Table 14.2.1-6. 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)
1	01F					
	04F					
	07F					
	09F					
	12F					
	13F					
	18F					
	22F					
	24F					
	27F					
	28F					
	33F					
	34F					
	36F					
	Mean	6.1	3.54	1.87	2.76	19.34
	SD	3.2	2.89	1.98	2.27	15.91
	%CV	52.3	81.56	105.91	82.23	82.23
	Median	8.0	2.85	1.25	1.97	13.80
	Minimum					
	Maximum					

Estradiol Data (Male)

Figure 3

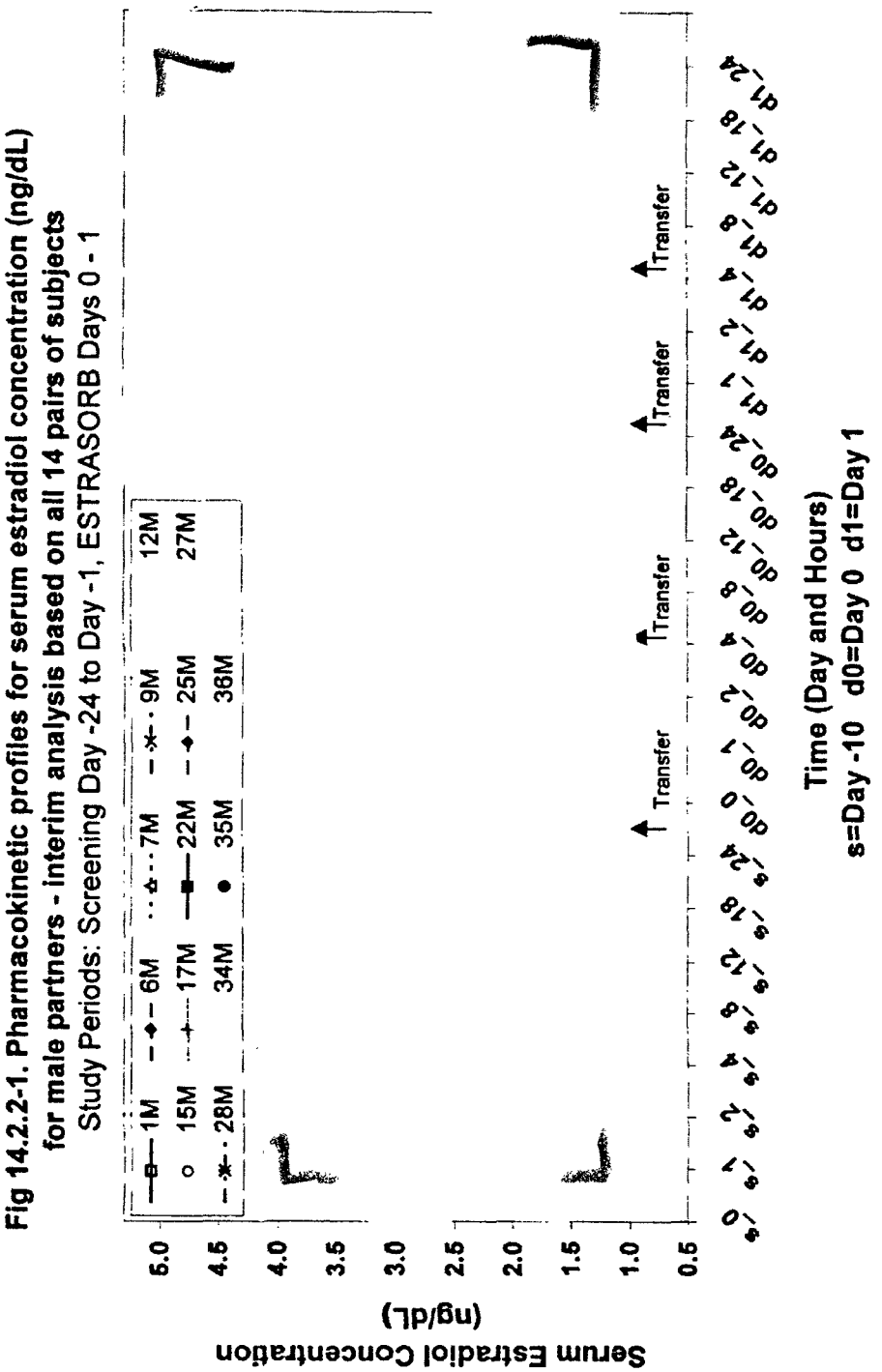


Figure 4

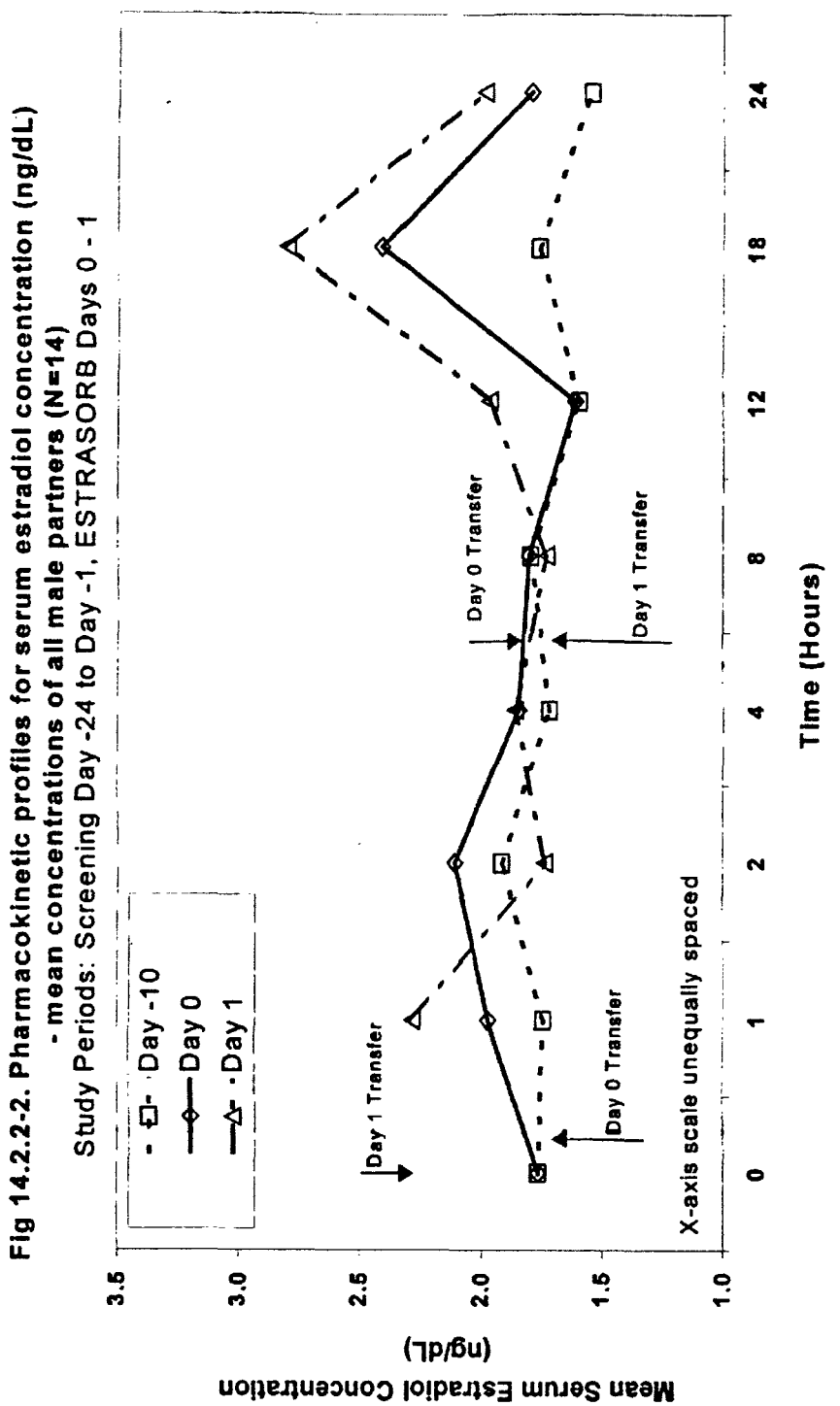


Fig 14.2.2-2. Pharmacokinetic profiles for serum estradiol concentration (ng/dL)
- mean concentrations of all male partners (N=14)
Study Periods: Screening Day -24 to Day -1, ESTRASORB Days 0 - 1
Day -10
Day 0
Day 1
Day 1 Transfer
Day 0 Transfer
Day 0 Transfer
Day 1 Transfer
X-axis scale unequally spaced
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

Figure 5

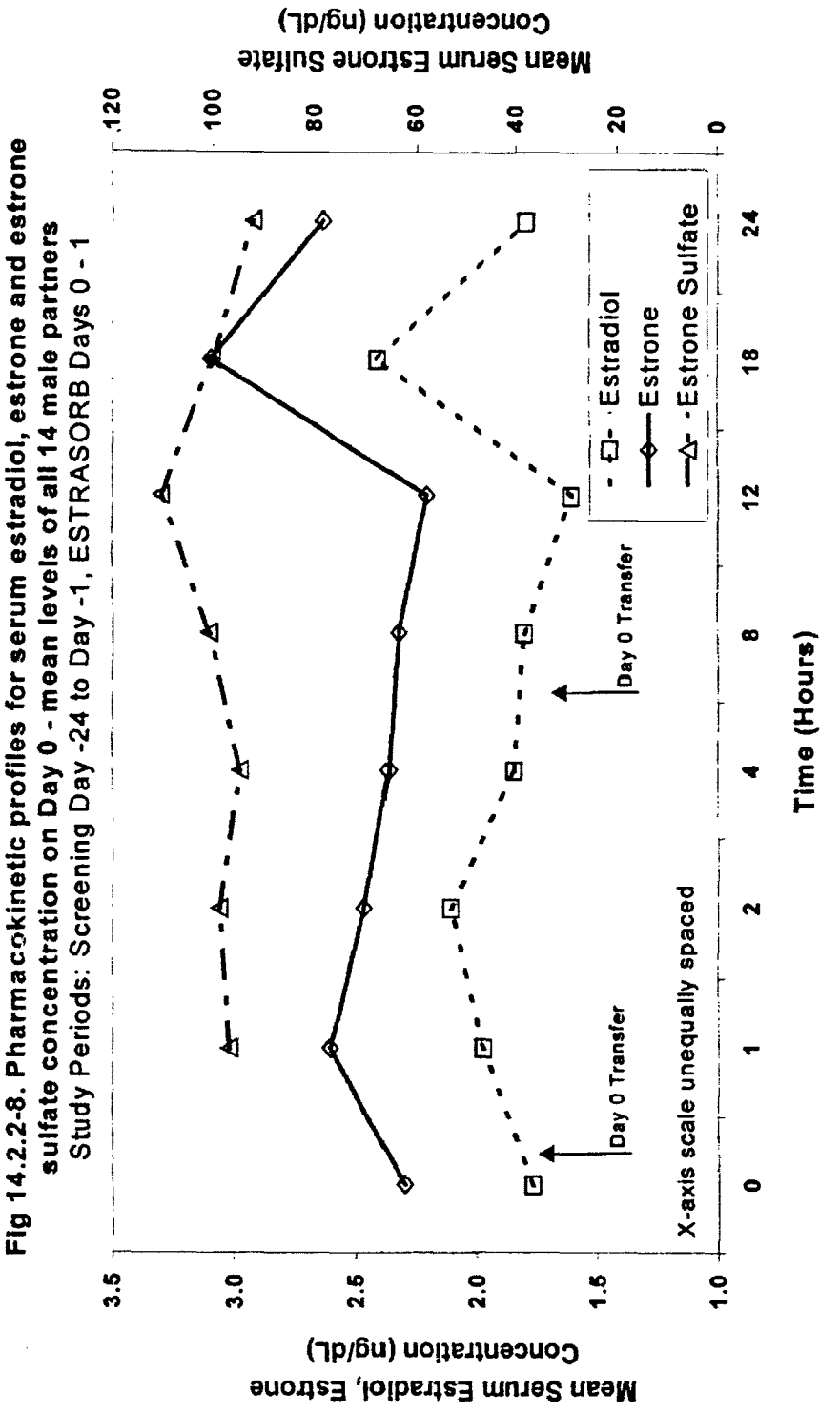


Fig 14.2.2-8. Pharmacokinetic profiles for serum estradiol, estrone and estrone sulfate concentration on Day 0 - mean levels of all 14 male partners
Study Periods: Screening Day -24 to Day -1, ESTRASORB Days 0 - 1
Mean Serum Estradiol, Estrone Concentration (ng/dL)
Mean Serum Estrone Sulfate Concentration (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 6

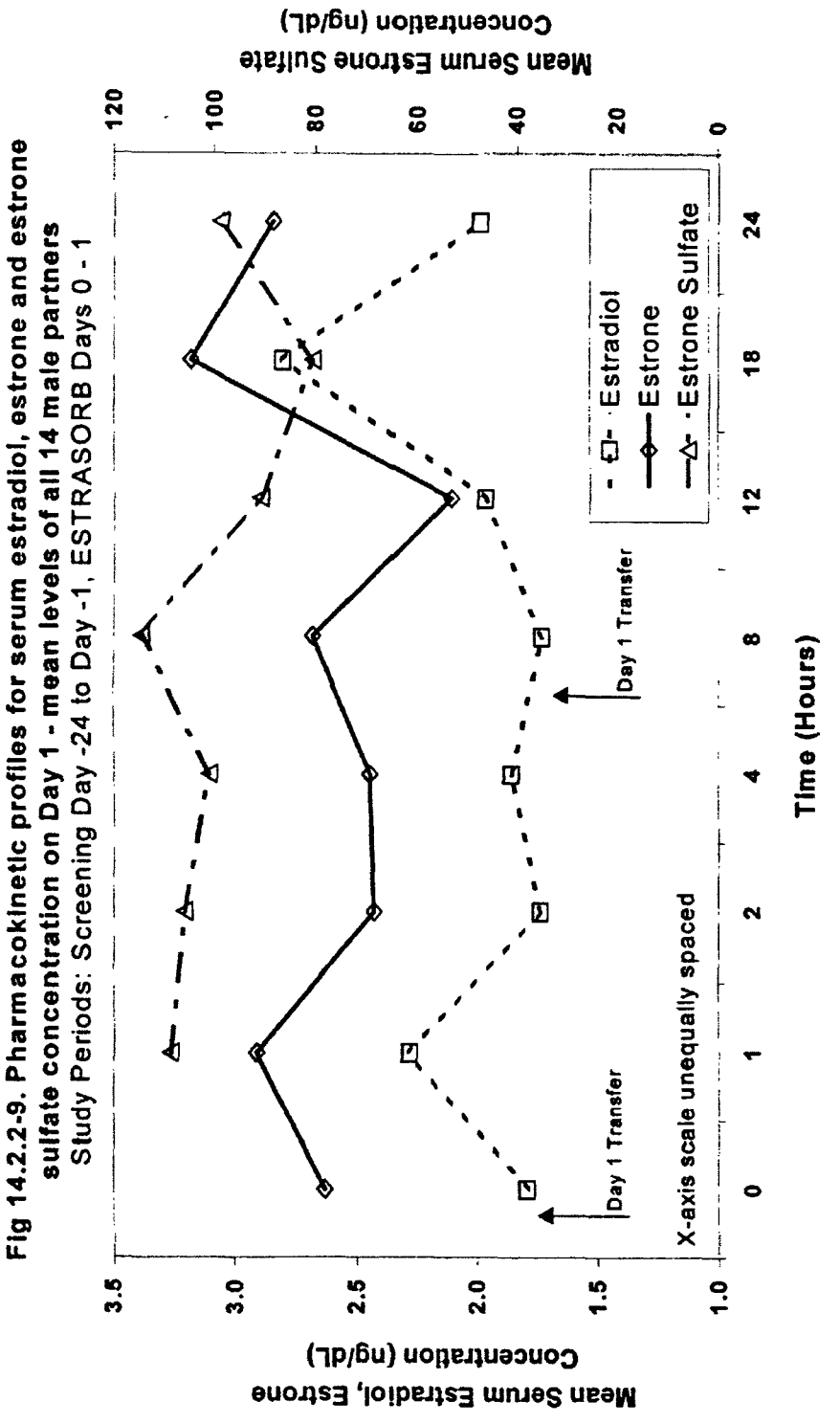


Fig 14.2.2-9. Pharmacokinetic profiles for serum estradiol, estrone and estrone sulfate concentration on Day 1 - mean levels of all 14 male partners
Study Periods: Screening Day -24 to Day -1, ESTRASORB Days 0 - 1
Mean Serum Estradiol, Estrone Concentration (ng/dL)
Mean Serum Estrone Sulfate Concentration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

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
	$AUC_{(0\text{-}24h)}$ (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
	$AUC_{(0\text{-}24h)}$ (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
	$AUC_{(0\text{-}24h)}$ (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

Table 14.2.2-1. Descriptive statistics of profile serum estradiol concentrations (ng/dL) for all male partners (N=14)

