C_{max} (ng/dL)	3.82 ± 1.63	8.15 ± 4.20	9.60 ± 5.11	10.51 ± 8.34
	C_{min} (ng/dL)	1.16 ± 0.90	5.09 ± 3.30	5.86 ± 3.86	5.79 ± 3.30
	$C_{average}$ (ng/dL)	2.32 ± 1.16	6.41 ± 3.33	7.63 ± 4.10	7.44 ± 5.39
	$AUC_{(0-24h)}$ (ng-h/dL)	55.74 ± 27.78	153.84 ± 79.91	183.11 ± 98.47	178.57 ± 129.34
Estrone Sulfate	T_{max} (hr)	19.43 ± 9.26	8.00 ± 7.95	13.36 ± 9.68	9.86 ± 9.95
	C_{max} (ng/dL)	95.00 ± 48.40	263.57 ± 179.52	296.79 ± 188.50	358.14 ± 294.22
	C_{min} (ng/dL)	41.57 ± 24.40	141.50 ± 83.94	191.00 ± 131.18	163.64 ± 120.69
	$C_{average}$ (ng/dL)	62.56 ± 28.44	188.90 ± 117.50	237.01 ± 154.92	212.66 ± 143.29
	$AUC_{(0-24h)}$ (ng-h/dL)	1501.5 ± 682.52	4533.6 ± 2820.1	5688.3 ± 3718.1	5104.0 ± 3438.9
FSH	T_{max} (hr)	4.43 ± 7.75	12.29 ± 11.45	5.43 ± 7.54	9.64 ± 10.26
	C_{max} (mIU/mL)	73.57 ± 20.12	55.79 ± 16.19	51.79 ± 16.13	49.57 ± 17.79
	C_{min} (mIU/mL)	58.07 ± 14.48	45.43 ± 14.03	39.57 ± 12.02	38.21 ± 13.26
	$C_{average}$ (mIU/mL)	63.88 ± 16.62	49.99 ± 14.46	44.14 ± 13.12	43.14 ± 14.02
	$AUC_{(0-24h)}$ (mIU-h/mL)	1533.2 ± 398.87	1199.7 ± 347.11	1059.3 ± 314.82	1035.4 ± 336.56

*Time unit in AUC is hour.

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Table B7

Table 14.2.1-22. Geometric means, geometric mean fold ratios and paired t-test findings in profile hormone $AUC_{(0\text{-}24h)}$ on Days 0, 7, 15 and 23 for all subjects (N=14)

PK Parameter			Serum Hormone			
			Estradiol	Estrone	Estrone Sulfate	FSH
Geometric Means	$AUC_{(0\text{-}24h)}$**	Day 0	26.96	48.71	1350.16	1485.57
		Day 7	76.54	137.61	3749.47	1155.87
		Day 15	102.33	162.72	4606.24	1014.47
		Day 23	98.83	148.97	4037.24	979.99
	Fold Ratio in $AUC_{(0\text{-}24h)}$ from	Day 0 to Day 7	2.84	2.83	2.78	0.78
		Day 0 to Day 15	3.80	3.34	3.41	0.68
		Day 0 to Day 23	3.67	3.06	2.99	0.66
		Day 7 to Day 15	1.34	1.18	1.23	0.88
		Day 7 to Day 23	1.29	1.08	1.08	0.85
		Day 15 to Day 23	0.97	0.92	0.88	0.97
Pair-wise Comparison p-value*	$AUC_{(0\text{-}24h)}$	Day 0 to Day 7	<0.0001	<0.0001	0.0002	<0.0001
		Day 0 to Day 15	0.0015	<0.0001	0.0003	<0.0001
		Day 0 to Day 23	<0.0001	0.0015	0.0005	<0.0001
		Day 7 to Day 15	0.0518	0.0044	0.0254	0.0006
		Day 7 to Day 23	0.1785	0.1449	0.1751	0.0017
		Day 15 to Day 23	0.3645	0.7084	0.1209	0.3099
	Fold Ratio in $AUC_{(0\text{-}24h)}$	Day 0 to Day 7	<0.0001	<0.0001	<0.0001	<0.0001
		Day 0 to Day 15	<0.0001	<0.0001	<0.0001	<0.0001
		Day 0 to Day 23	<0.0001	<0.0001	<0.0001	<0.0001
		Day 7 to Day 15	0.0149	0.0030	0.0071	0.0022
		Day 7 to Day 23	0.0859	0.3485	0.4009	0.0049
		Day 15 to Day 23	0.8045	0.2116	0.0975	0.1406

*Paired t-test

**Units for $AUC_{(0\text{-}24h)}$: estradiol, estrone and estrone sulfate – ng-h/dL; FSH – mIU-h/mL

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Table B8

Table 14.2.2-18. Geometric means, geometric mean fold ratios and paired t-test findings in trough hormone AUC and C_{max} outcomes for various study periods for all subjects (N=14)

PK Parameter				Serum Hormone			
				Estradiol	Estrone	Estrone Sulfate	FSH
AUC	Geometric Mean	AUC**	Days 0-7	14.67	31.16	931.42	390.50
			Days 8-15	21.18	44.55	1333.22	325.36
			Days 16-23	22.67	47.79	1344.31	304.02
		Fold Ratio in AUC from	Days 0-7 to Days 8-15	1.44	1.43	1.43	0.83
			Days 0-7 to Days 16-23	1.54	1.53	1.44	0.78
			Days 8-15 to Days 16-23	1.07	1.07	1.01	0.93
	Pair-wise comparison p-value*	AUC	Days 0-7 to Days 8-15	0.0002	0.0005	0.0012	<0.0001
			Days 0-7 to Days 16-23	0.0015	0.0015	0.0063	0.0001
			Days 8-15 to Days 16-23	0.5698	0.1253	0.5464	0.0606
		Fold Ratio in AUC	Days 0-7 to Days 8-15	<0.0001	0.0005	<0.0001	<0.0001
			Days 0-7 to Days 16-23	0.0001	0.0004	0.0002	0.0002
			Days 8-15 to Days 16-23	0.3476	0.1791	0.8632	0.0434
C_{max}	Geometric Mean	C_{max}***	Days 0-7	3.85	6.46	196.78	69.33
			Days 8-15	4.68	8.45	253.26	55.16
			Days 16-23	5.05	9.46	278.66	48.08
		Fold Ratio in C_{max} from	Days 0-7 to Days 8-15	1.22	1.31	1.29	0.80
			Days 0-7 to Days 16-23	1.31	1.46	1.42	0.69
			Days 8-15 to Days 16-23	1.08	1.12	1.10	0.87
	Pair-wise Comparison p-value*	C_{max}	Days 0-7 to Days 8-15	0.2038	0.0015	0.0015	<0.0001
			Days 0-7 to Days 16-23	0.0354	0.0114	0.0039	<0.0001
			Days 8-15 to Days 16-23	0.3835	0.1884	0.1613	0.0026
		Fold Ratio in C_{max}	Days 0-7 to Days 8-15	0.0525	0.0005	0.0004	<0.0001
			Days 0-7 to Days 16-23	0.0164	0.0011	<0.0001	<0.0001
			Days 8-15 to Days 16-23	0.4085	0.1665	0.1096	0.0027

*Paired t-test **Units for AUC: estradiol, estrone and estrone sulfate – ng-d/dL; FSH – mIU-d/mL

*** Units for C_{max}: estradiol, estrone and estrone sulfate – ng/dL; FSH – mIU/mL

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Figure B5.

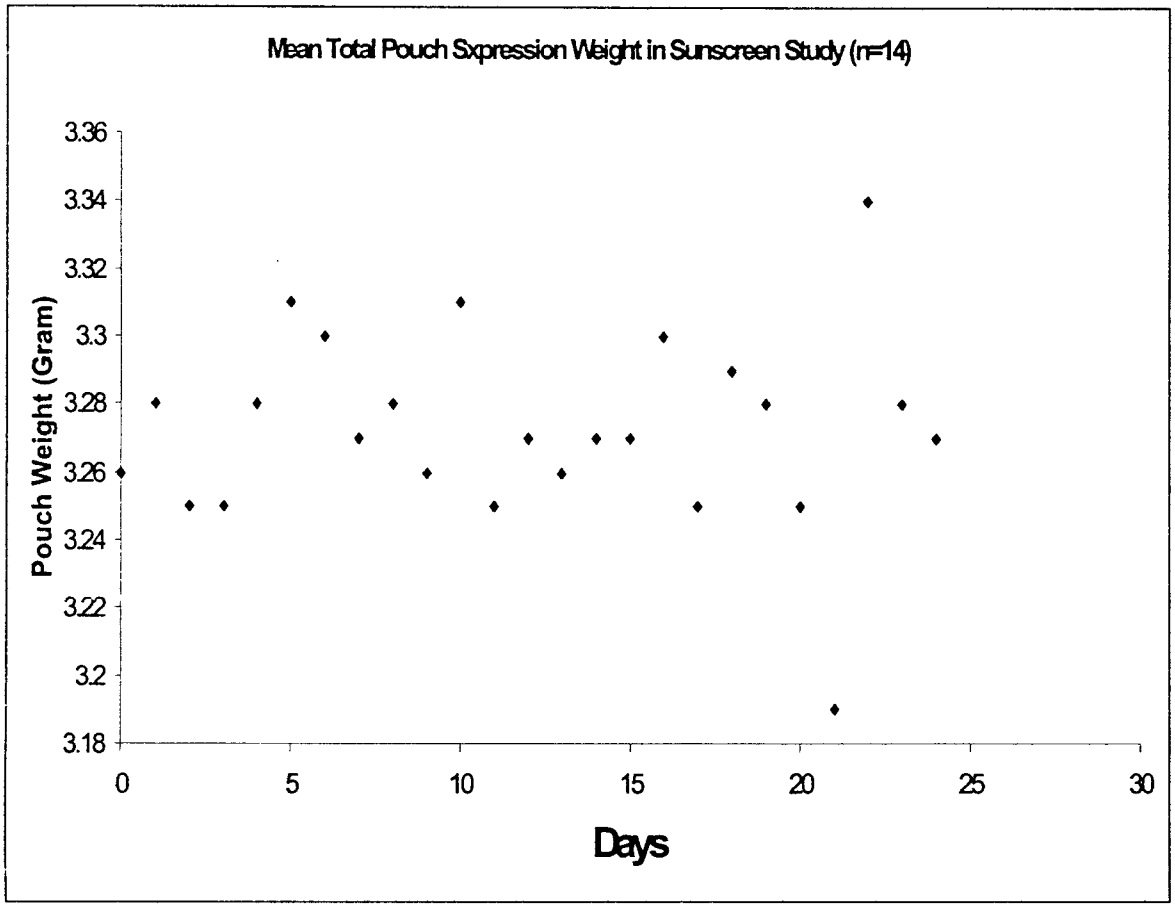
Mean Total Pouch Sxpression Weight in Sunscreen Study (n=14)
Pouch Weight (Gram)
3.36
3.34
3.32
3.3
3.28
3.26
3.24
3.22
3.2
3.18
0
5
10
15
20
25
30
Days

Table B9.