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

		Descriptive Statistics					
Day	Hour	N	Mean	Standard Deviation	Maximum	Median	Minimum
-10	0	14	1.76	0.51		1.60	
	1	14	1.74	0.54		1.65	
	2	14	1.91	0.70		1.70	
	4	14	1.71	0.52		1.60	
	8	14	1.79	0.64		1.70	
	12	14	1.59	0.41		1.60	
	18	14	1.76	0.51		1.70	
	24	14	1.54	0.36		1.50	
0	0	14	1.76	0.47		1.65	
	1	14	1.97	0.47		1.90	
	2	14	2.11	0.65		1.95	
	4	14	1.84	0.59		1.85	
	8	14	1.80	0.48		1.80	
	12	14	1.61	0.37		1.60	
	18	14	2.41	0.94		2.15	
	24	14	1.79	0.37		1.70	
1	0	14	1.79	0.37		1.70	
	1	14	2.29	0.59		2.20	
	2	14	1.74	0.50		1.75	
	4	14	1.86	0.56		1.80	
	8	14	1.73	0.36		1.80	
	12	14	1.96	0.44		1.90	
	18	14	2.80	0.82		2.80	
	24	14	1.99	0.40		1.90	

Table 12A

Table 14.2.2-4. Listing of PK parameters for serum estradiol concentration (ng/dL) for all male partners (N=14)

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

Day	Subject ID	PK Parameter				
		Tmax (hr)	Cmax	Cmin*	Caverage	AUC(0-24hr)** (ng-hr/dL)
-10	01M					
	06M					
	07M					
	09M					
	12M					
	15M					
	17M					
	22M					
	25M					
	27M					
	28M					
	34M					
	35M					
	36M					
	Mean	5.5	2.17	1.34	1.70	40.73
	SD	7.3	0.60	0.27	0.43	10.40
	%CV	130.4	27.63	20.47	25.57	25.57
	Median	2.0	2.25	1.30	1.65	39.07
	Minimum					
	Maximum					

Table 12B

Table 14.2.2-5. Listing of PK parameters for serum estradiol concentration (ng/dL) for all male partners (N=1

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

Day	Subject ID	PK Parameter				
		Tmax (hr)	Cmax	Cmin*	Average	AUC(0-24h)** (ng-h/dL)
0	01M					
	06M					
	07M					
	09M					
	12M					
	15M					
	17M					
	22M					
	25M					
	27M					
	28M					
	34M					
	35M					
	36M					
	Mean	10.0	2.49	1.48	1.93	46.37
	SD	8.3	0.90	0.40	0.52	12.48
	%CV	83.3	36.18	27.41	26.93	26.92
	Median	11.0	2.30	1.45	1.82	43.73
	Minimum					
	Maximum					

Table 12C

Table 14.2.2-6. Listing of PK parameters for serum estradiol concentration (ng/dL) for all male partners (N=14)

Study Days: Screening -24 to -1, ESTRASORB 2 - 1

Day	Subject ID	PK Parameter				
		Tmax (hr)	Cmax	Cmin*	Caverage	AUC(0-24hr)** (ng-h/dL)
1	01M					
	06M					
	07M					
	09M					
	12M					
	15M					
	17M					
	22M					
	25M					
	27M					
	29M					
	34M					
	35M					
	36M					
	Mean	13.1	2.68	1.49	2.10	50.46
	SD	8.0	0.81	0.41	0.44	10.54
	%CV	60.6	30.74	27.56	20.89	20.89
	Median	15.0	2.80	1.45	2.00	48.[illegible]
	Minimum					
	Maximum					

Estrone Data (Females)

Figure 7

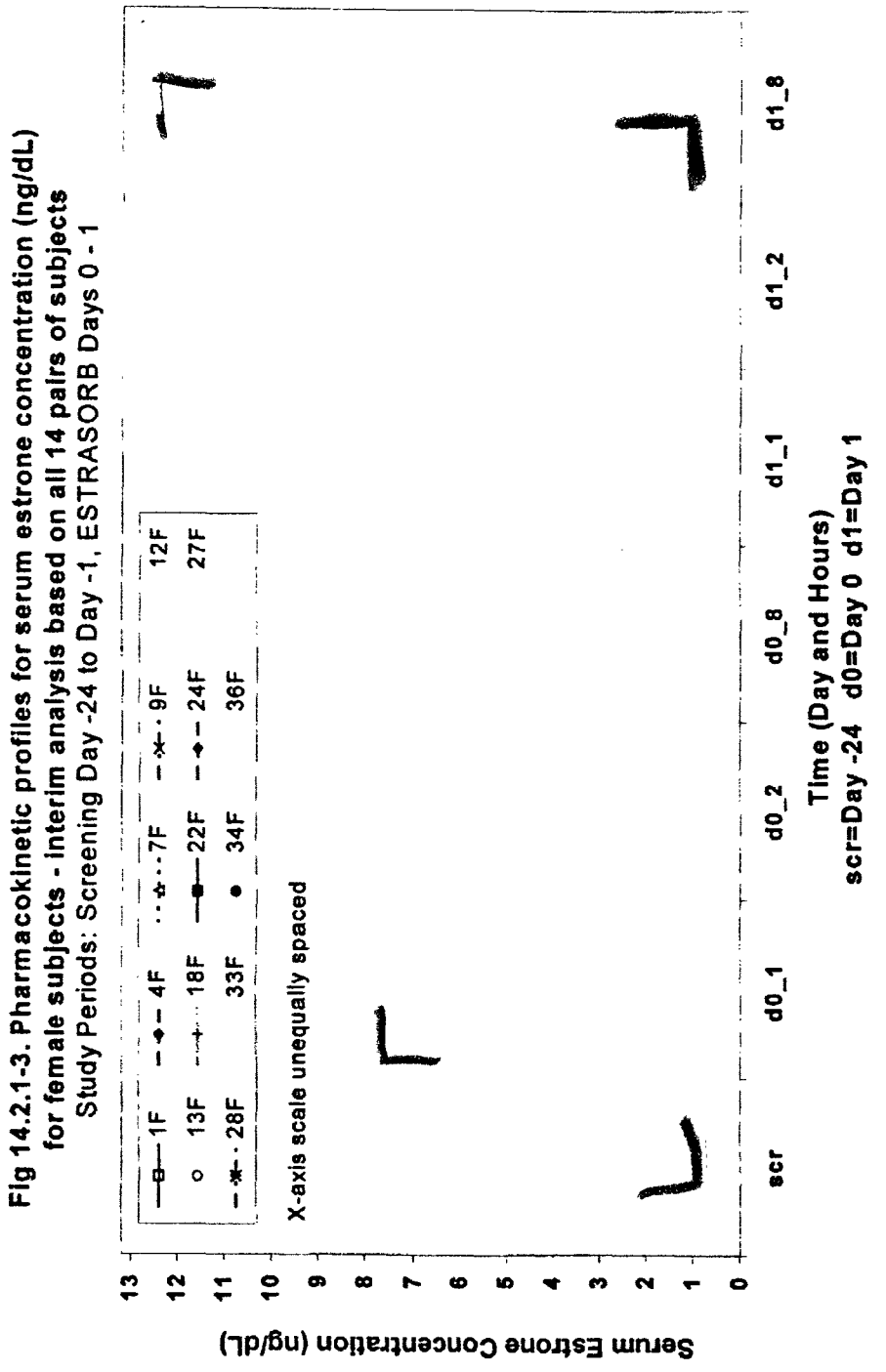


Figure 8

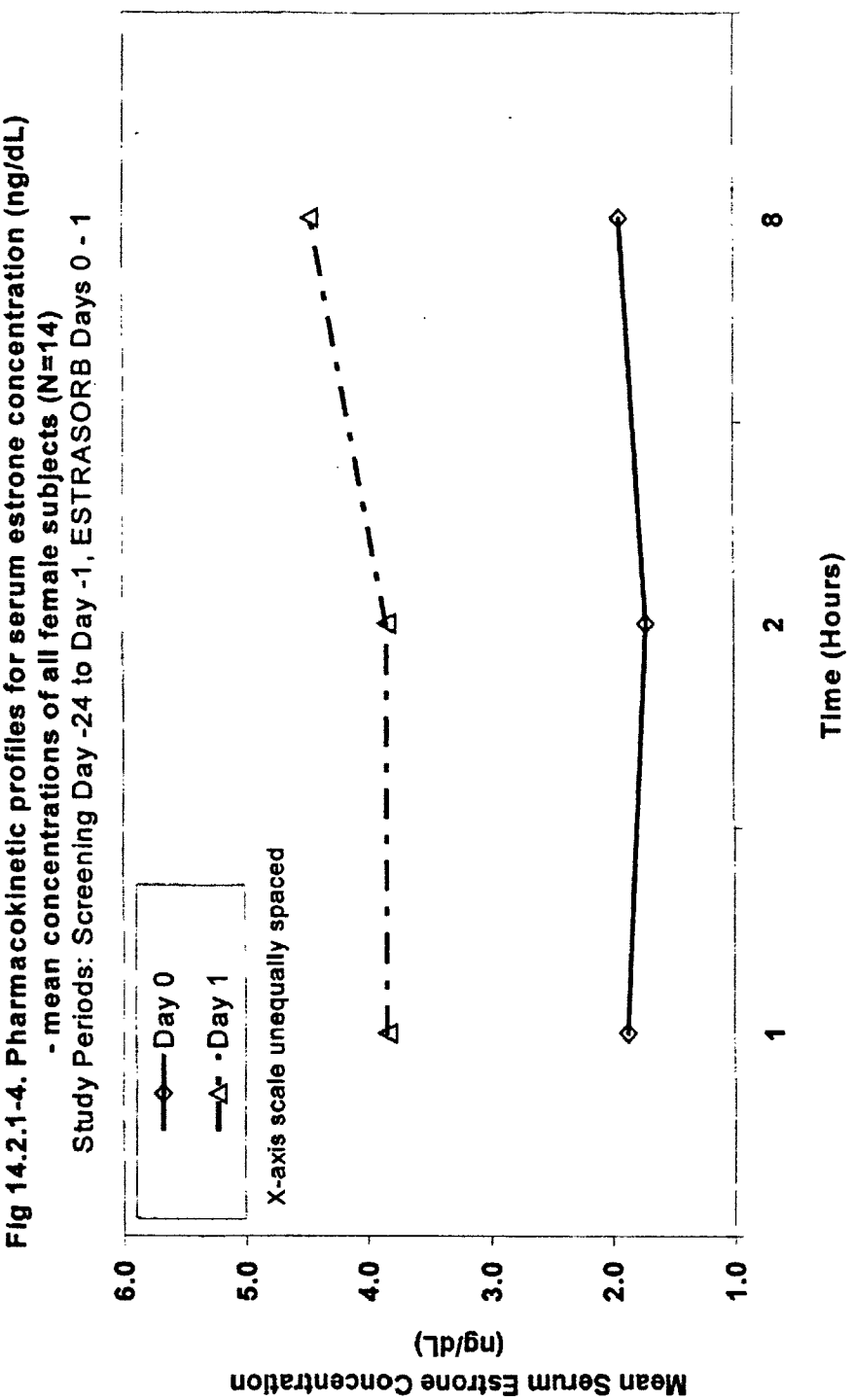


Fig 14.2.1-4. Pharmacokinetic profiles for serum estrone concentration (ng/dL)
- mean concentrations of all female subjects (N=14)
Study Periods: Screening Day -24 to Day -1, ESTRASORB Days 0 - 1
Day 0
Day 1
X-axis scale unequally spaced
Mean Serum Estrone Concentration
(ng/dL)
6.0
5.0
4.0
3.0
2.0
1.0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

Table 14.2.1-2. Descriptive statistics of serum estrone 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	1.60	1.34		1.35	
0	1	14	1.87	1.30		1.45	
	2	13	1.71	1.56		1.30	
	8	14	1.93	1.08		1.70	
1	1	14	3.84	2.36		2.90	
	2	14	3.84	2.46		3.00	
	8	14	4.46	2.87		3.45	

APPEARS THIS WAY
ON ORIGINAL

Table 14.2.1-7. Listing of PK parameters for serum estrone 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	4.4	2.31	1.38	1.79	12.50
	SD	3.3	1.28	1.25	1.26	8.79
	%CV	75.6	55.38	90.63	70.28	70.28
	Median	2.0	2.00	1.00	1.44	10.08
	Minimum					
	Maximum					

Table 14.2.1-8. Listing of PK parameters for serum estrone 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)
1	01F					
	04F					
	07F					
	09F					
	12F					
	13F					
	18F					
	22F					
	24F					
	27F					
	28F					
	33F					
	34F					
	36F					
	Mean	4.7	4.85	3.47	4.09	28.64
	SD	3.4	2.83	2.35	2.53	17.73
	%CV	72.7	58.32	67.83	61.89	61.89
	Median	5.0	4.40	2.65	3.44	24.05
	Minimum					
	Maximum					

Estrone Data (Males)