Table 14.2.3-1. Descriptive statistics of total pouch expression weight (gram) per day for all subjects (N=14)

Study Days: Screening (Scr) Day -24, ESTRASORB only Days 0 - 7, sunscreen then ESTRASORB Days 8-15, ESTRASORB then sunscreen Days 16-23, ESTRASORB then sun exposure Day 24

	Descriptive Statistics				
Day	N	Mean	Std Dev	Median	Minimum
0	14	3.26	0.09	3.28	
1	14	3.28	0.09	3.30	
2	14	3.25	0.08	3.26	
3	14	3.25	0.09	3.27	
4	14	3.28	0.09	3.30	
5	14	3.31	0.05	3.32	
6	14	3.30	0.09	3.31	
7	13	3.27	0.10	3.30	
8	14	3.28	0.07	3.29	
9	14	3.26	0.11	3.29	
10	14	3.31	0.05	3.31	
11	14	3.25	0.10	3.27	
12	14	3.27	0.09	3.27	
13	14	3.26	0.09	3.29	
14	14	3.27	0.10	3.30	
15	14	3.27	0.09	3.28	
16	14	3.30	0.05	3.29	
17	14	3.25	0.09	3.26	
18	14	3.29	0.07	3.31	
19	14	3.28	0.05	3.29	
20	14	3.25	0.10	3.24	
21	14	3.19	0.31	3.27	
22	14	3.34	0.25	3.28	
23	14	3.28	0.09	3.30	
24	14	3.27	0.08	3.27	