Figure 8

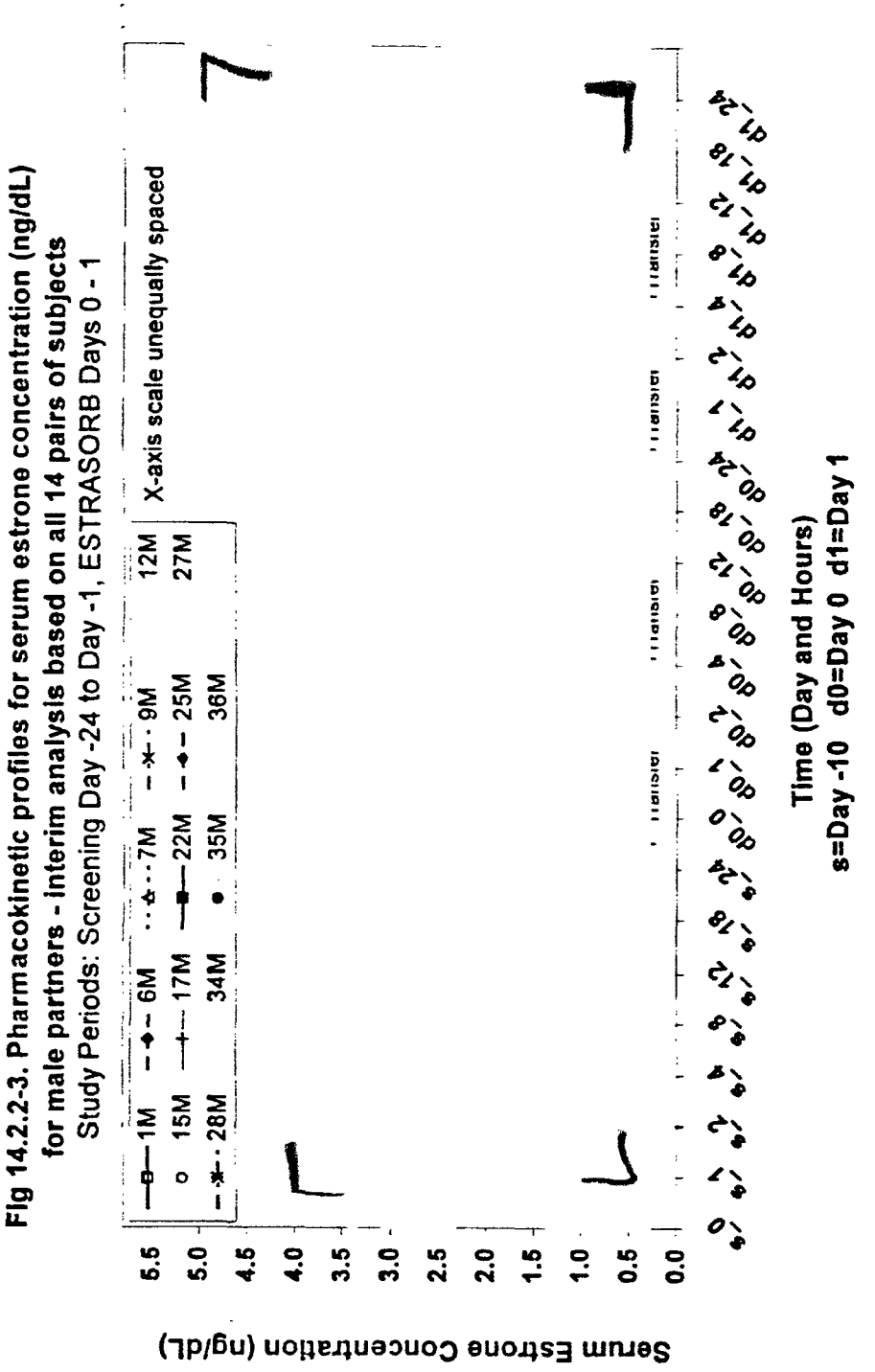


Figure 9

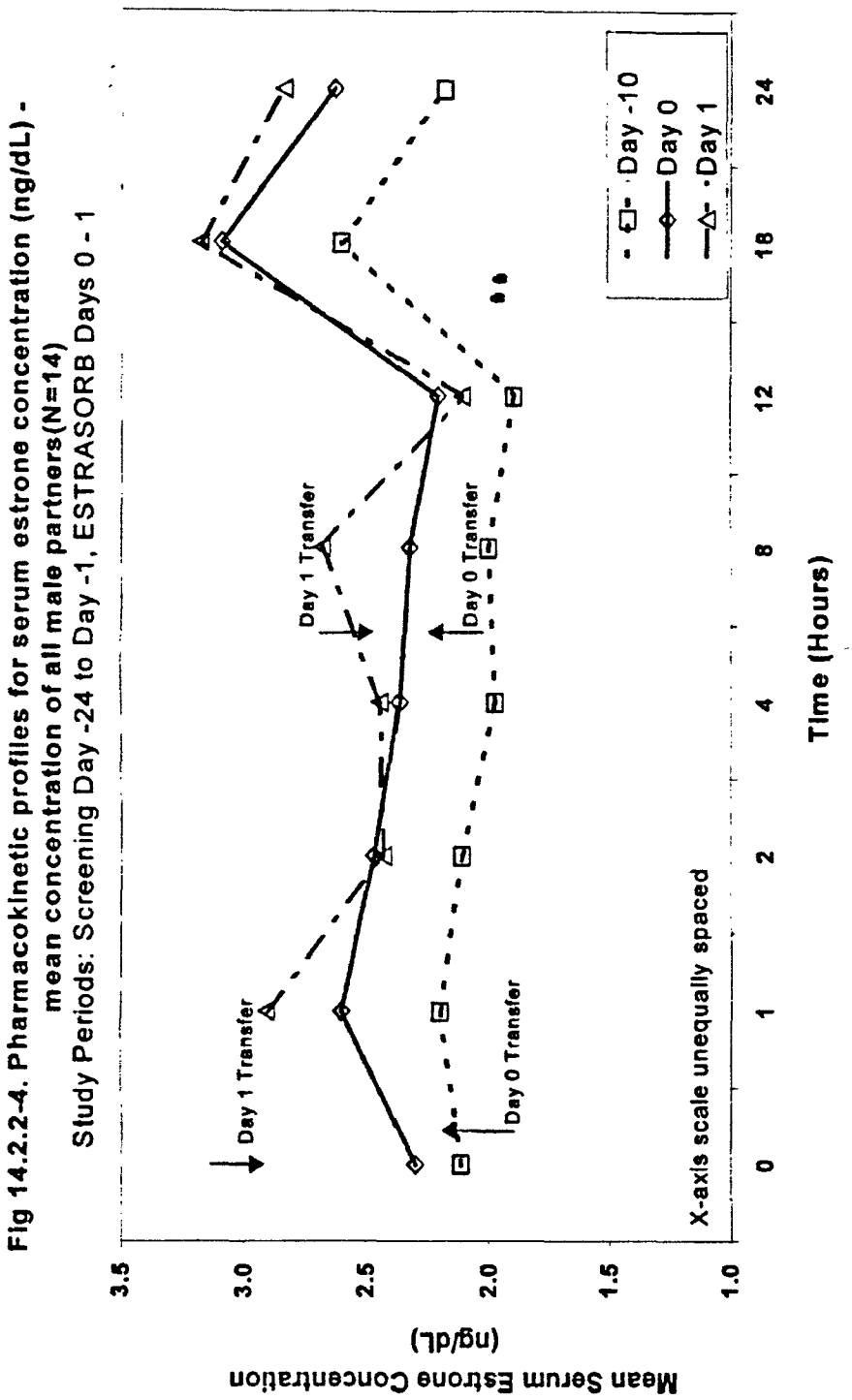


Fig 14.2.2-4. Pharmacokinetic profiles for serum estrone concentration (ng/dL) - mean concentration of all male partners(N=14)
Study Periods: Screening Day -24 to Day -1, ESTRASORB Days 0 - 1
Mean Serum Estrone Concentration (ng/dL)
Time (Hours)
X-axis scale unequally spaced
Day -10
Day 0
Day 1
Day 1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

Table 14.2.2-2. Descriptive statistics of profile serum estrone concentrations (ng/dL) for all male partners (N=14)

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

		Descriptive Statistics					
Day	Hour	N	Mean	Standard Deviation	Maximum	Median	Minimum
-10	0	14	2.11	1.15		2.00	
	1	14	2.20	0.92		1.95	
	2	14	2.11	0.97		2.00	
	4	14	1.97	0.96		1.60	
	8	14	2.00	1.03		1.75	
	12	14	1.89	1.06		1.50	
	18	14	2.60	0.92		2.30	
	24	14	2.18	1.09		2.10	
0	0	13	2.30	0.79		2.30	
	1	13	2.60	0.80		2.50	
	2	14	2.46	0.77		2.35	
	4	14	2.36	0.77		2.25	
	8	13	2.32	0.75		2.20	
	12	14	2.21	0.75		2.15	
	18	14	3.09	0.62		3.10	
	24	14	2.63	0.75		2.70	
1	0	14	2.63	0.75		2.70	
	1	13	2.91	0.78		2.80	
	2	13	2.43	0.84		2.50	
	4	14	2.44	0.58		2.55	
	8	14	2.68	0.65		2.60	
	12	13	2.11	0.42		2.00	
	18	14	3.18	0.96		3.10	
	24	13	2.84	0.54		2.80	

Table 14.2.2-7. Listing of PK parameters for serum estrone concentration (ng/dL) for all male partners (N=14)

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

Day	Subject ID	PK Parameter Tmax (hr)	Cmax	Cmin*	Caverage	AUC(0-24h)** (ng-h/dL)
-10	01M					
	06M					
	07M					
	09M					
	12M					
	15M					
	17M					
	22M					
	25M					
	27M					
	28M					
	34M					
	35M					
	36M					
	Mean	8.8	2.89	1.53	2.14	51.47
	SD	9.3	0.87	0.98	0.95	22.69
	%CV	106.1	30.06	64.00	44.08	44.08
	Median	2.0	2.60	1.15	1.83	43.87
	Minimum					
	Maximum					

Table 14.2.2-8. Listing of PK parameters for serum estrone concentration (ng/dL) for all male partners (N=14)

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

Day	Subject ID	PK Parameter: Tmax (hr)	Cmax	Cmin*	Caverage	AUC(0-24h)** (ng-h/dL)
0	01M					
	06M					
	07M					
	09M					
	12M					
	15M					
	17M					
	22M					
	25M					
	27M					
	28M					
	34M					
	35M					
	36M					
	Mean	12.9	3.34	1.82	2.54	61.02
	SD	8.6	0.57	0.70	0.58	13.92
	%CV	66.8	16.99	38.65	22.81	22.81
	Median	18.0	3.40	1.85	2.53	60.79
	Minimum					
	Maximum					

Table 14.2.2-9. Listing of PK parameters for serum estrone concentration (ng/dL) for all male partners (N=14)

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

Day	Subject ID	PK Parameter Tmax (hr)	Cmax	Cmin*	Caverage	AUC(0-24h)** (ng-h/dL)
1	01M					
	06M					
	07M					
	09M					
	12M					
	15M					
	17M					
	22M					
	25M					
	27M					
	28M					
	34M					
	35M					
	36M					
	Mean	11.5	3.64	1.88	2.69	64.68
	SD	9.8	0.79	0.57	0.56	13.56
	%CV	85.3	21.62	30.54	20.96	20.96
	Median	18.0	3.60	1.90	2.74	65.72
	Minimum					
	Maximum					

Estrone Sulfate Data (Females)

Figure 10

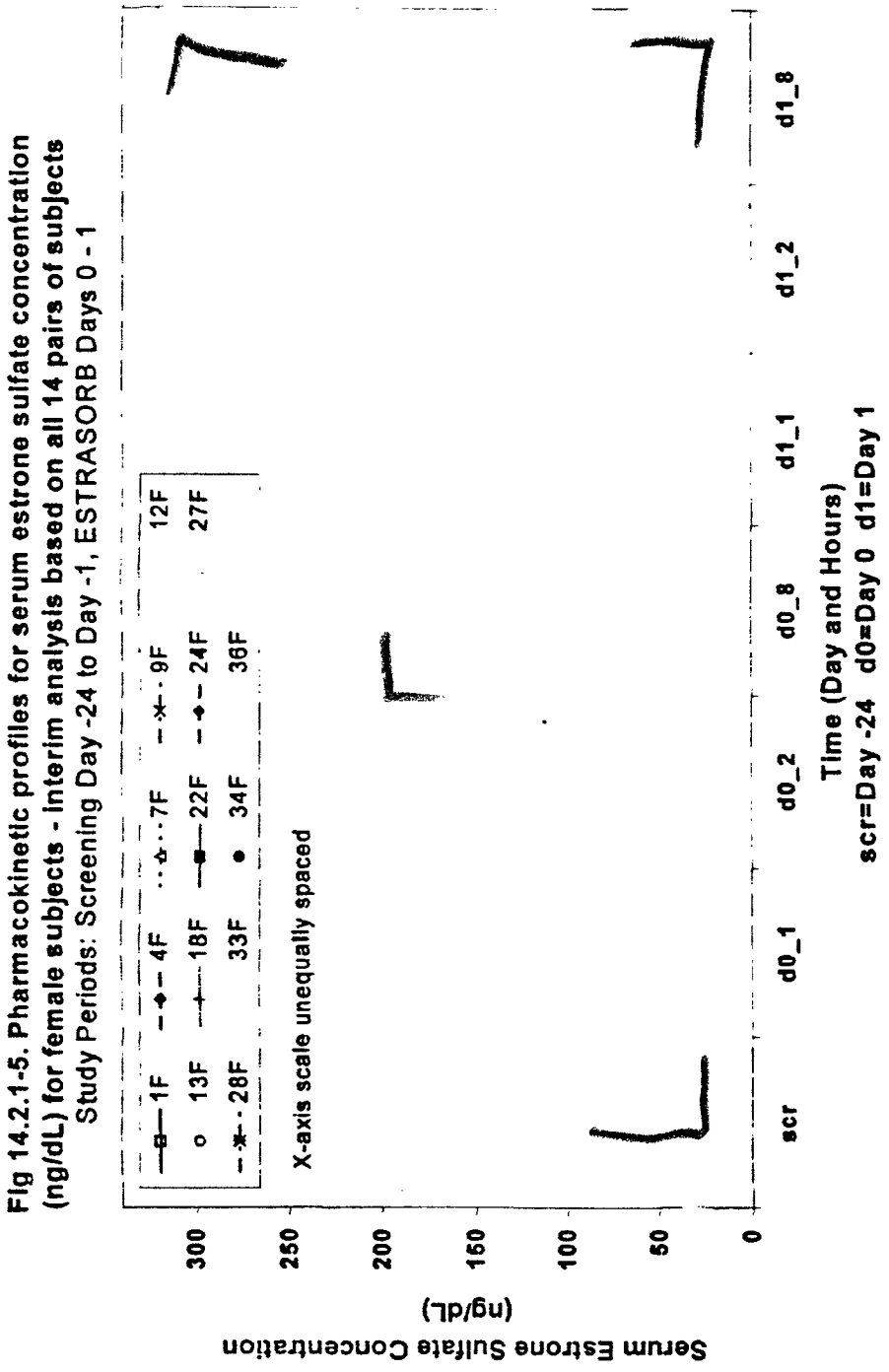


Figure 11

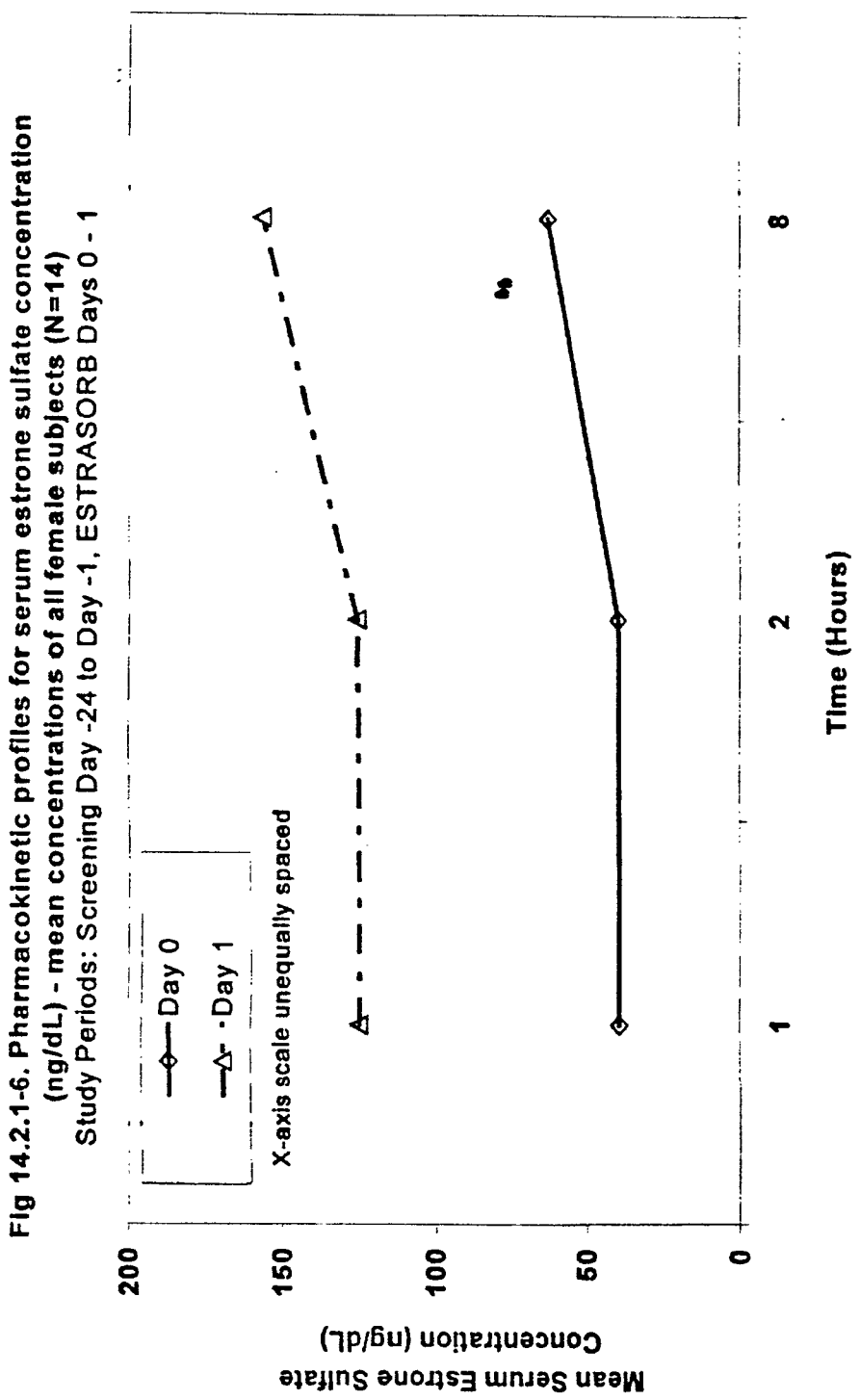


Fig 14.2.1-6. Pharmacokinetic profiles for serum estrone sulfate concentration (ng/dL) - mean concentrations of all female subjects (N=14)
Study Periods: Screening Day -24 to Day -1, ESTRASORB Days 0 - 1
Day 0
Day 1
X-axis scale unequally spaced
Mean Serum Estrone Sulfate Concentration (ng/dL)
200
150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

Table 14.2.1-3. Descriptive statistics of serum estrone sulfate 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	52.79	40.12		45.50	
0	1	14	39.29	24.46		33.00	
	2	14	39.57	23.53		34.50	
	8	14	62.71	37.02		52.50	
1	1	14	124.43	73.70		100.00	
	2	14	125.07	73.32		91.50	
	8	14	156.57	93.05		113.00	

Table 14.2.1-9. Listing of PK parameters for serum estrone sulfate 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	7.6	63	37	49.47	346.26
	SD	1.6	37	24	28.94	202.57
	%CV	21.2	58	65	58.50	58.50
	Median	8.0	53	33	43.25	302.75
	Minimum					
	Maximum					

Table 14.2.1-10. Listing of PK parameters for serum estrone sulfate 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)
1	01F					
	04F					
	07F					
	09F					
	12F					
	13F					
	18F					
	22F					
	24F					
	27F					
	28F					
	33F					
	34F					
	36F					
	Mean	6.6	159	117	138.50	969.48
	SD	2.8	94	69	79.38	555.68
	%CV	43.3	60	59	57.32	57.32
	Median	8.0	113	91	98.96	692.75
	Minimum					
	Maximum					

Estrone Sulfate Data (Males)

Figure 12

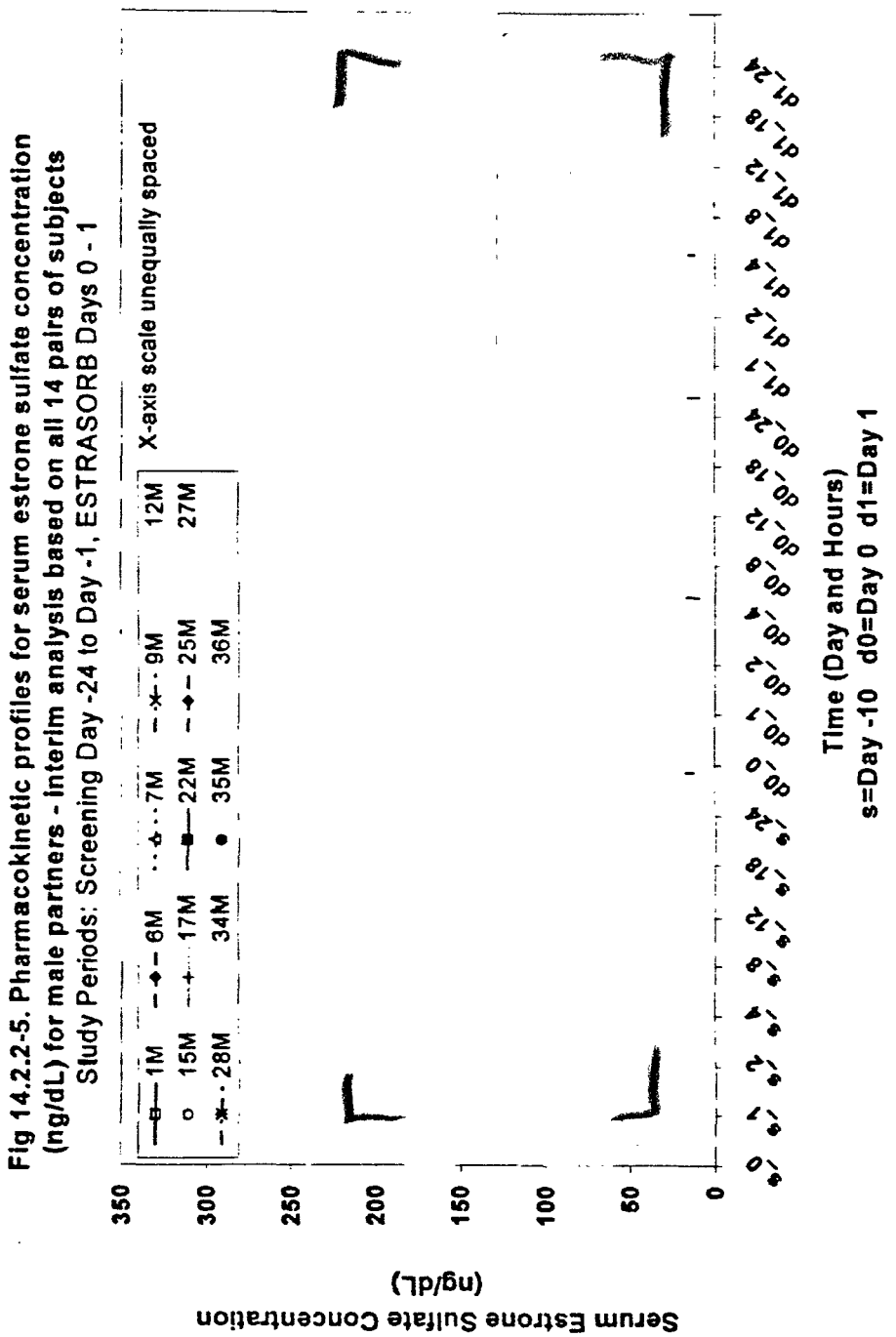


Figure 13

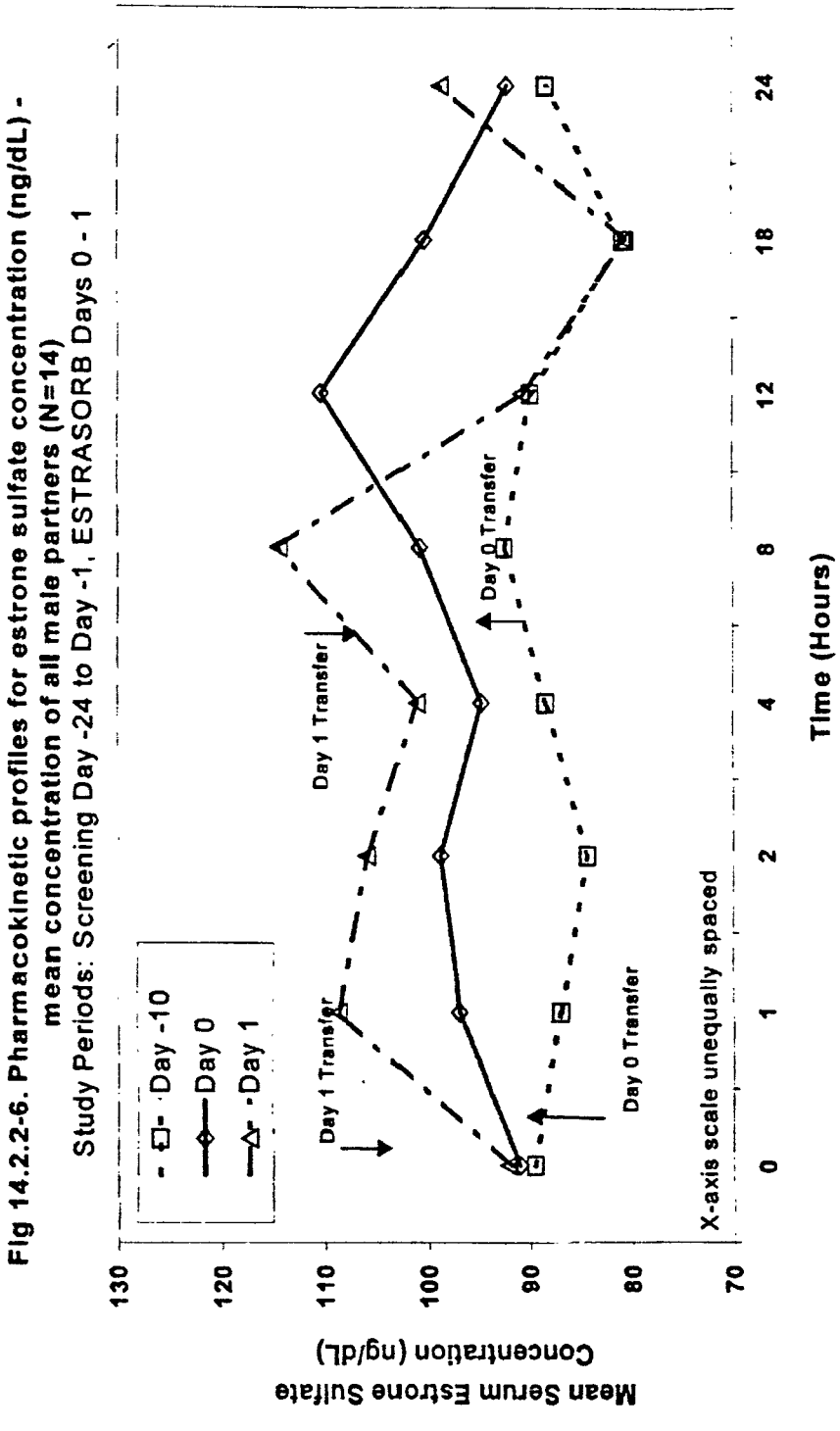


Fig 14.2.2-6. Pharmacokinetic profiles for estrone sulfate concentration (ng/dL) - mean concentration of all male partners (N=14)
Study Periods: Screening Day -24 to Day -1, ESTRASORB Days 0 - 1
Day -10
Day 0
Day 1
Day 1 Transfer
Day 1 Transfer
Day 0 Transfer
Day 0 Transfer
X-axis scale unequally spaced
Mean Serum Estrone Sulfate Concentration (ng/dL)
Time (Hours)
130
120
110
100
90
80
70
0
1
2
4
8
12
18
24

Table 14.2.2-3. Descriptive statistics of profile serum estrone sulfate concentrations (ng/dL) for all male partners (N=14)
Study Days: Screening -24 to -1, ESTRASORB 0 - 1

		Descriptive Statistics					
Day	Hour	N	Mean	Standard Deviation	Maximum	Median	Minimum
-10	0	14	89.50	44.69		77.50	
	1	14	86.86	42.48		79.50	
	2	14	84.29	37.48		73.50	
	4	14	88.36	41.02		71.50	
	8	14	92.36	50.57		69.50	
	12	14	89.79	41.45		81.00	
	18	14	80.71	40.54		73.50	
	24	14	88.21	35.94		76.50	
0	0	14	91.00	42.38		80.00	
	1	14	96.79	46.28		93.50	
	2	14	98.71	54.94		94.50	
	4	14	94.71	50.32		81.00	
	8	14	100.71	46.52		99.50	
	12	14	110.29	48.18		103.00	
	18	14	100.21	43.23		81.50	
	24	14	92.07	31.11		84.50	
1	0	14	92.07	31.11		84.50	
	1	14	108.57	42.00		104.50	
	2	14	105.86	37.89		95.00	
	4	14	101.00	37.49		89.50	
	8	14	114.36	45.17		92.00	
	12	14	90.64	31.69		84.00	
	18	14	80.43	19.79		77.00	
	24	14	98.57	23.32		91.00	

Table 14.2.2-10. Listing of PK parameters for serum estrone sulfate concentration (ng/dL) for all male partners (N=14)

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

Day	Subject ID	PK Parameter: Tmax (hr)	Cmax	Cmin*	Caverage	AUC(0-24h)** (ng-h/dL)
-10						
	Mean	6.2	104	73	86.93	2086.40
	SD	8.4	50	32	40.51	972.34
	%CV	135.4	48	43	46.60	46.60
	Median	3.0	82	63	73.27	1758.39
	Minimum					
	Maximum					

Table 14.2.2-11. Listing of PK parameters for serum estrone sulfate concentration (ng/dL) for all male partners (N=14)

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

Day	Subject ID	PK Parameter: Tmax (hr)	Cmax	Cmin*	Caverage	AUC(0-24h)** (ng-h/dL)
0	01M					
	06M					
	07M					
	09M					
	12M					
	15M					
	17M					
	22M					
	25M					
	27M					
	28M					
	34M					
	35M					
	36M					
	Mean	10.9	121	78	99.97	2399.25
	SD	7.2	52	33	43.26	1038.22
	%CV	65.8	43	42	43.27	43.27
	Median	12.0	117	74	95.34	2288.10
	Minimum					
	Maximum					

Table 14.2.2-12. Listing of PK parameters for serum estrone sulfate concentration (ng/dL) for all male partners (N=14)

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

Day	Subject ID	PK Parameter: Tmax (hr)	Cmax	Cmin*	Caverage	AUC(0-24h)** (ng-h/dL)
1	01M					
	06M					
	07M					
	09M					
	12M					
	15M					
	17M					
	22M					
	25M					
	27M					
	28M					
	34M					
	35M					
	36M					
	Mean	8.0	128	77	95.66	2295.90
	SD	9.2	45	22	29.36	704.56
	%CV	115.0	35	29	30.69	30.69
	Median	5.0	113	74	86.67	2080.14
	Minimum					
	Maximum					

FSH Data (Females)

Figure 14

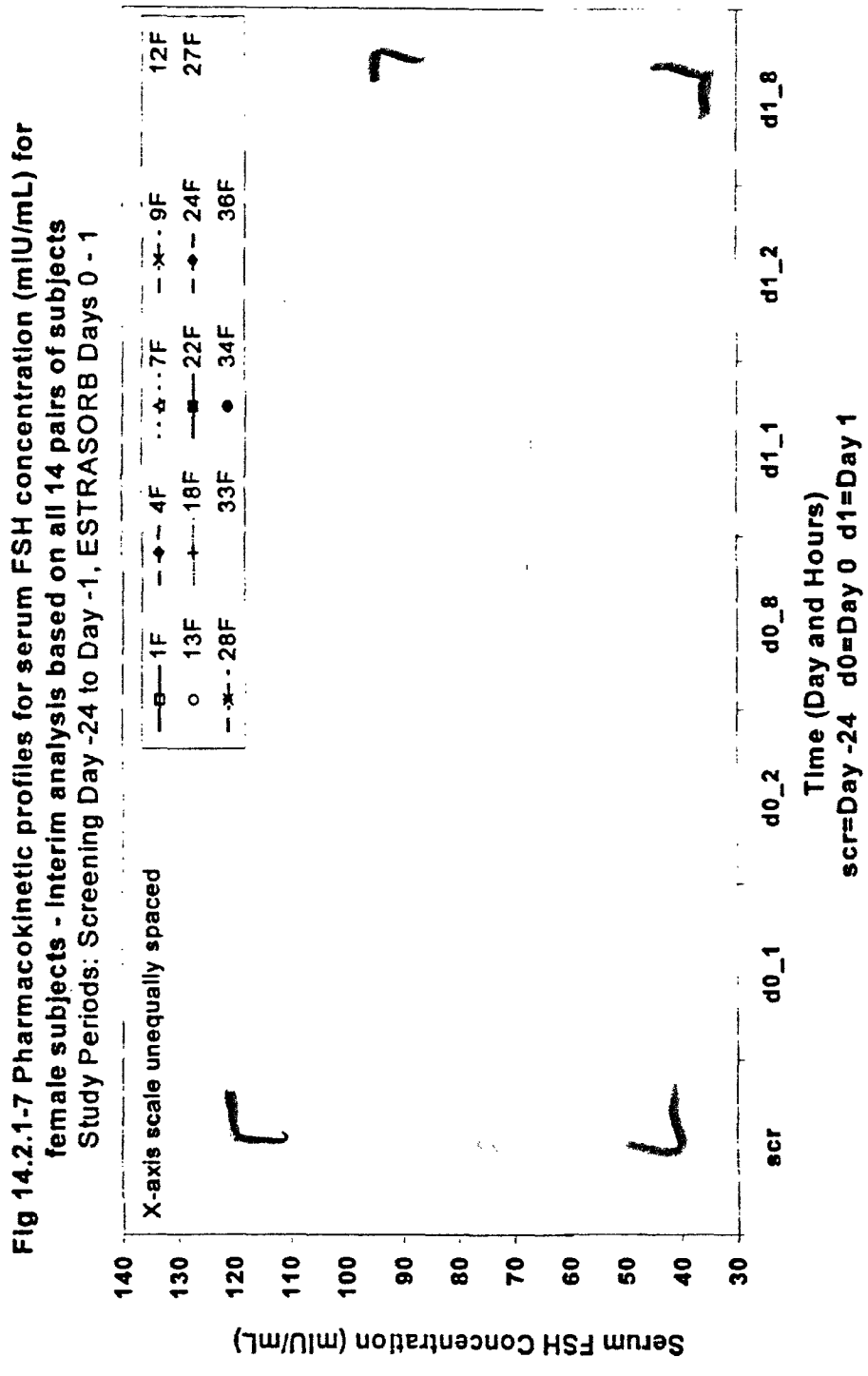


Figure 15

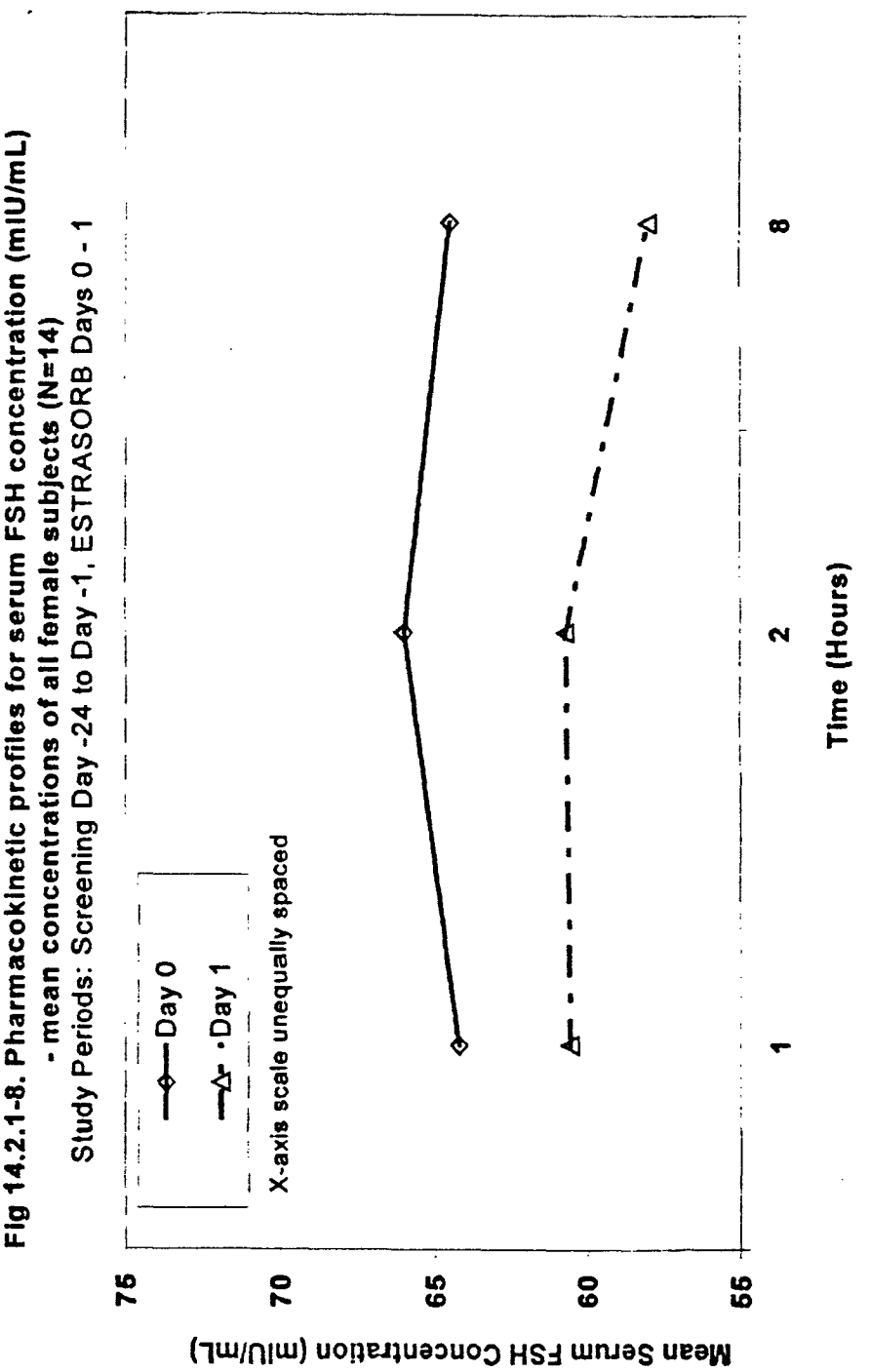


Fig 14.2.1-8. Pharmacokinetic profiles for serum FSH concentration (mIU/mL)
- mean concentrations of all female subjects (N=14)
Study Periods: Screening Day -24 to Day -1, ESTRASORB Days 0 - 1
Day 0
Day 1
X-axis scale unequally spaced
Mean Serum FSH Concentration (mIU/mL)
75
70
65
60
55
1
2
8
Time (Hours)