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Figure B6

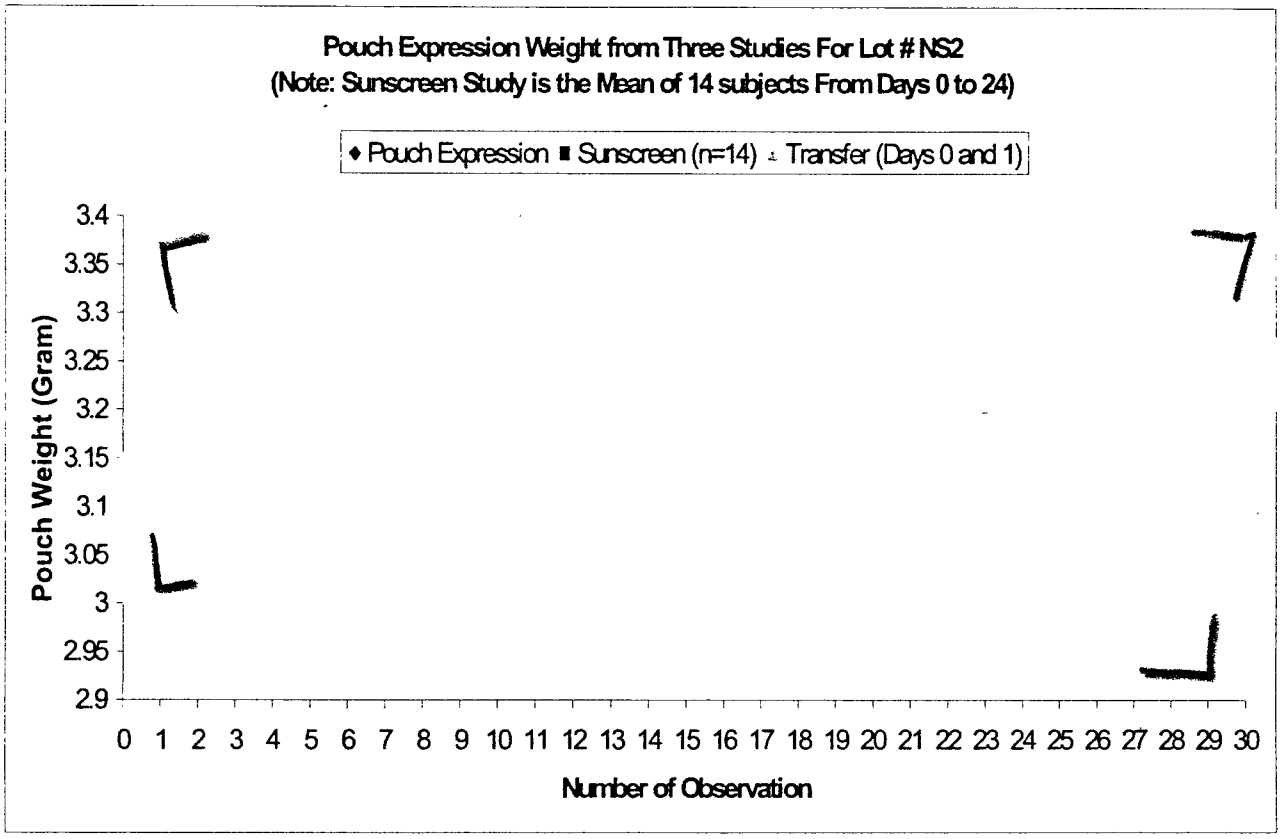

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Figure B7

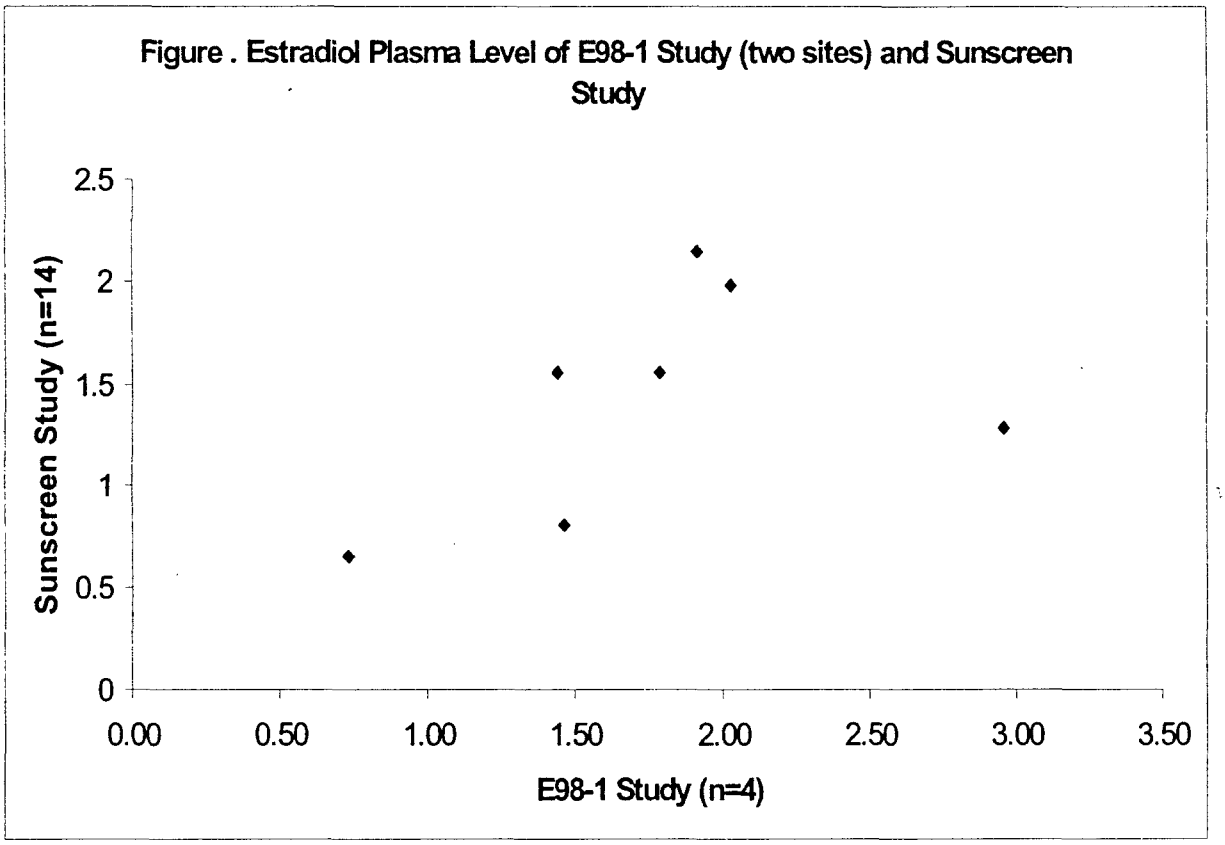

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Figure B8

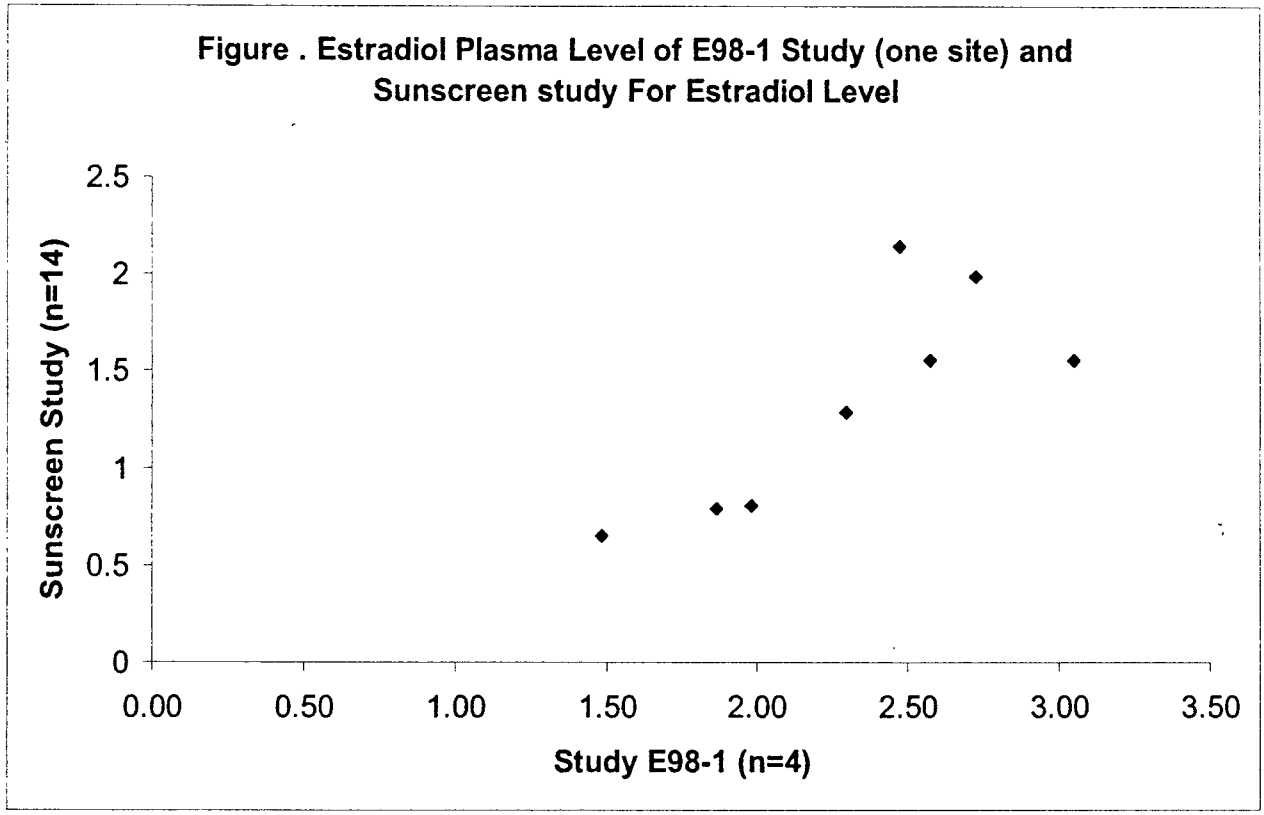

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Figure B9

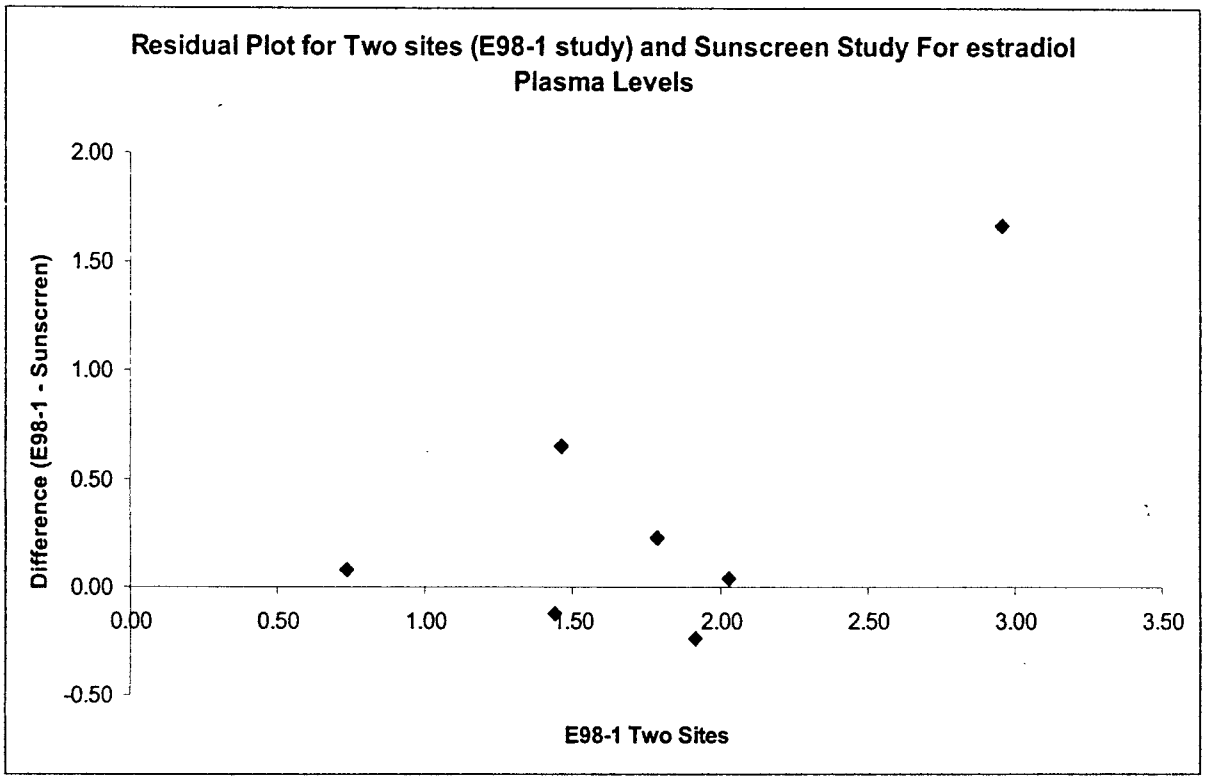

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Figure B10. Mean (±SE) of Estrone Serum Levels By Visit and Treatment Group (From Phase III Pivotal Study # E99-1, See Appendix III)

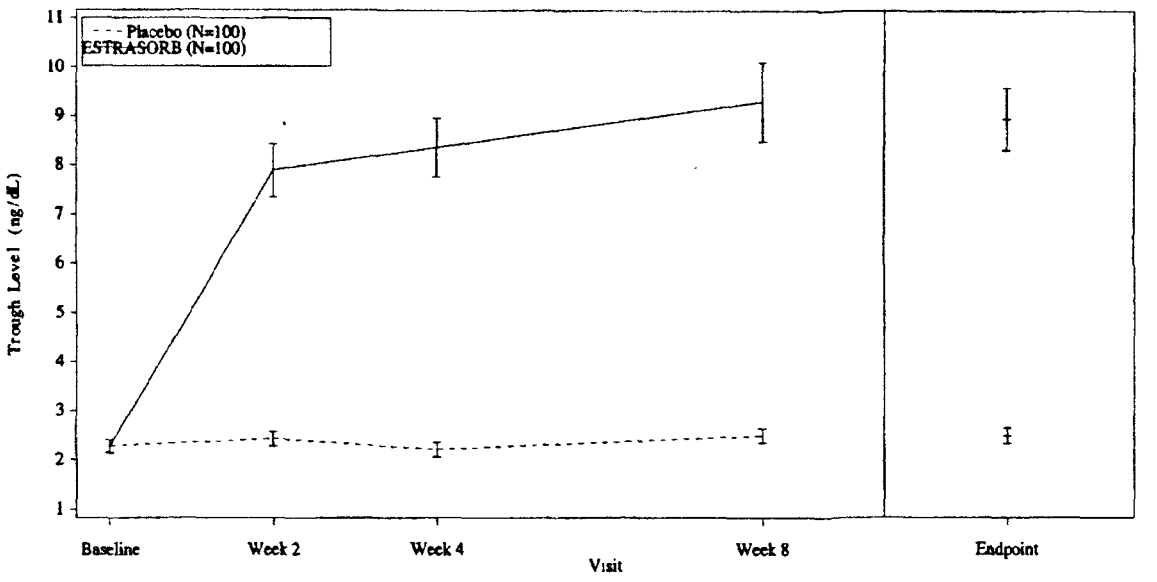

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Figure B11. Individual Estradiol Profiles for Study E98-1 (Day 1, One Site)

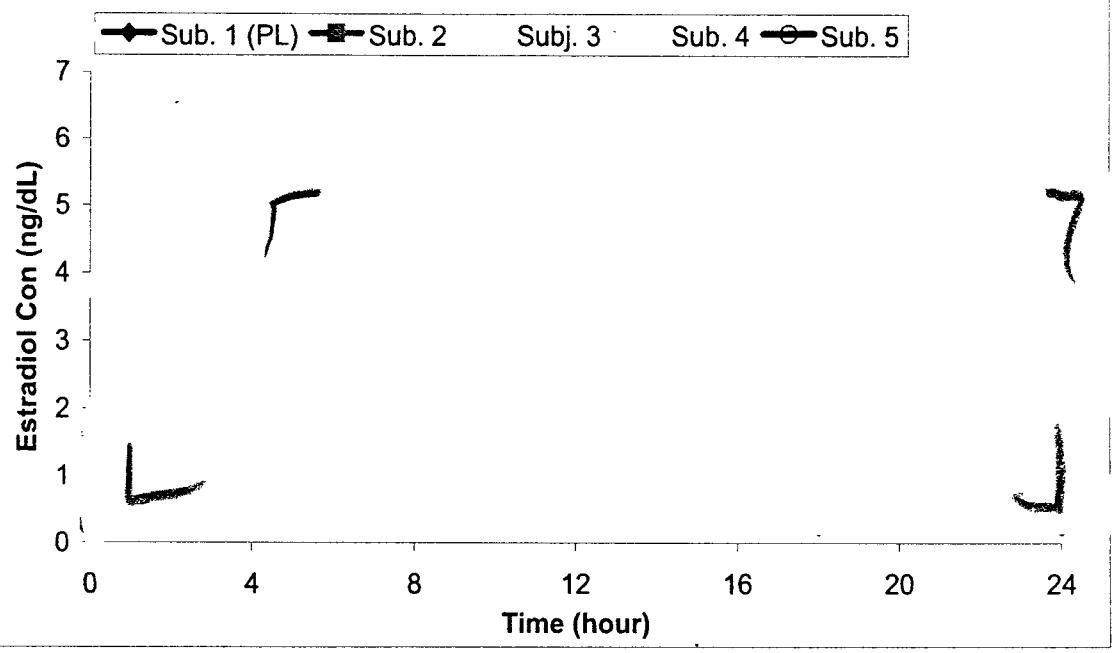

Figure B12. Individual Estradiol Profiles for Study E98-1 (Day 1, Two Sites)