Table 14.2.1-4. Descriptive statistics of serum FSH concentrations (mIU/mL) 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	73.29	18.11		77.50	
0	1	14	64.21	15.74		61.00	
	2	14	66.00	18.34		64.00	
	8	14	64.50	18.71		62.00	
1	1	14	60.57	15.90		57.50	
	2	14	60.71	14.91		61.00	
	8	14	58.00	13.67		54.50	

Table 14.2.1-11. Listing of PK parameters for serum FSH concentration (mIU/mL) for all female subjects (N=14)

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

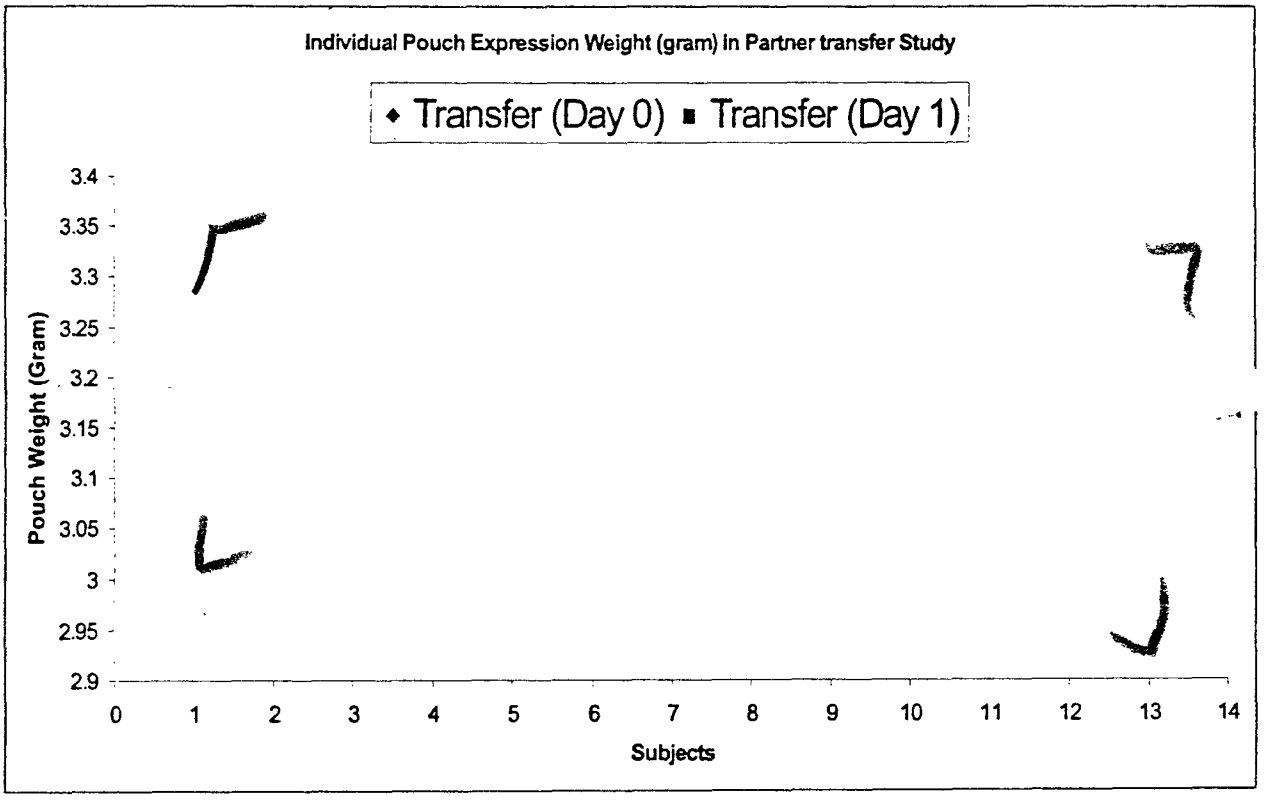
Day	Subject ID	PK Parameter Tmax (hr)	Cmax	Cmin*	Caverage	AUC(1-8h) (mIU-h/mL)
0	01F					
	04F					
	07F					
	09F					
	12F					
	13F					
	18F					
	22F					
	24F					
	27F					
	28F					
	33F					
	34F					
	36F					
	Mean	2.9	70	60	65.17	456.17
	SD	2.8	18	16	17.87	125.09
	%CV	98.9	26	27	27.42	27.42
	Median	2.0	69	55	63.14	441.95
	Minimum					
	Maximum					

Table 14.2.1-12. Listing of PK parameters for serum FSH concentration (mIU/mL) for all female subjects (N=14)

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

Day	Subject ID	PK Parameter: Tmax (hr)	Cmax	Cmin[4]	Caverage	AUC(1-8h) (mIU-h/mL)
1	01F					
	04F					
	07F					
	09F					
	12F					
	13F					
	18F					
	22F					
	24F					
	27F					
	28F					
	33F					
	34F					
	36F					
	Mean	2.9	64	56	59.46	416.25
	SD	2.8	15	13	14.03	98.24
	%CV	95.1	24	24	23.60	23.60
	Median	2.0	62	54	56.75	397.27
	Minimum					
	Maximum					

Figure 16.



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

	---- Pouch Expression Weights (g) ----		
Subject/ID	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			

Appendix II

Sponsor's New Proposed Label

39 pages redacted from this section of the approval package consisted of draft labeling

Appendix III
OCPB Original Review

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 Al-Habet, Ph.D.	Indication(s)	Vasomotor Symptoms
OCPB Team Leader	Ameeta Parekh, Ph.D.	Dosage Form	Topical
		Dosing Regimen	Once daily
Date of Submission	June 29, 2001	Route of Administration	Skin (thigh)
Estimated Due Date of OCPB Review	July 13, 2002	Sponsor	Novavax
PDUFA Due Date	June 29, 2002	Priority Classification	3S
Division Due Date	April 1, 2002		

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		
Primary reviewer Signature and Date	**Sayed Al-Habet, Ph.D.**	
Secondary reviewer Signature and Date	**Ameeta Parekh, Ph.D.**	

CC: NDA 21-289, HFD-850 (p. Lee), HFD-580 (Spell-LeSane), HFD-870 (Al-Habet, Parekh, Malinowski, Hunt), CDR (B. Murphy, biopharm file)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
(DFS Version, 2002)

NDAs: 21-371
Category: 3S

Submission Date:
June 29, 2001
February 20, 2002
March 21, 2002

Generic Name: 17β-Estradiol

Brand Name: Estrasorb™

Formulations: Transdermal [redacted]

Route of Administration: Topical

Indication: [redacted]

Sponsor: Novavax, Inc.
Rockville, MD

Type of Submission: New Topical Formulation (3S)

Reviewer: Sayed Al-Habet, Ph.D.

Dates of Review:

Received for Review:	July 5, 20001
First Draft:	February 27, 2002
Second Draft:	March 14, 2002
Briefing Draft:	April 1, 2002
Final/DFS Version:	April 23, 2002

TABLE OF CONTENTS

Synopsis:

ESTRASORB (estradiol [redacted] contains 17β-estradiol [redacted] 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 products. [redacted] of drug products. [redacted] 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 the same amount of drug product and estradiol as three 1.15 gram pouches. Each 1.74 gram pouch contains 4.35 mg of estradiol. [redacted] from the [redacted]

RECOMMENDATION:

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

General Comments:

1. There was a wide inter-subject variability in serum hormones level (estradiol, estrone, estrone sulfate, and FSH).
2. The sponsor is advised to determine the consistency in the amount/dose delivered from [redacted] nd pouches. This can be validated by conducting a simple *in vitro* experiment. At that time of review the data from the on-going study to address this issue has not been yet submitted.
3. Based on the Chemistry review by Dr. Amit Mitra, the product quality, methods, facilities, and manufacturing control are not adequate (see chemistry review).
4. In addition to the labeling changes related to PK, the sponsor should address the effect of showering, swimming, etc, after Estrsorb application.

1.

Executive Summary
Clinical Pharmacology and Biopharmaceutics

Background:

Estrasorb is an oil water base vehicle containing low concentrations of ethanol [redacted] that would deliver estradiol systemically and have a zero order pharmacokinetic profile. The final to-be-marketed formulation is packaged in foil-laminated pouches [redacted]

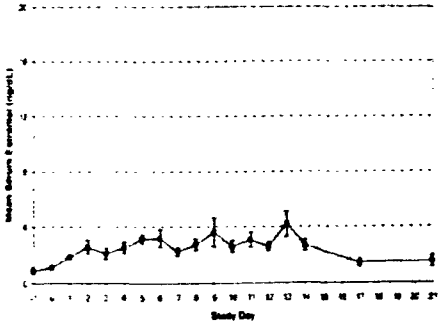
From the clinical pharmacology and biopharmaceutics point of view, the main studies that were conducted to support labeling are briefly summarized here in chronological order.

A) Pilot Formulation:

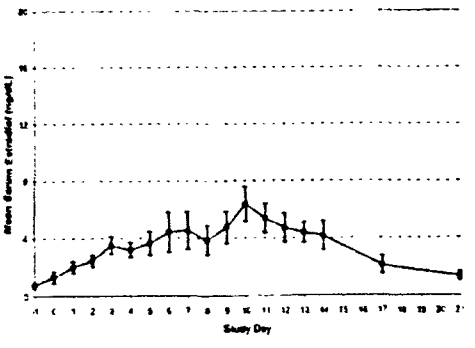
Three studies were conducted using a pilot formulation that contain the same excipients, but different ratios from the "to-be-marketed" formulation (study #N95-3, N96-1, and N97-3). The formulation used in these studies contains [redacted] water. No PK data were generated from study # 95-3. The other two preliminary studies were conducted for dose finding following daily application of Estrasorb for 14 days corresponding to estradiol doses of 5 and 7.5 mg (study # N96-1) or 7.5 mg or placebo (study #N97-3). Trough serum estradiol samples were drawn daily on Day 0 through Day 13 and up to 21 days after the last dose on Day 13. A total of 18-20 subjects completed each study. Serum concentrations of estradiol and estrone after 7.5 mg were slightly higher than 5 mg (**Figures A and B**). From both studies, the steady state level was reached within 3-4 days.

Figures AB. Mean (± SE) Trough Estradiol Serum Concentration-Time Profiles for Subjects Receiving Once Daily Estrasorb 5 mg (A) or 7.5 mg (B)dose (study # 96-1).

A) 5 mg QD X 13 Days



B) 7.5 mg QD X 13 days



B) Final Formulation:

A new — formulation was later developed which is containing surfactant and — water. This is the "to-be-marketed" formulation, designated as ESTRASORB, and was used in three main studies (#E98-1, E98-2, E99-1 and E2000-1). **Figure C** shows that Estrasorb dose can be applied either to one site (i.e., one thigh) as 2 X 1.15 gram (7.5 mg estradiol) or split into two sites (i.e., two thighs) as 1 X 3 gram Estrasorb (7.5 mg estradiol).

Figure C. Median Trough Plasma Concentrations for Estradiol, estrone, and Estrone Sulfate Following 7.5 mg Estradiol Daily Dose for 8 Days to One Site (i.e., One Thigh, n=4) or Split Into Two Sites (i.e., Two Thighs, n=4) (study # E98-1).

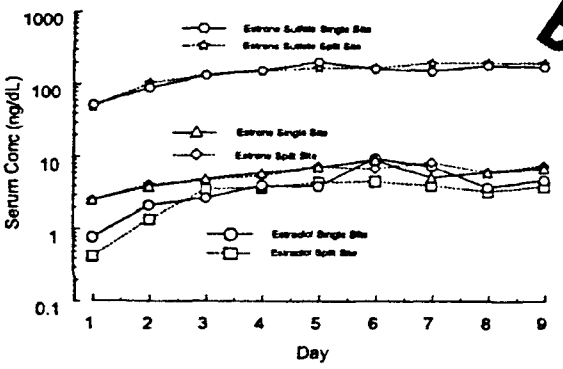
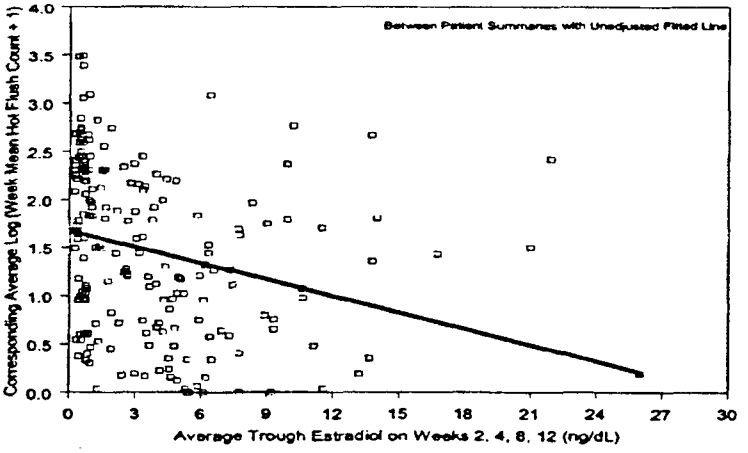


Figure D shows some relationship between estradiol serum trough concentration and hot flush count ($R^2 = 0.1205$). This is from the pivotal Phase III study following estradiol daily application for 12 weeks at estradiol daily dose of 7.5 mg (3 gram Estrasorb) in 200 symptomatic postmenopausal women. In this study 100 women were on active treatment and 100 were on placebo (study # E99-1).

Figure D. Relationship Between Estradiol Trough Serum Concentration and Hot Flush Count Following Daily Application of Estrasorb for 12 Weeks at Estradiol Dose of 7.5 mg (study # 99-1) ($R^2 = 0.3971$)



Study # E2000-1 was a skin residual study. From this study it was shown than no estradiol

was detected on the skin after washing with soap 8 hours after Estrasorb application.

Overall Conclusions:

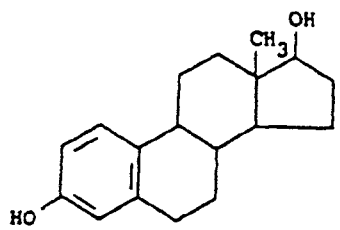
1. Estradiol steady state concentration reached in 3 to 4 days.
2. At steady state, estradiol concentration is approximately 4-fold higher than Day 1.
3. The absorption phase of estradiol is slower than the disposition/elimination phase. This suggests a "Flip-Flop" phenomenon.
4. Estrasorb dose can be applied either at a single site or split into two sites. Therefore, the choice of the site of application should be left to individual preference.
5. There is some relationship between estradiol serum concentration and hot flushes count.
6. Essentially no estradiol residual was detected on the skin after washing with soap 8 hours after application.

SUMMARY REVIEW
OF PHARMACOKINETICS AND BIOAVAILABILITY
(Question Based Review, QBR)

A) BACKGROUND:

What are the Physico-Chemical Properties of [redacted]

Estrasorb is a [redacted] transdermal delivery system composed of an oil, water, surfactant (polysorbate 80), ethanol, and estradiol. Chemically, the active ingredient in ESTRASORB is 17β-estradiol. The empirical formula of 17β-estradiol is $C_{18}H_{24}O_2$, representing a molecular weight of 281.4 with the following structural formula:



[redacted]

What Are the Process of Formulation Development ?

Early nonclinical and clinical studies were conducted using ESTRASORB [redacted] formulations containing [redacted] These were packaged in syringes, but must be stored at 4°C, due to its thermal instability. Later, a new [redacted] formulation was developed using additional [redacted]. This was packed in [redacted] (**Figure 1 A & B**) and [redacted] (**Figure 2**). This formulation was stable at 30°C for 24 months and subsequently used in four clinical PK studies (#E98-1, E08-2, E-99-1, and E2000-1). **Table 1** shows the composition of all formulations used in this NDA.

[redacted]

Redacted 6

page(s) of trade secret and/or confidential commercial information (b4)

Table 2. Validated Analytical Methods Used in this NDA

Report No.	Biological fluid	Method	Sensitivity of method/range	Specificity
VP0208 V1.3	Serum	[redacted]		Estradiol
VP0208 V1.0	Serum			Estrone
VP0256 V1.0	Serum			Estrone Sulfate
VP0316 V1.1	Serum			FSH
VP0246 V1.6	Serum			Testosterone

FSH-ICMA=Follicle Stimulating Hormone-Immunochemiluminometric

How Estradiol is Metabolized and Eliminated?

17β-estradiol is catabolized to either 2-hydroxyestradiol, 4-hyroxyestradiol or 16β-hydroxyestradiol. Catechol O-methyltrasferase converts 2-hydroxyestradiol to either 4-methyoxyestradiol or 4-hydroxyestradiol 3-methyl ether, 4-hydroxestradiol to either 2-methyoxyestradiol or 2-hydroxestradiol 3-methyl ether and 16α-hydroxyestradiol to estriol.