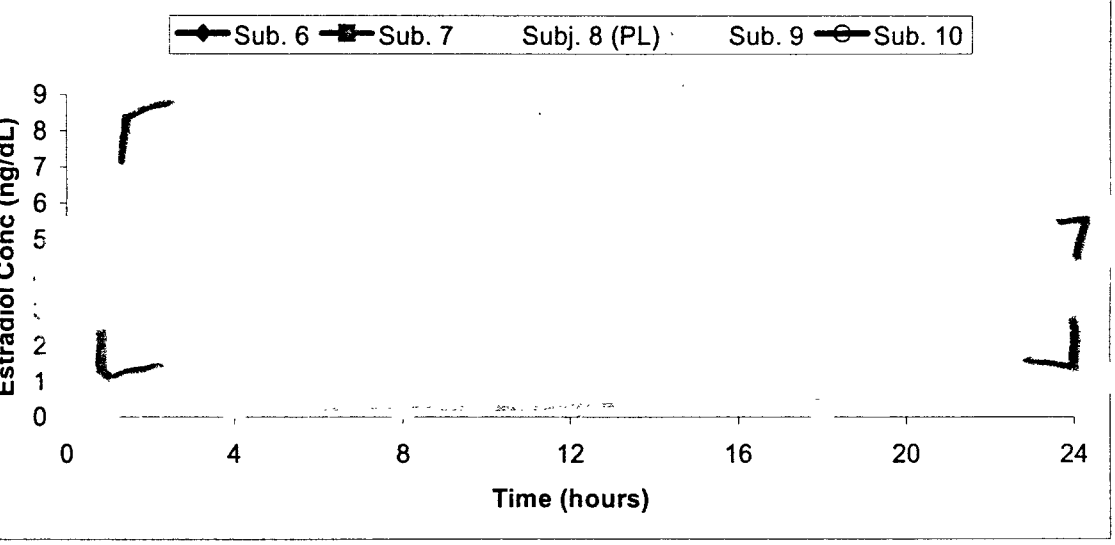

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Table B10

Table 11.4.1.1-1. Comparison of serum profile estradiol concentrations between studies E98-1 and E2002-2				
	C_{max} (ng/dL)		$AUC_{(0\text{-}24hr)}$ (ng-h/dL)	
	E98-1 (N = 4)	E2002-2 (N = 14)	E98-1 (N = 4)	E2002-2 (N = 14)
1st dose	3.45 ± 2.66	2.5 ± 2.11	37.3 ± 25.1	38.91 ± 32.27
8th dose	5.48 ± 1.40	5.54 ± 3.56	92.7 ± 28.9	92.35 ± 57.63

Table B11

Table 11.4.1.1-2. Comparison of serum profile estrone concentrations between studies E98-1 and E2002-2				
	C_{max} (ng/dL)		$AUC_{(0\text{-}24hr)}$ (ng-h/dL)	
	E98-1 (N = 4)	E2002-2 (N = 14)	E98-1 (N = 4)	E2002-2 (N = 14)
1st dose	4.48 ± 1.85	3.82 ± 1.63	82.1 ± 36.7	55.74 ± 27.78
8th dose	8.65 ± 1.94	8.15 ± 4.2	173 ± 55	153.84 ± 79.91

Table B12

Table 11.4.1.1-3. Comparison of serum profile estrone sulfate concentrations between studies E98-1 and E2002-2				
	C_{max} (ng/dL)		$AUC_{(0\text{-}24hr)}$ (ng-h/dL)	
	E98-1 (N = 4)	E2002-2 (N = 14)	E98-1 (N = 4)	E2002-2 (N = 14)
1st dose	136 ± 95	95 ± 48.4	2137 ± 1325	1502 ± 683
8th dose	320.3 ± 225.5	263.6 ± 179.5	6200 ± 4362	4534 ± 2820

C) *In vitro* **Pouch Expression:**

What is the Rational:

This expression study was conducted to demonstrate that the content of the drug product expressed in two of the package configuration (2 X 1.74 gm each, lot #NS2) is similar to the content of the drug product expressed in three of the 3-package dose configuration (3 X 1.15 gm each, lot #0038). One analyst and 12 women participated in this study. The lot # NS2 is the to-be-marketed formulation and packaging size and lot # 0038 is the clinical formulation and packaing size. No difference between the formulations, except the packaging size. Lot #NS2 has never been used in any of the clinical studies except in the partner transfer and sunscreen studies. Therefore, the pouch expression study was conducted to establish the link between the clinical batch (3 X 1.15 gram pouches, lot #0038) and the-to-e marketed batch (2 X 1.74 gram pouches lot # NS2).

How the Study Was Designed:

This was an imbalanced, factorial design with three lots, one trained analyst and 12 untrained subjects. In this study, 36 pouches were used for 1.15 gram (lot # 038 and NS1) and 24 pouches for 1.74 grams (lot # NS2). Thus, within a lot, an untrained subject expressed three pouches (two pouches for NS2 lot) and the analyst expressed 36 pouches (24 pouches for the NS2 lot). Since a pouch could be expressed only once, all amounts expressed are independent. The design crossed subject and lot (the same 13 persons, 12 subjects and one analyst, were tested for all three lots).

The focus of the analysis was on the following:

1. To demonstrate that the content of the drug product expressed in two of the packages (2 X 1.74 gram) is similar to the content of the drug product expressed in three packages (3 X 1.15 gram).
2. Is there any difference between the trained analyst and the untrained subjects in the amount expressed?
3. Is there any difference in the amount expressed in different lots by the analyst or by the subject?

What Statistical Analysis Was Used? (see also Statistical Review):

The data was subjects to various statistical analysis (please see statistical review for detail). Briefly, two types of analysis were carried out using either scaled or standardized weights. For the scaled weight analysis, the amount expressed from the pouches by the raters was scaled to reflect different nominal pouch weights. More specifically, observed weights from 2-pack NS2 lot were multiplied by a factor of 2/3 so the weight is on the same scale as those from 3-pack lot # 038 and lot # NS1. For the standardized analysis, the pouch weights were standardized by the nominal pouch contents. For the lots with three and two pouches, respectively, the standardization was relative to the nominal content of 1.15 grams (for 038 and NSI lots) and 1.74 grams (for NS2 lot).

In addition, two-way Analysis of Variance (ANO VA) was used to estimate sources of variation in this design. Among thirteen persons (one analyst, twelve subjects) and three lots, there were 192 observations.

Results:

- The summary data are shown in **Figures C1-C6 and Tables C1-C4.**
- The mean (± SD) percent underweight was 8.84% ± 2.97%. The median was 8.80%, which range from 2.84% to 22.0%. Thus, on average, the amounts expressed from the foil pouches were 0.1 grams or 9% below the nominal weights of 1.15 or 1.74 grams.
- Across all sources of variation (analyst or subject and lot) the coefficients of variation of 27.3% and 33.6% for the two transformed quantities.
- The data from the ANOVA analysis showed a significant difference at all levels (<0.0001). In terms of weight, the overall difference is <0.07 gram (**Table C1**).
- There were significant effects for both raters (subjects compared to the analyst) and for lots (the 1.15 gram lots 038 and NSl compared to the 1.74 gram lot NS2). When the data are pooled across all 12 subjects, between-lot differences were similar across raters (no significant rater by lot interaction). However, when the 12 subjects were examined individually, significant interaction terms were identified, primarily due to subjects 8 and 12.
- A few additional models were performed with subjects 8 and 12 removed as outliers. According to the Division statistician, Kate Meaker, the exclusion of subject 8 and 12 as low performers is not acceptable.
- Adjusting for analyst and subject effects, and also for the pouches' nominal content of 1.15 grams or 1.74 grams, pouches in lot NS2 were the heaviest. Pouches in lot NS2 were 0.018 and 0.0097 grams heavier than pouches in lots 038 and NS1, respectively.
- In terms of ratio, pouches in lot NS2 were 4.5% and 3.8% heavier than pouches in lots 038 and NSI, respectively.
- Based on model-estimated least-square means, underweight (differences between expressed and nominal weights) for the three lots (038, NSl and N52) were 0.123, 0.120 and 0.108, respectively. The maximum inter-lot difference was 0.015 grams.
- In terms of mean percent underweight, the three lots (038, NS I and NS2) were under-weighted by 10.7%, 10.4%, and 6.2% respectively. As the result, the largest difference among lots was 4.5% between lots 038 and NS2.
- The difference between the analyst and an average subject was 0.018 grams (1.4%) greater than subjects.
- Based on model-estimated least-square means, underweight for the two raters (12 subjects pooled and the analyst) were 0.118 and 0.100 grams, respectively.
- When 12 subjects were treated as separate individuals, the range of underweight among these twelve subjects was from — grams (for subject #12) to — grams (for subject #4). In terms of percent underweight, the analyst had a mean underweight of 7.80% compared to 9.19% for all 12 subjects combined. This ranges from 7.15% to 12.31%.
- The data obtained from this study is within the range of the data from the partner transfer and sunscreen for lot # NS2 (**Figure B6**). It should be noted, however, the data used from the

sunscreen study is the mean of 14 subjects from Days 0 to 24 (see sunscreen study).

Conclusions:

- Statistically, there was a difference between lots and rater (subject or analyst). However, quantitatively (i.e., in terms of weights), the difference may be considered small.