Estrone is catabolized to either 2-hydroxyestrone, 4-hydroxyestrone or 16α-hydroxyestrone. Catechol O-methyltransferase converts 2-hydroxyestrone to either 4-methoxyestrone or 4-hydmxyestrone 3-methyl ether and 4-hydroxyestrone to either 2-methoxyestrone or 2-hydroxyestrone 3-methyl ether. 16α-hydroxyestrone is converted by 17β-hydroxysteroid dehydrogenase to estriol.

When given orally, estradiol is extensively metabolized by the liver (first-pass effect). The elimination half life is approximately 1 hour. In the liver estradiol is primarily converted by 17β-hydroxysteriod dehydrogenase to estrone, which undergoes conversion by 16α-hydroxylation and 17-keto reduction to estriol, which is the major urinary metabolite. A variety of sulfate and glucoronide conjugates are formed, and these are excreted in the urine and the bile. Those excreted in the bile undergo enterhepatic recycling or are excreted in the feces. In contrast, the skin metabolizes estradiol only to a small extent. Administration of estradiol via a topical transdermal route results in slow and sustained release of the hormone in the systemic circulation than that found after oral administration.

What is the Target Serum level of Estradiol?

Estradiol levels in women vary throughout the ovulatory cycle: in the follicular phase, 1 to 9 ng/dl; midcycle, 10 to 50 ng/dL; and the luteal phase, 5 to 24 ng/dL. With the onset of

menopause, serum or plasma estradiol levels fall to 1 to 3 ng/dL. Therefore, from the PK and clinical point of views, to be acceptable, Estrasorb should deliver or sustain serum estradiol levels within the naturally occurring serum levels.

What is the Plasma Protein Binding of estradiol?

Estrogens are tightly bound to plasma proteins. Estradiol, estrone and other endogenous estrogens are mainly bound to sex hormone binding globulin (SHBG), and to a lesser degree to serum albumin.

B) CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS STUDIES:

From the clinical pharmacology and biopharmaceutics point of view, the main studies were conducted to support labeling are briefly summarized in chronological order below:

A) Pilot Formulation:

Three studies were conducted using a pilot formulation that contain the same excipients, but different ratios from the "to-be-marketed" formulation. This pilot formulation contains [redacted] water (**Table 1**). The three studies conducted using a pilot formulation are briefly described below.

Study # N95-3 (Phase I):

The blood samples collected for the PK analysis in this study were not analyzed. This was a very preliminary PK study in 10 symptomatic post-menopausal women. Estrasorb was applied to the abdomen as a single dose of 1 ml micellar nanoparticles containing 2.42 mg estradiol. Serum estradiol and estrone samples were drawn at 0.5, 1, 2, 4, and 8 hours postdose and then daily from day 1 through day 10. Since PK blood samples were not analyzed in this study no conclusions can be made regarding the PK profiles and formulation performance.

Study #N96-1 (Phase I):

This was also a preliminary dose finding PK study following multiple doses of either 5 mg or 7.5 mg estradiol daily for 14 days. The study was initiated with 10 subjects at the lower dose and since this was found to be well tolerated, additional 10 subjects were enrolled for the higher dose. Trough serum estradiol samples were drawn daily on Day 0 through Day 13. Following the last dose on Day 13, serum estradiol concentrations were measured at 0.5, 1, 2, 4, 6, 8, 24, 120, and 216 hours postdose. A total of 20 subjects completed the study. **Figures 4-6 and Table 4** summarize the PK profiles of estradiol from this study.

Figure 4. Mean (± SE) Trough Estradiol Serum Concentration-Time Profiles for

Subjects Receiving Once daily Estrasorb 5 mg dose for 14 days (study # 96-1).

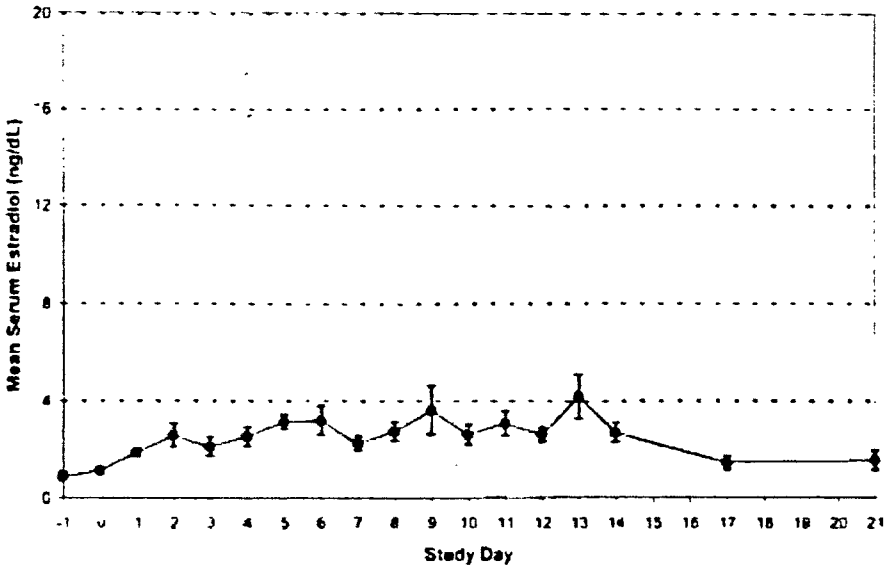


Figure 5. Mean (± SE) Trough Estradiol Serum Concentration-Time Profiles for Subjects Receiving Once daily Estrasorb 7.5 mg dose for 14 days (study # 96-1).

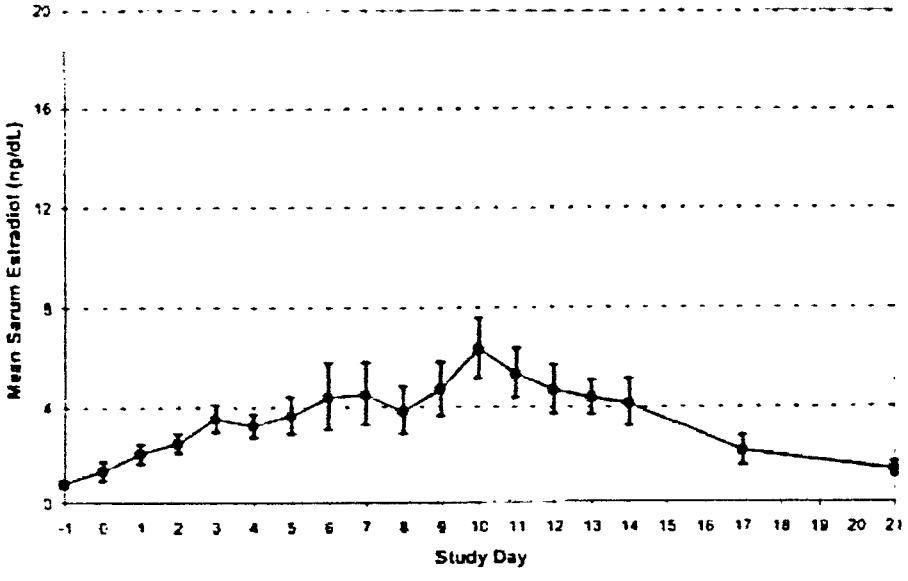
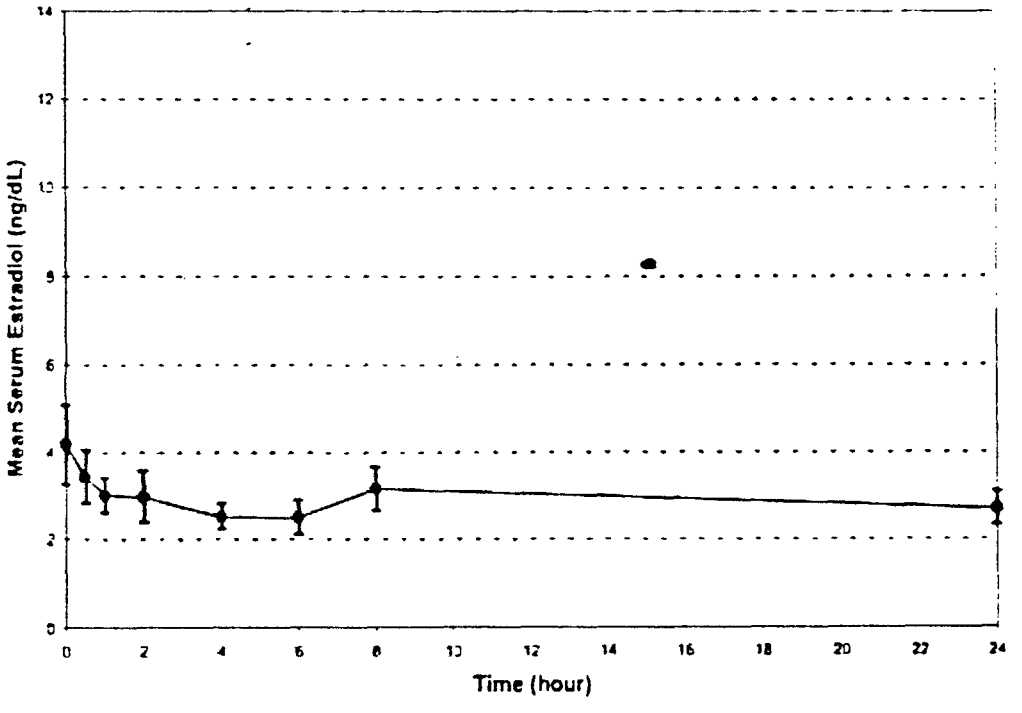
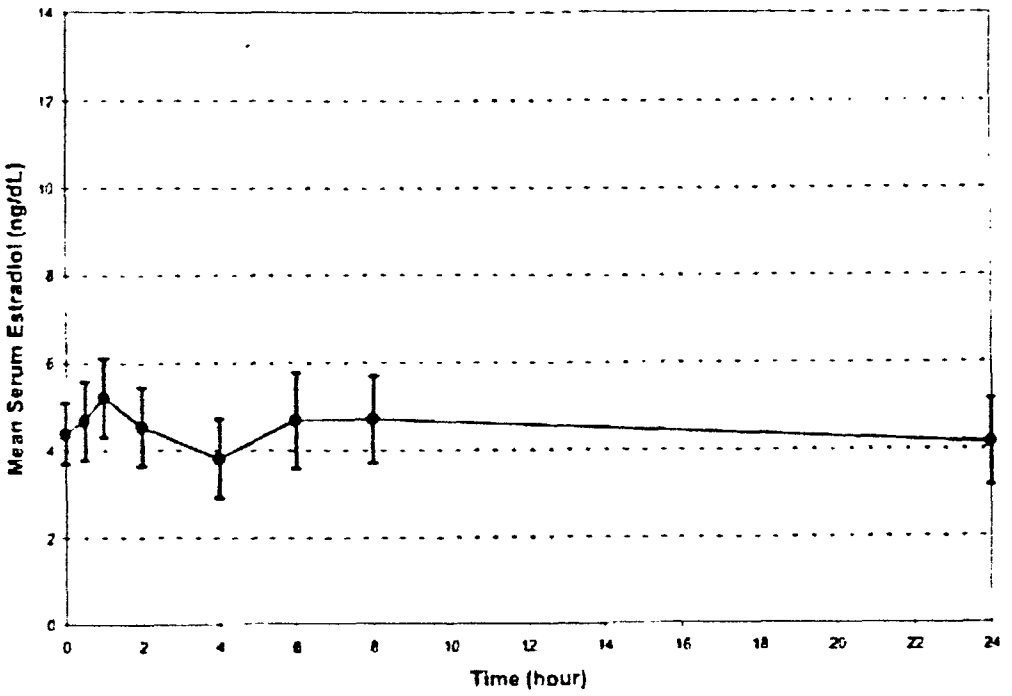


Figure 6. Mean (± SE) Trough Estradiol Serum Concentration-Time Profiles on Day 13 (last and 14th Dose) for Subjects Receiving Once Daily Estrasorb 5 mg Dose (study # 96-1).



APPEARS THIS WAY
ON ORIGINAL

Figure 7. Mean (± SE) Trough Estradiol Serum Concentration-Time Profiles on Day 13 (Last and 14th Dose) for Subjects Receiving Once Daily Estrasorb 7.5 mg Dose (study # 96-1).



APPEARS THIS WAY
ON ORIGINAL

Table 4. Mean (± SD) PK Parameters for Estradiol on Day 13 (14th and Last Dose) (study # 96-1).

Parameter (units)	Hormone	Dose	Mean (SD)	CV%
AUC(0-24hr) (ng•h/dL)	estradiol	5.0 mg	69.82 (31.6)	45.2
		7.5 mg	106.63 (66.0)	61.8
C_{max} (ng/dL)	estradiol	5.0 mg	5.1 (2.9)	56.4
		7.5 mg	7.1 (3.5)	49.4
Cmin (ng/dL	estradiol	5.0 mg	2.0 (0.9)	44.7
		7.5 mg	2.6 (1.9)	72.4
C_{avg} (ng/dL	estradiol	5.0 mg	2.9 (1.3)	45.2
		7.5 mg	4.4 (2.7)	61.9
Dosage Form Index (DFI)[a]	estradiol	5.0 mg	1.3 (1.9)	143.5
		7.5 mg	1.1 (0.6)	56.4

[a]DFI=Dosage Form Index = $(C_{max} - C_{min})/C_{avg}$

Table 5 and Figure 8 show the mean data for hot flush counts following 5 and 7.5 mg doses over three weeks period. The primary efficacy parameter in this study was Moderate Plus Severe Hot Flush Count (MSHFC) and Total Hot Flush Counts (HFCs). From this data it can be concluded that the 7.5 mg dose may be superior to 5 mg dose in reducing hot flushes.

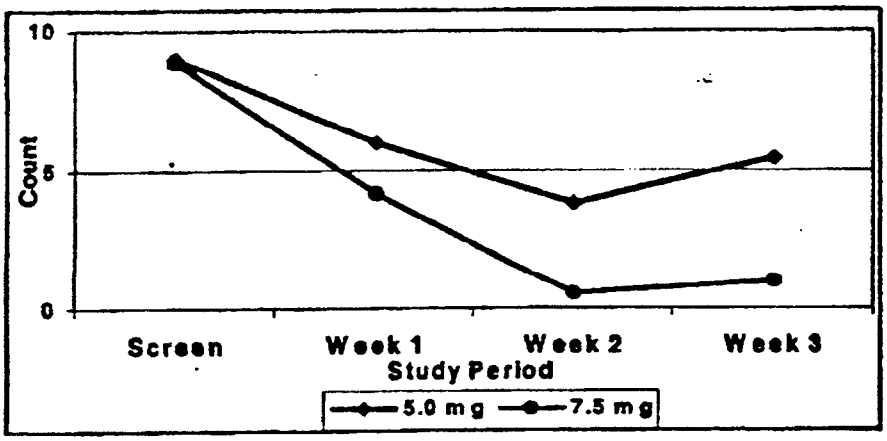
APPEARS THIS WAY
ON ORIGINAL

Table 5. Mean (± SD) Moderate Plus Severe Hot Flush Count (MSHFC) and Total Hot Flush Counts (HFCs) (study # 96-1).

Study Period		MSHFCs		Total HFCs	
		7.5 mg	5.0 mg	7.5 mg	5.0 mg
Baseline (Screen)	N	10	10	10	10
	Mean ± SD	8.8 ± 1.5	9.0 ± 1.6	9.7 ± 1.7	9.1 ± 1.5
Week 1 (Dosing)	N	10	10	10	10
	Mean ± SD	4.2 ± 1.2*	6 ± 1.9	5.7 ± 1.4*	6.2 ± 1.7
	Mean change ± SD	-4.7 ± 1.9*	-3 ± 1.7	-4.0 ± 1.9*	-2.9 ± 1.7
	Mean % change ± SD	-51.5 ± 16.6*	-33.4 ± 19.2	-40.2 ± 17.6*	-31.4 ± 17.8
Week 2 (Dosing)	N	10	10	10	10
	Mean ± SD	0.6 ± 0.5*	3.8 ± 2.7	1.4 ± 1.0*	4.1 ± 2.9
	Mean change ± SD	-8.2 ± 1.3*	-5.2 ± 2.4	-8.3 ± 1.8*	-5.0 ± 2.5
	Mean % change ± SD	-93.2 ± 5.2*	-58.2 ± 28	-85.7 ± 10.5*	-55.5 ± 28.9
Week 3	N	10	10	10	10
	Mean ± SD	1 ± 1.2*	5.4 ± 3	2.1 ± 1.9*	5.6 ± 2.9
	Mean change ± SD	-7.8 ± 1.9*	-3.6 ± 3	-7.6 ± 2.1*	-3.5 ± 2.9
	Mean % change ± SD	-88.3 ± 14.4*	-39.6 ± 32.6	-79.1 ± 17.3*	-38.1 ± 30.3

* Significant intergroup difference ($p = 0.05$) by two-sample t-test
Source: Section 14.2.1a and Section 14.2.1b.

Figure 8. Mean Moderate Plus Severe Hot Flush Count (MSHFC) Following 5 and 7.5 mg Doses of Estradiol (study # 96-1)

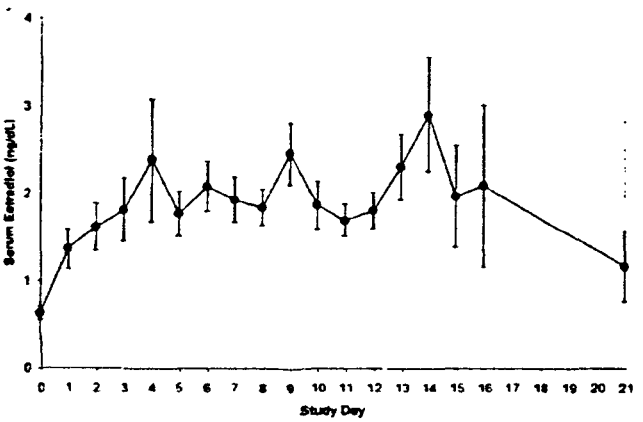


Study #N97-3 (Phase I):

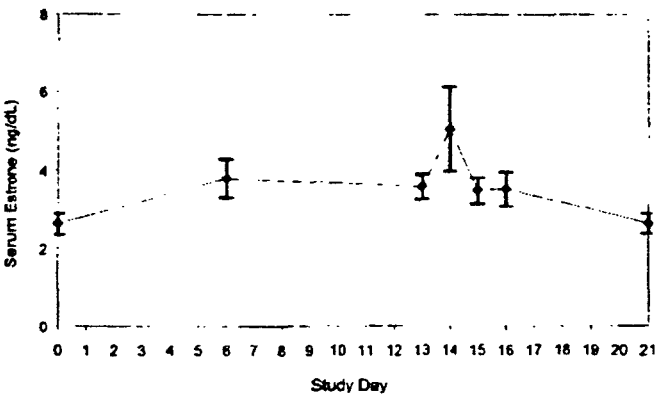
This was a preliminary double blind placebo controlled study in 20 subjects at a daily dose of 7.5 mg estradiol for 14 days. Estrasorb or placebo was applied as 3 ml (7.5 mg estradiol) to both calves and legs (split-dose). A total of 18 subjects completed the study. Trough serum estradiol samples were drawn daily on Days 0 through Day 13. In addition, trough serum estrone, estrone sulfate and FSH samples were drawn on Days 0, 6 and 13. Following the last dose on Day 13, serum estradiol, estrone and estrone sulfate concentrations were measured at 0, 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, and 192 hours postdose. Serum FSH levels were also drawn on Days 21 for subjects in the ESTRASORB group. **Figures 9 A-C** and **10 A-C** and **Table 6** show the summary of the PK profiles and parameters of estradiol, estrone, and estrone sulfate. The primary efficacy parameter in this study is hot flushes count. **Figure 11** shows the relationship between % change from baseline in hot flushes count and the AUC for the trough level of estradiol from Day 0 to Day 13.

Figure 9 A-C. Mean (± SE) Trough Estradiol, Estrone, and Estrone Sulfate Serum Concentration-Time Profiles for Subjects Receiving Once daily Estrasorb 7.5 mg dose for 14 Days (study # 97-3).

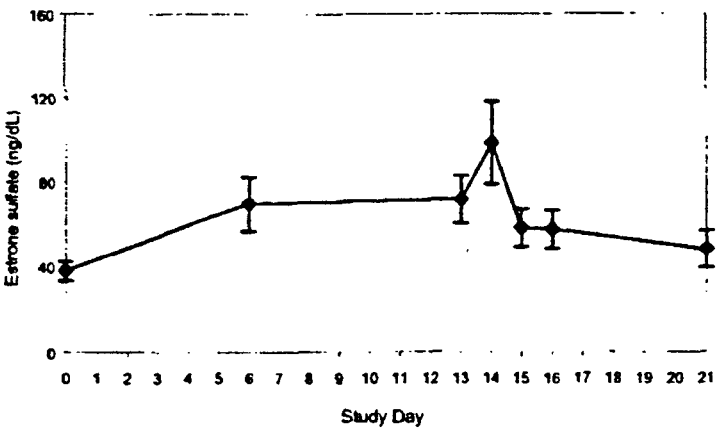
A: Estradiol



B: Estrone

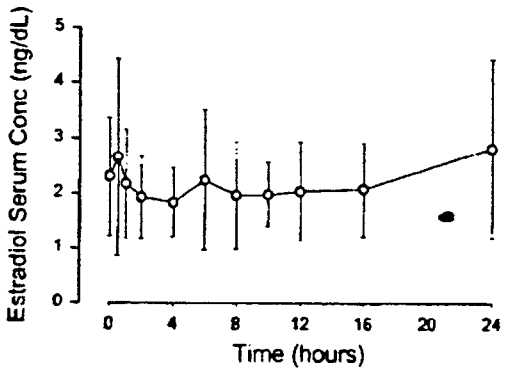


C: Estrone Sulfate

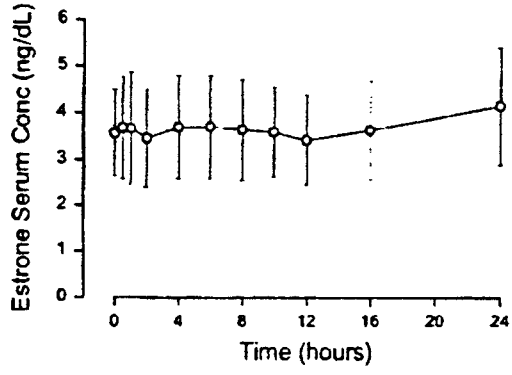


Figures 10 A-C. Mean (± SE) Trough Estradiol, Estrone, and Estrone Sulfate Serum Concentration-Time Profiles on Day 13 (last dose) for Subjects Receiving Once Daily Estrasorb 7.5 mg Dose (study # 97-3).

A: Estradiol



B: Estrone



C: Estrone Sulfate

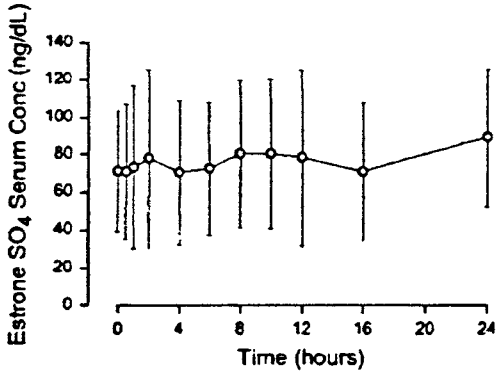


Table 6. Mean (± SD) PK Parameters for Estradiol, Estrone, and Estrone Sulfate on Day 13 (study # N97-3)

Parameter (units)	Hormone	Site Description	Mean (SD)	CV%
$AUC_{(0\text{-}24hr)}$ (ng•h/dL)	estradiol	Split-site	52.6 (19.5)	37.1
	estrone		88.5 (23.3)	26.4
				48.0
C_{max} (ng/dL)				52.0
				28.0
				43.8
C_{min} (ng/dL)				32.2
				28.3
				58.2
C_{avg}				37.1
				26.4
				48.0
Tmax (h)				76.8
				89.7
				90.6
Dosage For (DFI)[a]				46.1
				58.1
				66.5

[a]DFI=Dosage

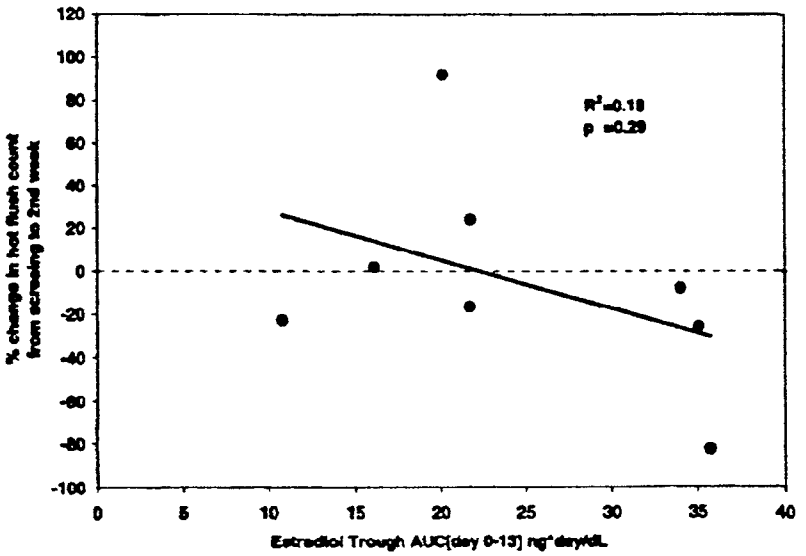


Figure 11. Relationship Between % Change in Hot Flushes Count and Estradiol AUC From Day 0 to Day 13 (Study # N97-3).

APPEARS THIS WAY
ON ORIGINAL

Overall Conclusions From the Pilot Studies (#N95-3, N96-1, and N97-3):

- The steady-state level is reached between 3 to 4 days.
- Delivery rate is approximately 0.05 mg/day.
- In terms of efficacy, there is a relatively good dose/concentration response relationship.
- The 7.5 mg dose of estradiol appears superior to 5 mg dose in terms of reduction in hot flushes count.

B. Final Formulation:

A new [redacted] formulation was later developed containing surfactant [redacted] water (**Table 1**). This is the "to-be-marketed" formulation, designated as ESTRASORB and was used in the following studies.

Phase I Study (#E98-1):

This was a small (n=10) preliminary parallel arms study to investigate the PK and PD of a single dose of 7.5 mg estradiol applied to one thigh or split to both thighs. The study was conducted in symptomatic post-menopausal women randomized into two groups, each consists of five subjects: 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 subject 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. For trough levels samples were also collected pre-dose on the following Days: 0, 2, 3, 4, 5, 6, and 7. The data from this study are summarized in **Figures 12-14** and **Tables 7-10.**

Figure 12. Day 1 Median Plasma Concentrations for Estradiol, estrone, and Estrone Sulfate Following Both Single and Split-Site Applications (study # E98-1)

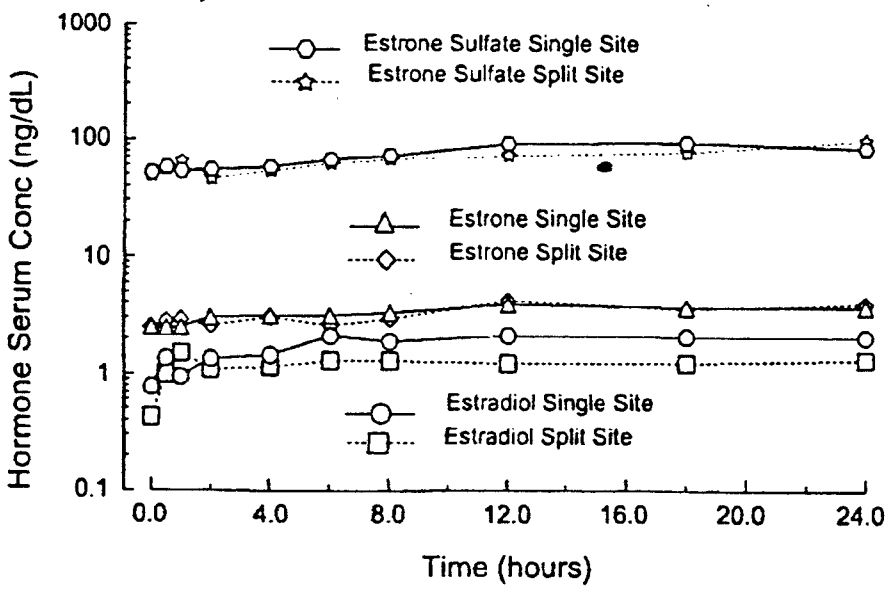


Figure 13. Median Trough Plasma Concentrations for Estradiol, estrone, and Estrone Sulfate Following 7.5 mg Estradiol Dose to One Site (i.e., One Thigh) or Split Into Two Sites (i.e., Two Thighs) (study # E98-1)

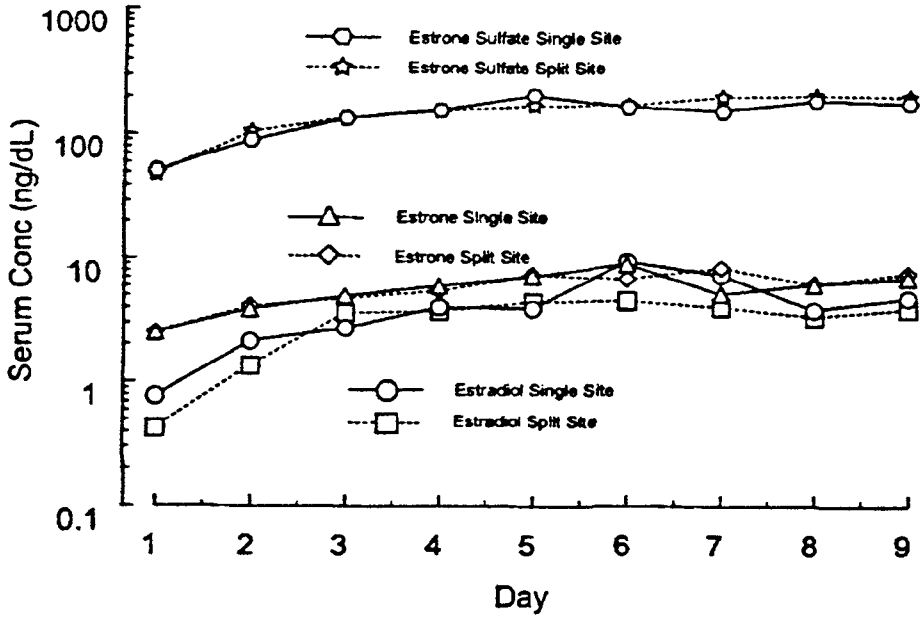
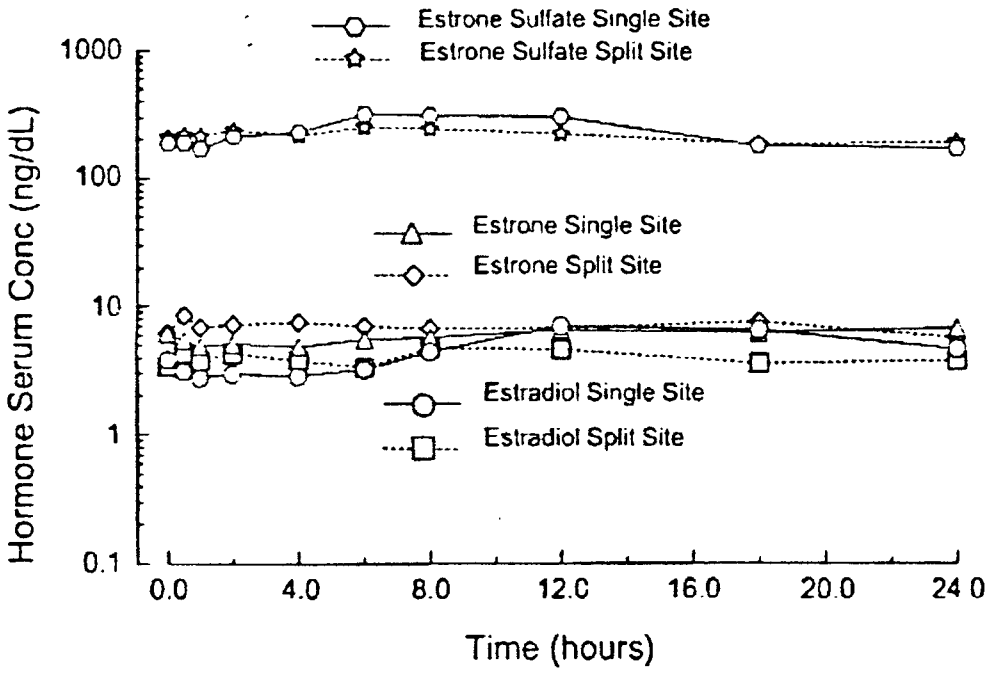


Figure 14. Median Plasma Concentrations for Estradiol, estrone, and Estrone Sulfate on Day 8 Following Both Single and Split-Site Applications (study # E98-1)



APPEARS THIS WAY
ON ORIGINAL

Table 7. Mean (± SD) PK Parameters for Estradiol, Estrone, and Estrone Sulfate for Dose 1 (study # E98-1)

Parameter (units)	Hormone	Site Description	Mean (SD)	CV%
$AUC_{(0\text{-}24hr)}$ (ng•h/dL)	estradiol	Single-site	52.3 (38.5)	73.6
	estrone		81.8 (26.5)	32.4
	estrone sulfate		2389 (1526)	63.9
	estradiol	Split-site	37.3 (25.1)	67.4
	estrone		82.1 (36.7)	44.6
	estrone sulfate		2137 (1325)	62
C_{max} (ng/dL)	estradiol	Single-site	3.05 (2.04)	67.0
	estrone		4.65 (1.35)	29.0
	estrone sulfate		161 (153)	94.9
	estradiol	Split-site	3.45 (2.66)	77.1
	estrone		4.48 (1.85)	41.3
	estrone sulfate		136 (95)	70.1
T_{max} (h)	estradiol	Single-site	15.5 (7.00)	45.2
	estrone		19.5 (5.74)	29.5
	estrone sulfate		21.0 (3.46)	16.5
	estradiol	Split-site	10.3 (10.28)	100.2
	estrone		19.5 (5.74)	29.5
	estrone sulfate		12.3 (9.39)	76.7

Table 8. Mean (± SD) PK Parameters for Estradiol, Estrone, and Estrone Sulfate for Dose 8 (study # E98-1)