- There was a small differences in the amounts expressed from the two-pouch (2 X 1.74 grams) and three-pouch lots (3 x 1.15 grams).
- The amount expressed by women and the analyst appears to be identical.
- The differences in the amount between the two packages may not be clinically significant for chronically administered topical products. However, the final call should be expressed by the clinical Division (see also Medical Officer's Review).

Figure C1

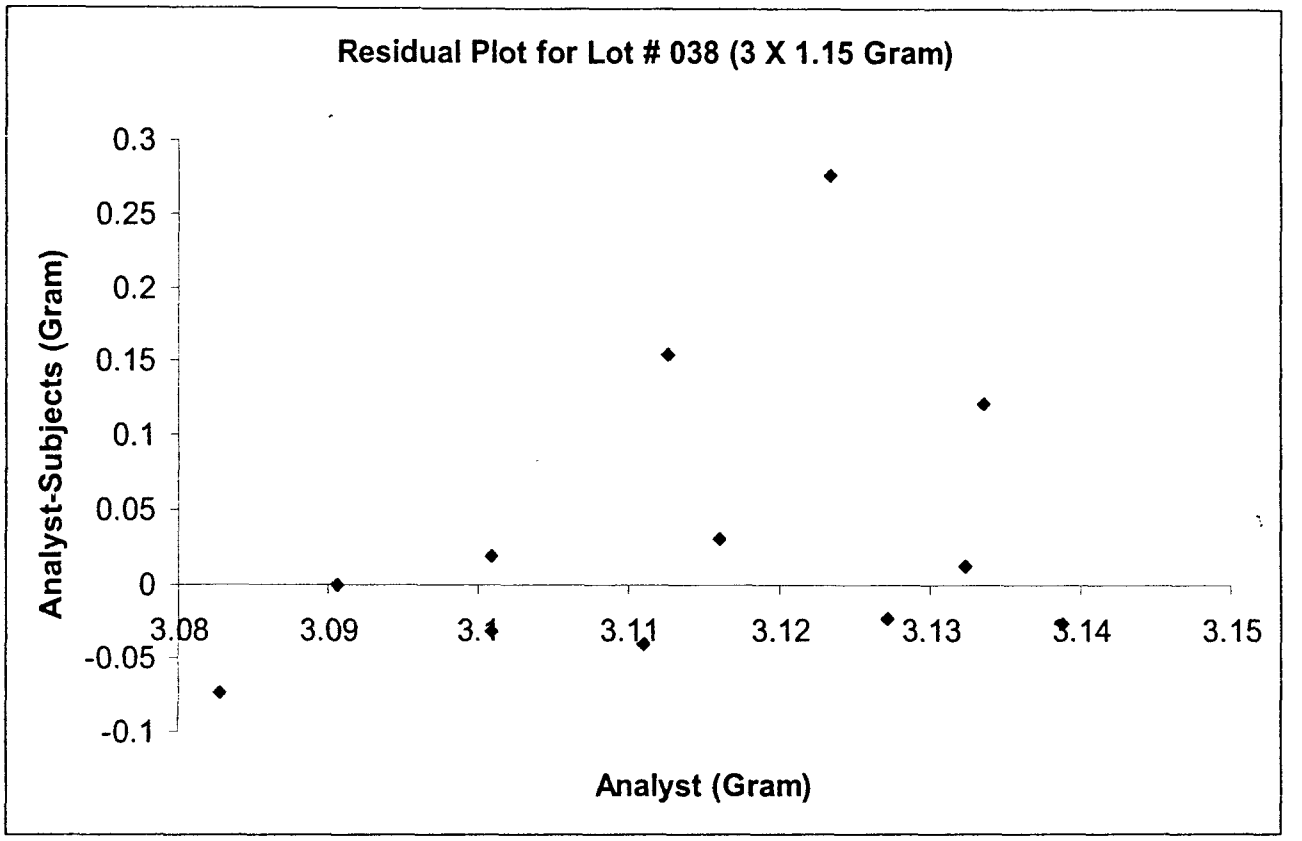

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Figure C2

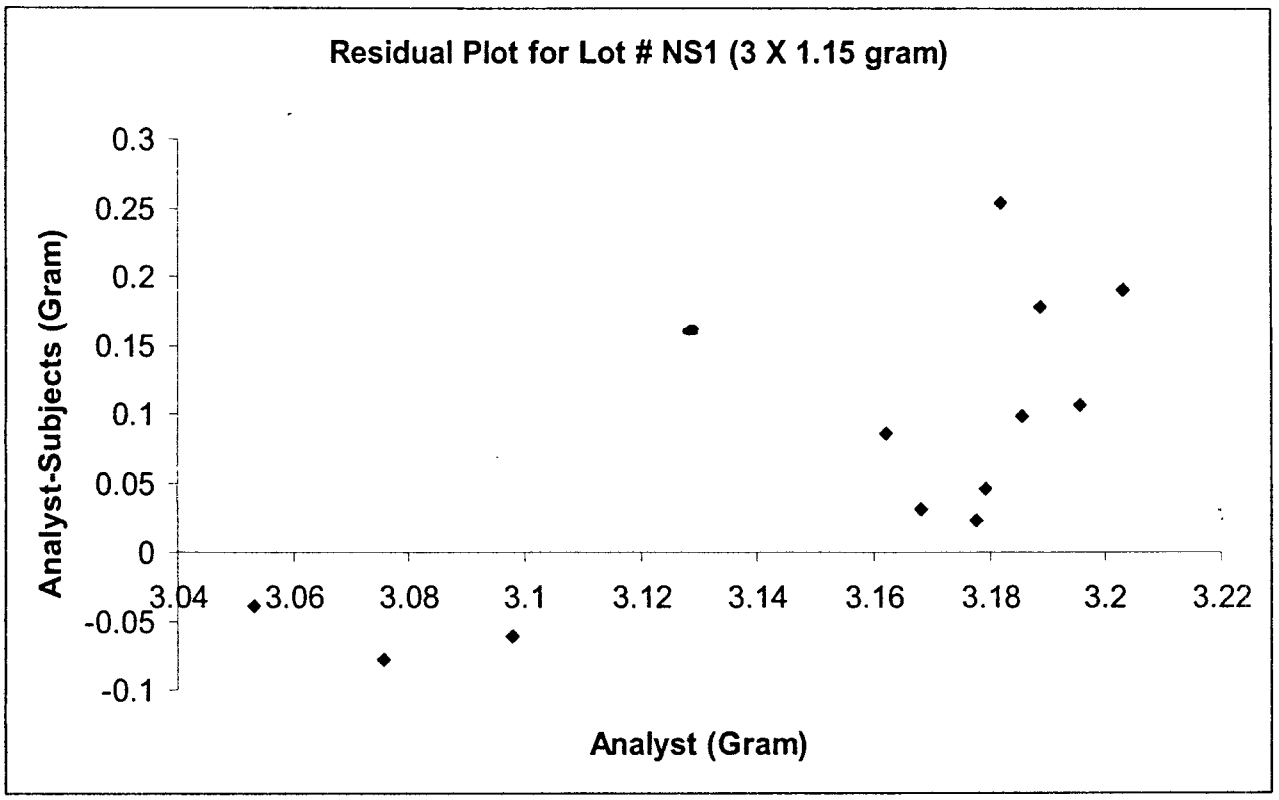

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Figure C3

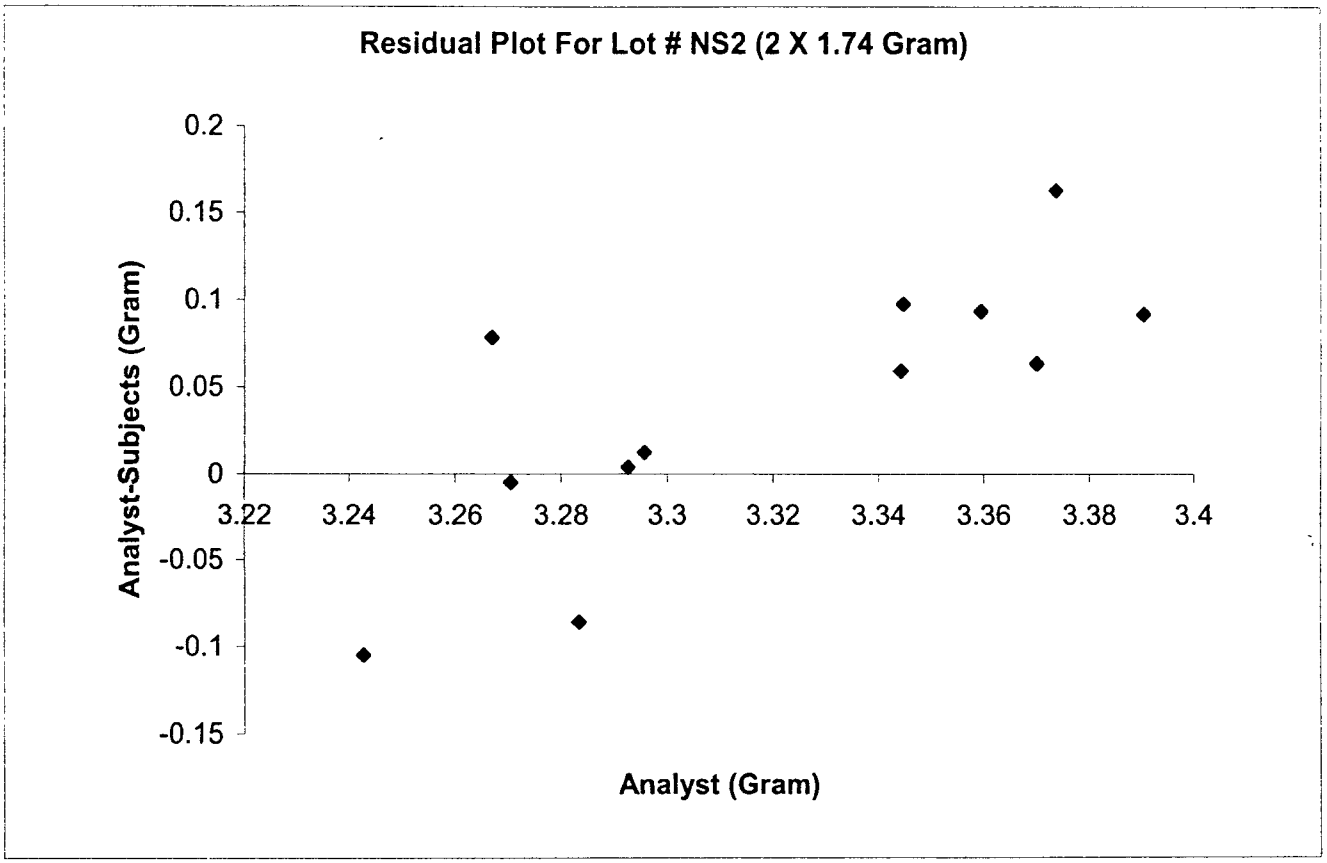

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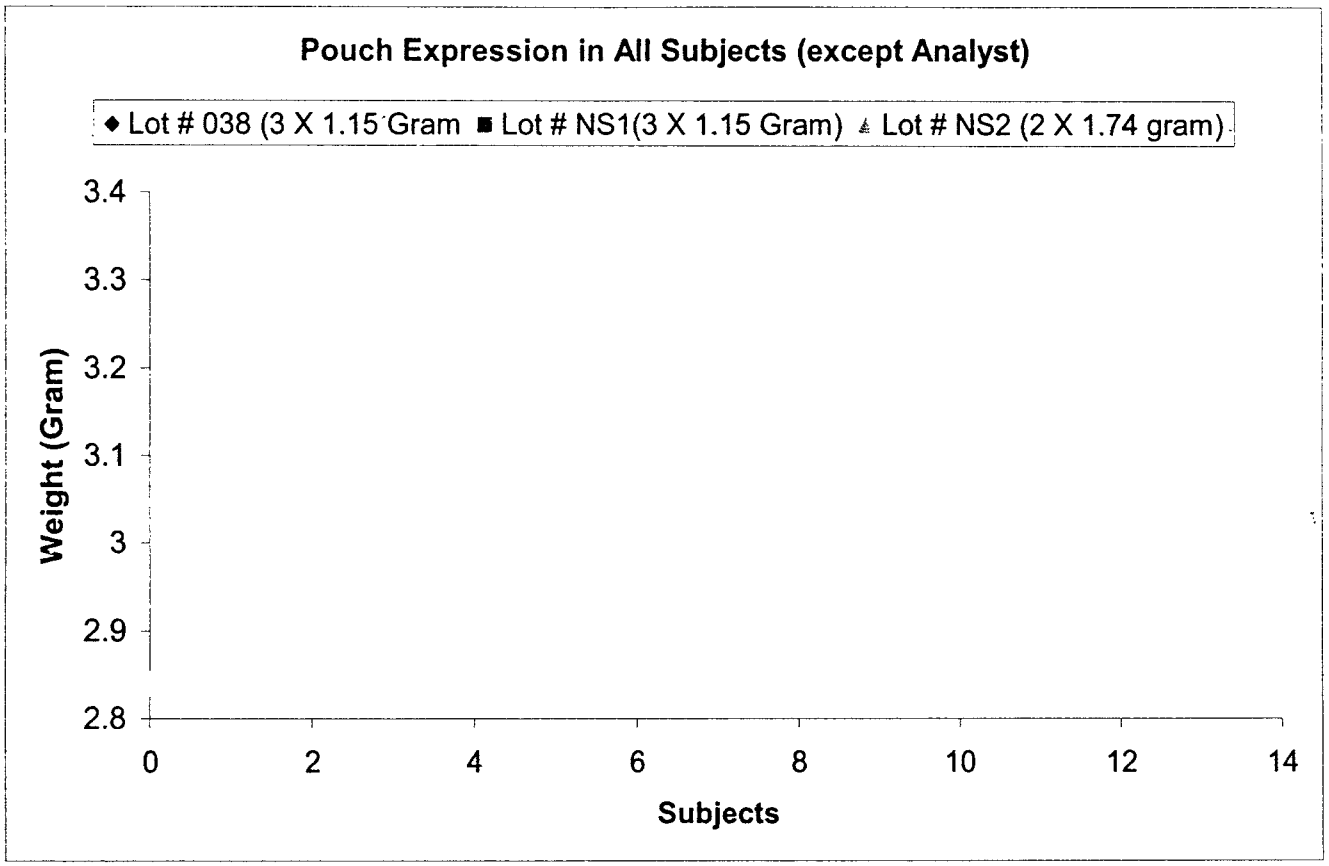
Figure C4



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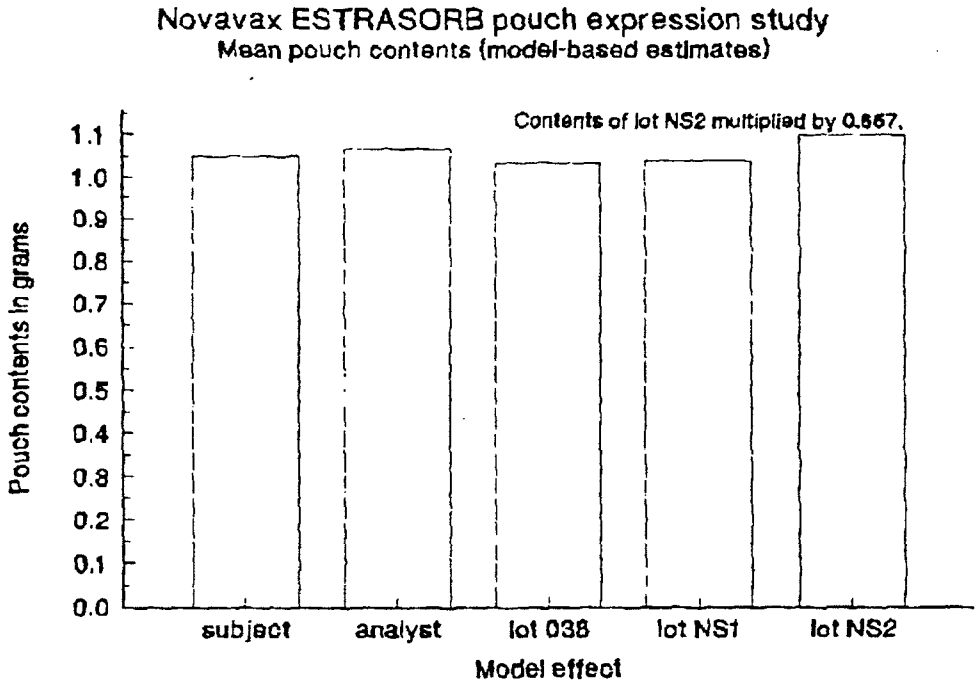
Figures C5 and C6



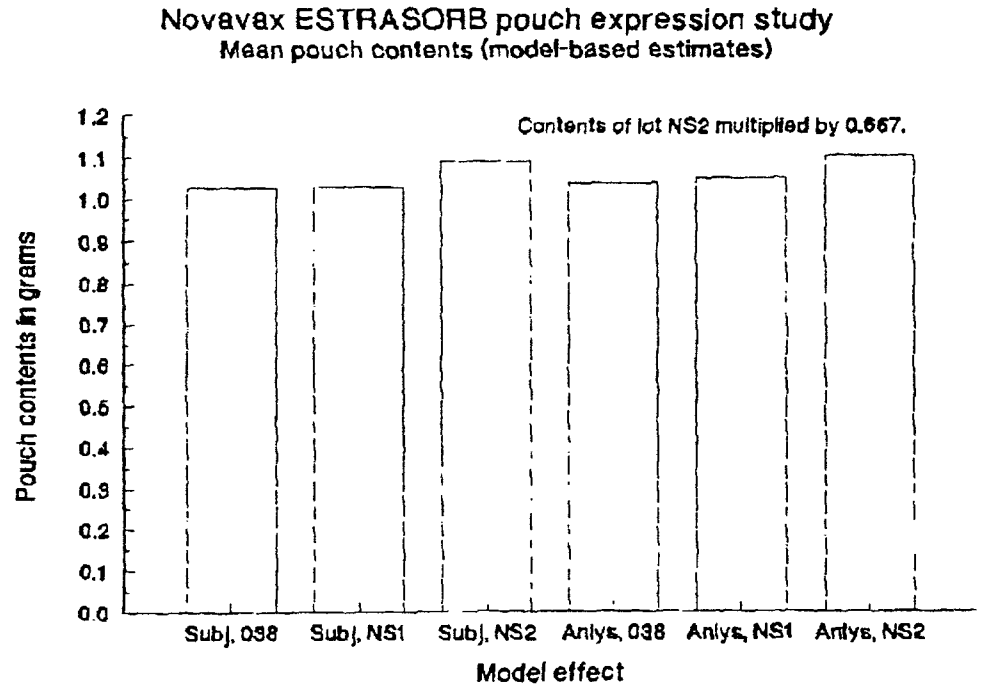


Table C1

Table 1: ESTRASORB pouch study, contrasts from two-way ANOVA using			
Contrast		Estimate ± SE (Grams)	p-value
No interaction of subject (or analyst) and lot			
NS1 vs. NS2		0.060 ± 0.0048	< 0.0001
038 vs. NS2		0.068 ± 0.0048	< 0.0001
038 and NS1 Combined vs. NS2		0.064 ± 0.0043	< 0.0001
With interaction of subject (or analyst) and lot			
NS1 vs. NS2	Subjects	0.065 ± 0.0068	< 0.0001
	Analyst	0.055 ± 0.0068	< 0.0001
038 vs. NS2	Subjects	0.067 ± 0.0068	< 0.0001
	Analyst	0.068 ± 0.0068	< 0.0001
038 and NS1 Combined vs. NS2	Subjects	0.066 ± 0.0061	< 0.0001
	Analyst	0.061 ± 0.0061	< 0.0001

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Table C2

Table 2: ESTRASORB pouch study, DIFF and RATIO outcomes,
summary of statistical significance for regression models

Outcome	Rater	Rater*Lot Interaction	Findings
DIFF in grams	Combined Subject vs. Analyst	No	Highly significant rater and lot effects (p-values < 0.0001 and 0.0038, respectively). Analyst 0.018 gr. > subject, and lots 038 and NS1 0.018 gr. (p-value 0.0009) and 0.0097 (ns) below lot NS2. Exclude lot 038: p-values < 0.0001 and 0.057 for subjects and lots.
		Yes	P-value for rater*lot interaction (2 d.f.) 0.47
	12 Subjects vs. Analyst	No	P-value < 0.0001 for subjects (12 d.f.), 0.0008 for lot (2 d.f.). Compared to the Analyst, subject effects ranged from –0.059 to 0.008. Large negative effects for subjects 8 and 12 (both p < 0.0001). Lots 038 and NS1 < NS2 (p-values 0.0002 and 0.036) with effect size -0.018 (038) and -0.0098 (NS1). Exclude subjects 8 and 12: p-values 0.0020 (10 d.f.) and 0.0011 (2 d.f.) for subjects and lots.
		Yes	P-value 0.0022 for the 24 d.f. interaction but only 1/24 interaction terms is individually significant, p-value 0.0026 for subject 1 x lot 038 term. Effect sizes from –0.066 to 0.042. Exclude subjects 8 and 12: p-values 0.031 for the 20 d.f. interaction.
RATIO in %	Combined Subject vs. Analyst	No	Highly significant rater and lot effects (p-values < 0.0001 for both). Analyst 1.43% > subject, and lots 038 and NS1 4.5% and 3.8% (p-values < 0.0001) below lot NS2. Exclude lot 038: p-values < 0.0001 for both subjects and lots.
		Yes	P-value for rater*lot interaction (2 d.f.) 0.36.
	12 Subjects vs. Analyst	No	P-value < 0.0001 for subjects (12 d.f.), < 0.0001 for lot (2 d.f.). Compared to the Analyst, subject effects ranged from –4.61 to 0.55. Large negative effects for subjects 8 and 12 (both p < 0.0001). Lots 038 and NS1 < NS2 (p-values < 0.0001) with effect size –4.52 (038) and –3.83 (NS1). Exclude subjects 8 and 12: p-values 0.0007 and < 0.0001 for subjects and lots.
		Yes	P-value 0.0004 for interaction but only 3/24 interaction terms are individually significant, p-values 0.0020, 0.042, and 0.019 for (subject 1, lot 038), (subject 8, lot NS1), and (subject 12, lot 038) terms. Effect sizes from –5.36 to 2.50. Exclude subjects 8 and 12: p-value 0.018 for interaction.

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Table C4

	All Data			Exclude Subjects 8 & 12			Exclude Lot 038		
	F(df1, df2)	R^2	% MSE /mean	F(df1, df2)	R^2	% MSE/ mean	F(df1, df2)	R^2	% MSE/ mean
DIFF outcome									
1	10.5 (3,188)	0.14	25.5%	7.1 (3, 172)	0.11	22.7%	11.5 (2, 117)	0.16	25.6%
2	6.57 (5, 186)	0.15	25.5%	5.0 (5, 170)	0.13	22.7%	7.6 (3, 116)	0.17	25.7%
3	7.6 (14, 177)	0.37	21.8%	3.6 (12, 163)	0.21	22.1%	5.4 (13, 106)	0.40	22.9%
4	4.7(38, 153)	0.54	20.7%	2.6 (32, 143)	0.37	21.1%	3.5 (25, 94)	0.48	22.6%
RATIO outcome									
5	49.1 (3,188)	0.44	25.4%	53.7 (3, 172)	0.48	22.4%	60.9 (2, 117)	0.51	25.4%
6	29.9 (5, 186)	0.45	25.4%	33.6 (5, 170)	0.50	22.2%	41.3 (3, 116)	0.52	25.4%
7	18.5 (14, 177)	0.59	22.2%	16.6 (12, 163)	0.55	21.4%	15.2 (13, 106)	0.65	22.5%
8	9.8(38,153)	0.71	20.3%	8.1 (32, 143)	0.64	20.4%	9.0 (25, 94)	0.70	22.0%

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Briefing: September 17, 2003 at 9:00 AM

Briefing Attendees: Drs. Hank Malinowski, John Hunt, Ameeta Parekh, Theresa van der Vlugt, Amit Mitra, and Sayed Al Habet.

Reviewed by:

Sayed (Sam) Al Habet, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD/FT initialed by Ameeta Parekh, Ph.D. _____

cc: NDAs # 21-371: HFD-580, HFD-870 (Al Habet, Parekh, and Malinowski), and Drug files (Biopharm File, CDR).

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-371	Brand Name	ESTRASORB
OCPB Division I	HFD-870	Generic Name	Estradiol
Medical Division	HFD-580	Drug Class	Hormone
OCPB Reviewer	Sayed (Sam) Al Habet, R.Ph., Ph.D.	Indication(s)	Vasomotor Symptoms
OCPB Team Leader	Ameeta Parekh, Ph.D.	Dosage Form	Topical
		Dosing Regimen	Once daily
Date of Submission	September 12, 2002	Route of Administration	Skin (thigh)
Estimated Due Date of OCPB Review	June 12, 2003	Sponsor	Novavax
PDUFA Due Date	July 12, 2003	Priority Classification	
Division Due Date	June 30, 2003		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		
multiple dose:	X	1		
Patients-				
single dose:	X	1		
multiple dose:	X	1		
Dose proportionality -				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1		
Phase 3 clinical trial:	X	1		
Population Analyses -				
Data rich:	Yes	1		
Data sparse:	Yes	1		
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:	X	1		
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**5**		

Filability and QBR comments

	"X" if yes	**Comments**
Application filable ?		Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above	**This is a resubmission of the original NDA. The original NDA was reviewed by OCPB. No new information was submitted except an *in vitro* study to determine the actual weight of the contents of the proposed pouches. In addition, two studies are expected to be submitted during the review cycle. These are partner transfer and effect of sunscreen studies.**	
Primary reviewer Signature and Date	**Sayed Al-Habet, Ph.D.**	
Secondary reviewer Signature and Date	**Ameeta Parekh, Ph.D.**	

Appendix I

Individual Data for Partner Transfer Study

Estradiol Data (Females)

Figure 1

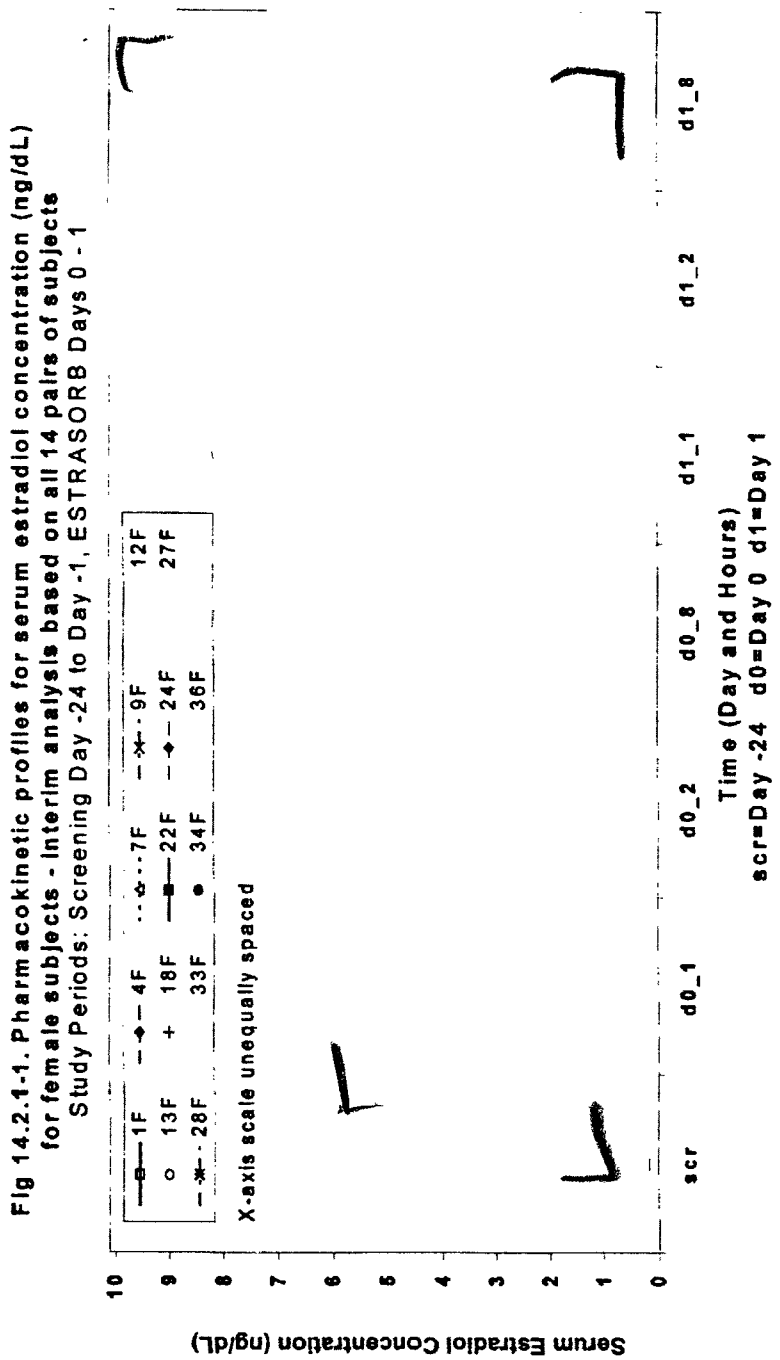

Figure 2

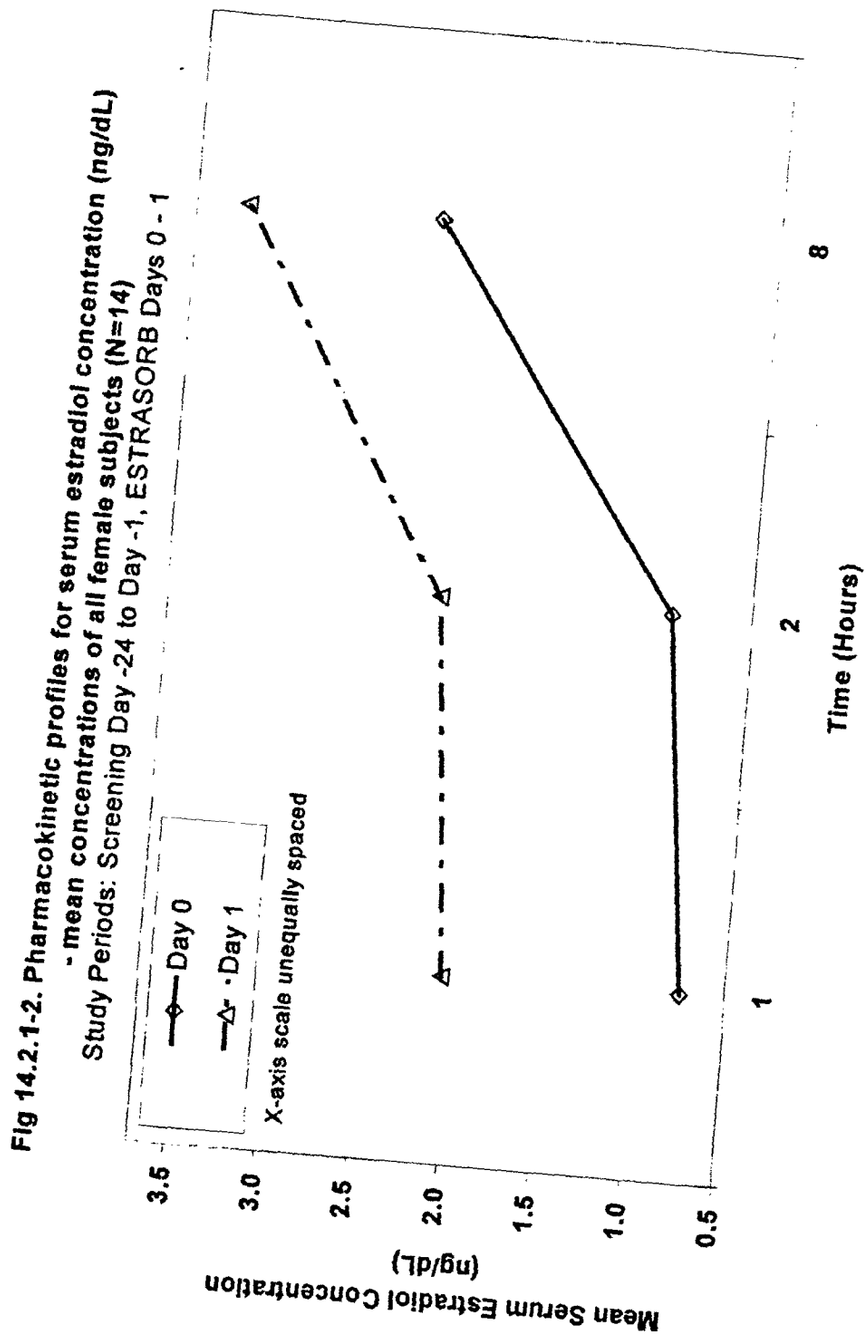
Fig 14.2.1-2. Pharmacokinetic profiles for serum estradiol concentration (ng/dL)
- mean concentrations of all female subjects (N=14)
Study Periods: Screening Day -24 to Day -1, ESTRASORB Days 0 - 1
Day 0
Day 1
X-axis scale unequally spaced
Mean Serum Estradiol Concentration (ng/dL)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1
2
8
Time (Hours)

Table 14.2.1-13. Descriptive statistics of pharmacokinetic parameters on profiling Days 0 and 1 for all female subjects (N=14)

Hormone	PK Paramcter (Mean ± SD)	Profiling Day	
		Day 0	Day 1
Estradiol	T_{max} (hr)	6.57 ± 2.85	6.07 ± 3.17
	C_{max} (ng/dL)	2.35 ± 2.11	3.54 ± 2.89
	C_{min} (ng/dL)	0.72 ± 1.19	1.87 ± 1.98
	$C_{average}$ (ng/dL)	1.53 ± 1.48	2.76 ± 2.27
	$AUC_{(1-8h)}$ (ng-h/dL)	10.70 ± 10.39	19.34 ± 15.91
Estrone	T_{max} (hr)	4.36 ± 3.30	4.71 ± 3.43
	C_{max} (ng/dL)	2.31 ± 1.28	4.85 ± 2.83
	C_{min} (ng/dL)	1.38 ± 1.25	3.47 ± 2.35
	$C_{average}$ (ng/dL)	1.79 ± 1.26	4.09 ± 2.53
	$AUC_{(1-8h)}$ (ng-h/dL)	12.50 ± 8.79	28.64 ± 17.73
Estrone Sulfate	T_{max} (hr)	7.57 ± 1.60	6.57 ± 2.85
	C_{max} (ng/dL)	62.93 ± 36.77	158.64 ± 94.47
	C_{min} (ng/dL)	36.64 ± 23.68	116.86 ± 68.67
	$C_{average}$ (ng/dL)	49.47 ± 28.94	138.50 ± 79.38
	$AUC_{(1-8h)}$ (ng-h/dL)	346.26 ± 202.57	969.48 ± 555.68
FSH	T_{max} (hr)	2.86 ± 2.82	2.93 ± 2.79
	C_{max} (mIU/mL)	70.14 ± 18.40	63.50 ± 15.45
	C_{min} (mIU/mL)	59.64 ± 15.84	56.14 ± 13.22
	$C_{average}$ (mIU/mL)	65.17 ± 17.87	59.46 ± 14.03
	$AUC_{(1-8h)}$ (mIU-h/mL)	456.17 ± 125.09	416.25 ± 98.24

Table 14.2.1-14. Geometric means, geometric mean fold ratios and paired t-test findings in $AUC_{(1\text{-}8h)}$ and C_{max} for hormones on profiling Days 0 and 1 for all female subjects (N=14)

PK Parameter			Serum Hormone			
			Estradiol (ng/dL)	Estrone (ng/dL)	Estrone Sulfate (ng/dL)	FSH (mIU/mL)
$AUC_{(1\text{-}8h)}$						
Geometric Mean	$AUC_{(1\text{-}8h)}$	Day 0	7.30	10.10	297.68	442.30
		Day 1	15.02	25.15	834.32	405.83
	Fold Ratio in $AUC_{(1\text{-}8h)}$ from Day 0 to Day 1		2.06	2.49	2.80	0.92
Pair-wise comparison p-value*	$AUC_{(1\text{-}8h)}$: Day 0 vs. Day 1		0.0011	0.0005	< 0.0001	0.0072
	Fold Ratio in $AUC_{(1\text{-}8h)}$: Day 0 vs. Day 1		0.0006	< 0.0001	< 0.0001	0.0038
C_{max}						
Geometric Mean	C_{max}	Day 0	1.50	1.98	54.27	68.09
		Day 1	2.73	4.29	134.13	61.76
	Fold Ratio in C_{max} from Day 0 to Day 1		1.82	2.16	2.47	0.91
Pair-wise Comparison p-value*	C_{max}: Day 0 vs. Day 1		0.0057	0.0013	< 0.0001	0.0086
	Fold Ratio in C_{max}: Day -10 vs. Day 0		0.0052	0.0004	< 0.0001	0.0047

*Paired t-test

Table 14.1-2. Descriptive statistics of screening hormone parameters - all 14 female subjects and 14 male partners

VARIABLE		by Gender: Female Subjects	by Gender: Male Partners
ESTRADIOL (ng/dL)	N	14	14
	MEAN	0.29	1.94
	STD	0.15	0.92
	MAX	[redacted]	
	MEDIAN	0.25	1.95
	MIN	[redacted]	
ESTRONE (ng/dL)	N	14	14
	MEAN	1.60	2.27
	STD	1.34	0.77
	MAX	[redacted]	
	MEDIAN	1.35	2.20
	MIN	[redacted]	
ESTRONE SULFATE (ng/dL)	N	14	14
	MEAN	52.79	109.43
	STD	40.12	42.32
	MAX	[redacted]	
	MEDIAN	45.50	95.50
	MIN	[redacted]	
FSH-ICMA (mIU/mL)	N	14	.
	MEAN	73.29	.
	STD	18.11	.
	MAX	[redacted]	.
	MEDIAN	77.5	.
	MIN	[redacted]	.

Table 14.2.1-1. Descriptive statistics of serum estradiol concentrations (ng/dL) for all female subjects (N=14)

Study Days: Screening -24 to -1, ESTRASORB 0 - 1

		Descriptive Statistics					
Day	Hour	N	Mean	Standard Deviation	Maximum	Median	Minimum
-24	0	14	0.29	0.15		0.25	
0	1	13	0.75	1.23		0.50	
	2	14	0.94	1.35		0.60	
	8	14	2.35	2.11		1.45	
1	1	14	2.05	1.97		1.30	
	2	13	2.21	2.02		1.30	
	8	14	3.41	2.95		2.60	

Table 14.2.1-5. Listing of PK parameters for serum estradiol concentration (ng/dL) for all female subjects (N=14)

Study Days: Screening -24 to -1, ESTRASORB 0 - 1

Day	Subject ID	PK Parameter				
		Tmax (hr)	Cmax	Cmin*	Caverage	AUC(1-8h) (ng-h/dL)
0	01F					
	04F					
	07F					
	09F					
	12F					
	13F					
	18F					
	22F					
	24F					
	27F					
	28F					
	33F					
	34F					
	36F					
	Mean	6.6	2.35	0.72	1.53	10.70
	SD	2.8	2.11	1.19	1.48	10.39
	%CV	43.3	89.66	165.97	97.13	97.13
	Median	8.0	1.45	0.33	1.12	7.83
	Minimum					
	Maximum					