Parameter (units)	Hormone	Site Description	Mean (SD)	CV%
$AUC_{(0\text{-}24hr)}$ (ng•h/dL)	estradiol	Single-site	148 (104)	70.6
	estrone		185 (117)	63.5
	estrone sulfate		6967 (5059)	72.6
	estradiol	Split-site	92.7 (28.9)	31.1
	estrone		173 (55)	31.9
	estrone sulfate		6200 (4362)	70.4
C_{max} (ng/dL)	estradiol	Single-site	8.65 (5.12)	59.2
	estrone		8.95 (5.53)	61.8
	estrone sulfate		410 (289)	70.5
	estradiol	Split-site	5.48 (1.40)	25.5
	estrone		8.65 (1.94)	22.4
	estrone sulfate		320.3 (225.5)	70.4
T_{max} (h)	estradiol	Single-site	11.00 (8.72)	79.3
	estrone		16.0 (9.80)	61.2
	estrone sulfate		10.5 (5.97)	56.9
	estradiol	Split-site	4.25 (4.33)	101.9
	estrone		9.25 (11.23)	121.4
	estrone sulfate		8.50 (4.12)	48.5

Table 9. Mean (± SD) Uncorrected and Corrected PK Parameters for Estradiol, Estrone, and Estrone Sulfate for Dose 1 and 8 (study # E98-1)

Hormone	$AUC_{(0\text{-}24hr)}$ ng•h/dL (Dose 1)	$AUC_{(0\text{-}24hr)}$ ng•h/dL (Dose 8)	Rc	CL/F (mL/min/kg)
		Single-Site Application		
Estradiol Uncorrected	52.2 (38.3)	148 (104)	2.97 (0.54)	N/A
Estradiol Corrected	21.8 (9.12)	117 (71.0)	5.50 (2.39)	2407 (1831)
Estrone Uncorrected	81.8 (26.5)	185 (117)	2.23 (1.08)	N/A
Estrone Corrected	18.1 (10.4)	119 (117)	6.43 (3.09)	N/A
Estrone Sulfate Uncorrected	2389 (1526)	6967 (5059)	2.74 (0.84)	N/A
Estrone Sulfate Corrected	935 (691)	5497 (4310)	5.74 (1.59)	N/A
		Split-Site Application		
Estradiol Uncorrected	37.3 (25.2)	92.7 (28.9)	3.60 (3.02)	N/A
Estradiol Corrected	22.4 (14.46)	77.7 (23.6)	5.64 (5.86)	2645 (1560)
Estrone Uncorrected	82.2 (36.6)	173 (55.3)	2.36 (1.03)	N/A
Estrone Corrected	23.7 (16.08)	113 (58.2)	5.36 (1.27)	N/A
Estrone Sulfate Uncorrected	2137 (1325)	6200 (4362)	2.98 (1.45)	N/A
Estrone Sulfate Corrected	942 (945)	5000 (4144)	5.83 (2.72)	N/A

Table 10. Statistical Analysis Derived From PK Parameters Estimates Using the Mann-Whitney U Test-Single Versus Split-Site Application (study # E98-1)

Hormone	C_{max} (ng/dL)[a]	T_{max} (h)[a]	$AUC_{(0\text{-}24hr)}$ ng•h/dL[a]	Rc[a]
		Dose 1		
Estradiol Uncorrected	0.886	0.486	0.686	N/A
Estradiol Corrected	0.886	0.486	0.886	N/A
Estrone Uncorrected	0.886	1	1	N/A
Estrone Corrected	0.886	1	0.686	N/A
Estrone Sulfate Uncorrected	0.686	0.2	0.686	N/A
Estrone Sulfate Corrected	0.886	0.2	0.886	N/A
		Dose 8		
Estradiol Uncorrected	0.886	0.486	0.686	0.486
Estradiol Corrected	0.686	0.486	0.686	0.486
Estrone Uncorrected	0.686	0.343	0.886	0.886
Estrone Corrected	0.343	0.343	0.686	1
Estrone Sulfate Uncorrected	0.886	0.686	1	0.886
Estrone Sulfate Corrected	0.686	0.686	1	0.886

[a]Values represent p-values for treatment effect on pharmacokinetic parameters

Comments and Conclusions (study # E98-1):

1. No differences in PK parameters were noted between the single site and the split-site applications.
2. Steady-state levels appear to reach by approximately 3-4 days.
3. There is approximately 4-fold accumulation of estradiol on Day 8 (steady-state level) compared to Day 1.
4. Examining the serum concentration-time profiles shows that the absorption phase is slower than the disposition/elimination phase. This suggests a "Flip-Flop" phenomenon. The absorption of estradiol continued over extended period of time following application.
5. Based on these results, the dose can be either applied to a single site or can be split to two sites. This choice will be left to individual preference.

Phase II Study (#E98-2):

The objective of this study was to investigate the safety and efficacy of Estrasorb and the PK/PD relationship. This was a split-site (both thighs and calves), four arm parallel, dose ranging, double blind, placebo controlled trial in 125 symptomatic post-menopausal women. Following the screening period, subjects were treated with placebo for 7 consecutive days then randomly assigned to 1 gram, 2 gram, or 3 grams of Estrasorb corresponding to 2.5 mg, 5 mg, or 7.5 mg dose of estradiol or placebo for 28 consecutive days, respectively. Estrasorb was applied to the anterior surface of each thigh and calf area. This was followed by a one-week placebo period in all subjects. The primary efficacy parameters for hot flushes were monitored on Weeks 3 and 4. At least 30 subjects completed the study at each dose level. Trough serum estradiol, estrone, estrone sulfate, and FSH levels were measured on Days 1, 8, 15, 22, 29, and 36.

Figures 15-18 show mean (±SE) serum estradiol, estrone, estrone sulfate and FSH levels at each visit. In terms of dose response relationship on hot flushes count, the 7.5 mg dose was more superior than 5 mg dose (**Table 11 and Figures 19,20**). However, there was no apparent difference between 2.5 mg and 5 g doses. The relationship between hot flush counts and trough serum concentrations of estradiol, estrone, or FSH are shown in **Figures 21-23**, respectively.

Figure 15. Mean (± SE) Estradiol Serum Concentration by Visit (study # E98-2)

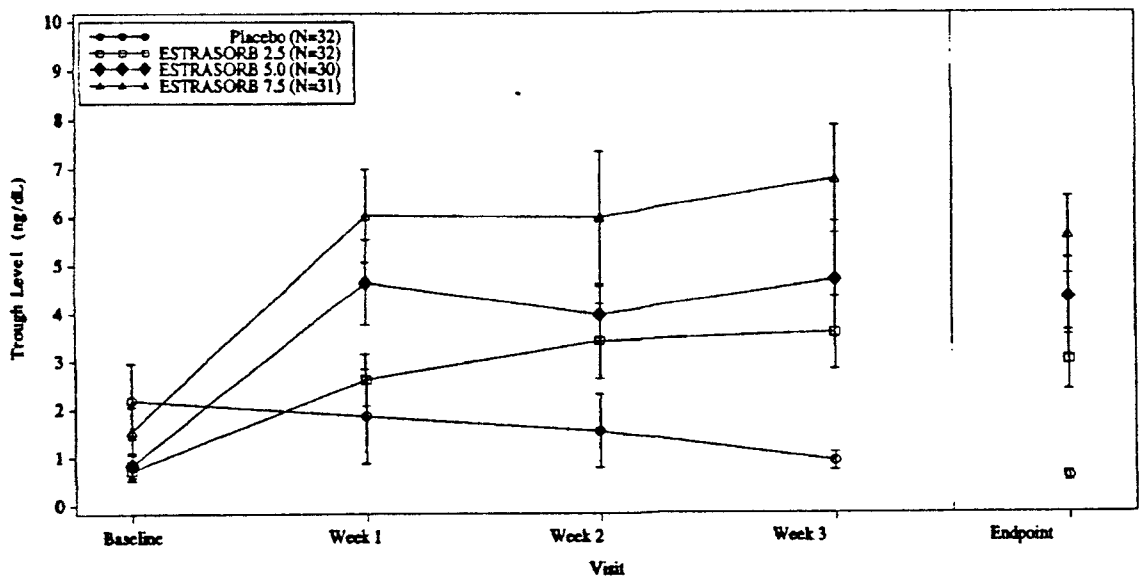


Figure 16. Mean (± SE) Estrone Serum Concentration by Visit (study # E98-2)

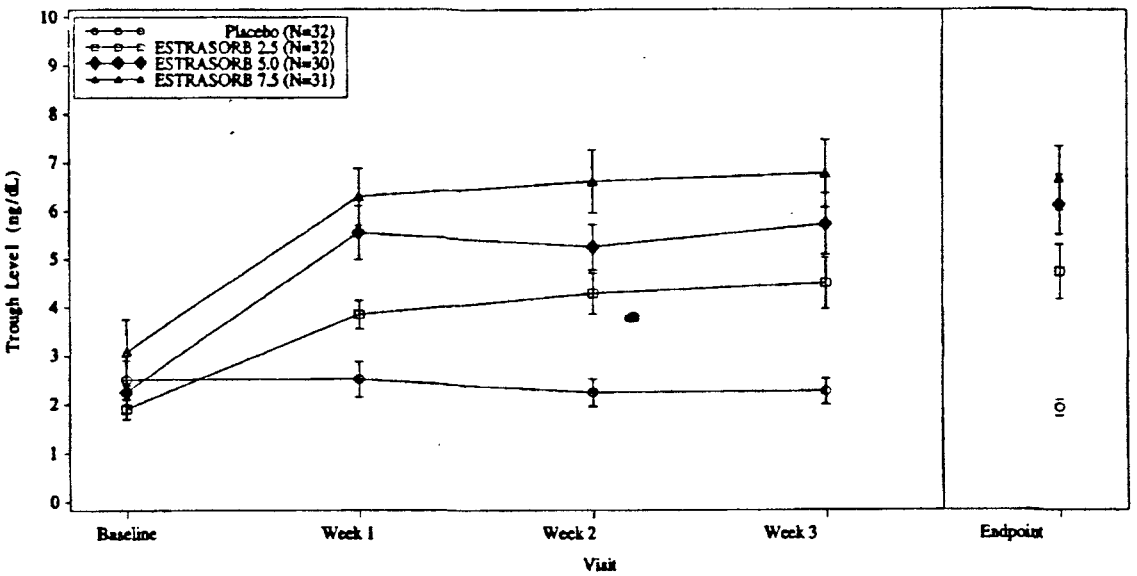


Figure 17. Mean (± SE) Estrone Sulfate Serum Concentration by Visit (study # E98-2)

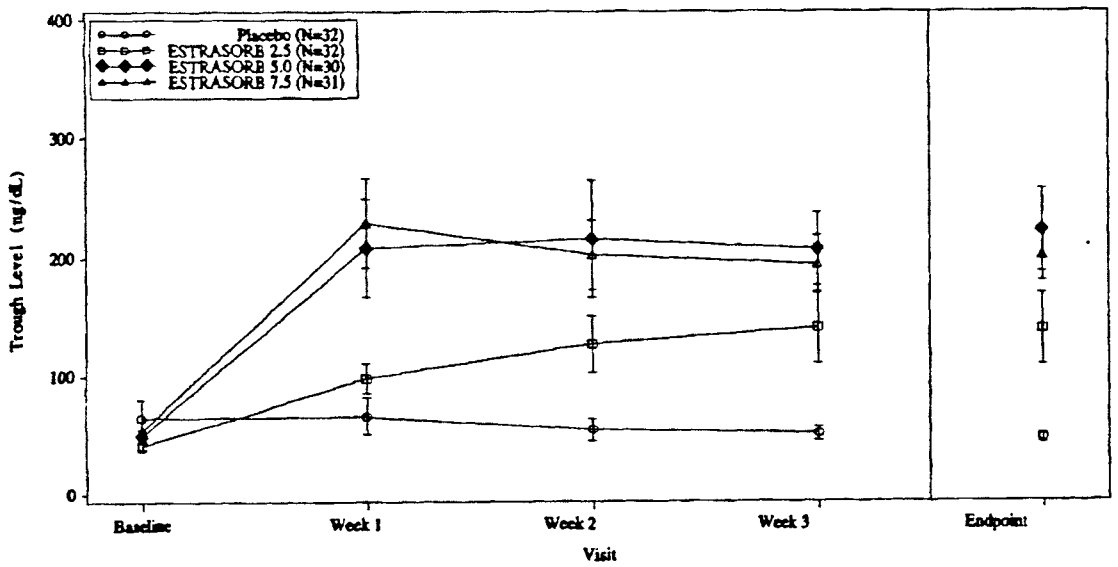
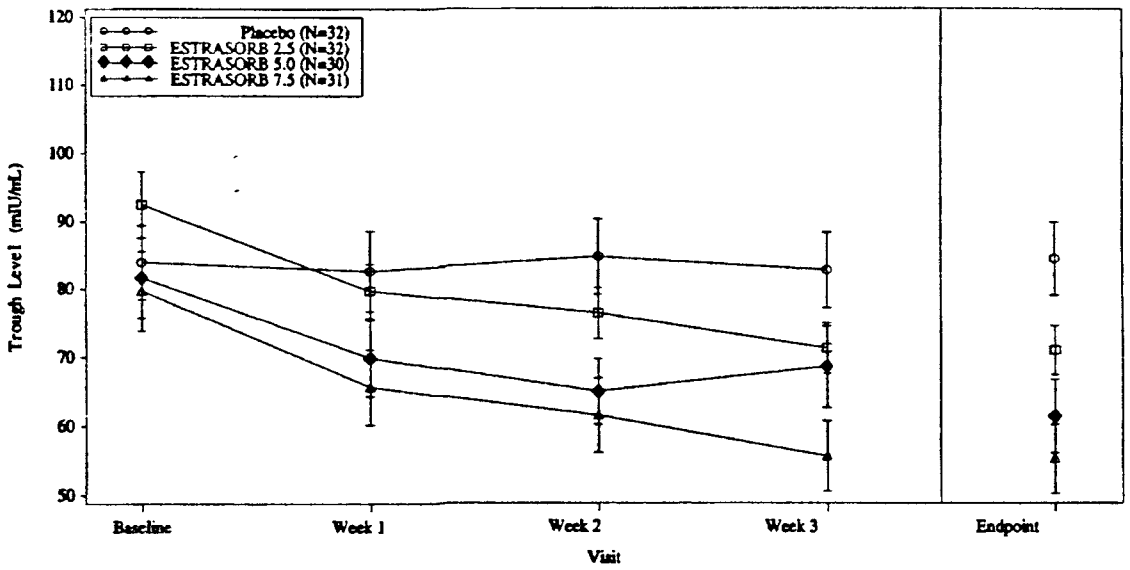


Figure 18. Mean (± SE) FSH Serum Concentration by Visit (study # E98-2)



APPEARS THIS WAY
ON ORIGINAL

Table 11. Summary of Changes from Screening in Average Daily Moderate and Severe Hot Flush Count (study # E98-2)

Time Point	Statistic	Treatment Group				Overall P-value
		Placebo	ESTRASORB$_{HS2430}$ 2.5	5.0	7.5	
Week 3	n	29	31	27	30	0.086
	Mean (S.D.)	-4.57 (7.00)	-5.71 (4.29)	-5.80 (4.16)	-6.75 (5.83)	
	Median	-5.4	-5.3	-5.7	-7.4	
	Min, Max					
	Pairwise p-value		ND	ND	ND	
Week 4	n	29	31	27	29	0.003**
	Mean (S.D.)	-5.06 (7.30)	-6.32 (4.41)	-6.62 (3.77)	-8.12 (5.29)	
	Median	-5.6	-6.6	-6.6	-7.9	
	Min, Max					
	LS Mean	0.63	0.46	0.51	0.38	
	Pairwise p-value		0.024*	0.188	< 0.001**	
Weeks 3 and 4 Combined	n	29	31	27	29	0.014*
	Mean (S.D.)	-4.82 (7.06)	-6.02 (4.30)	-6.21 (3.89)	-7.51 (5.47)	
	Median	-5.5	-6.4	-6.5	-7.6	
	Min, Max					
	LS Mean	0.62	0.46	0.50	0.40	
	Pairwise p-value		0.043*	0.180	0.002**	

*significant at the 0.050 level; **significant at the 0.010 level.

Time Point	Statistic	Treatment Group				Overall P-value
		Placebo	ESTRASORB$_{HS2430}$ 2.5	5.0	7.5	
Week 3	n	29	31	27	30	0.086
	Mean (S.D.)	-4.57 (7.00)	-5.71 (4.29)	-5.80 (4.16)	-6.75 (5.83)	
	Median	-5.4	-5.3	-5.7	-7.4	
	Min, Max					
	Pairwise p-value		ND	ND	ND	
Week 4	n	29	31	27	29	0.003**
	Mean (S.D.)	-5.06 (7.30)	-6.32 (4.41)	-6.62 (3.77)	-8.12 (5.29)	
	Median	-5.6	-6.6	-6.6	-7.9	
	Min, Max					
	LS Mean	0.63	0.46	0.51	0.38	
	Pairwise p-value		0.024*	0.188	< 0.001**	
Weeks 3 and 4 Combined	n	29	31	27	29	0.014*
	Mean (S.D.)	-4.82 (7.06)	-6.02 (4.30)	-6.21 (3.89)	-7.51 (5.47)	
	Median	-5.5	-6.4	-6.5	-7.6	
	Min, Max					
	LS Mean	0.62	0.46	0.50	0.40	
	Pairwise p-value		0.043*	0.180	0.002**	

*significant at the 0.050 level; **significant at the 0.010 level.

Figure 19. Mean Daily Hot Flushes Count By Study Day in All Treatment Group

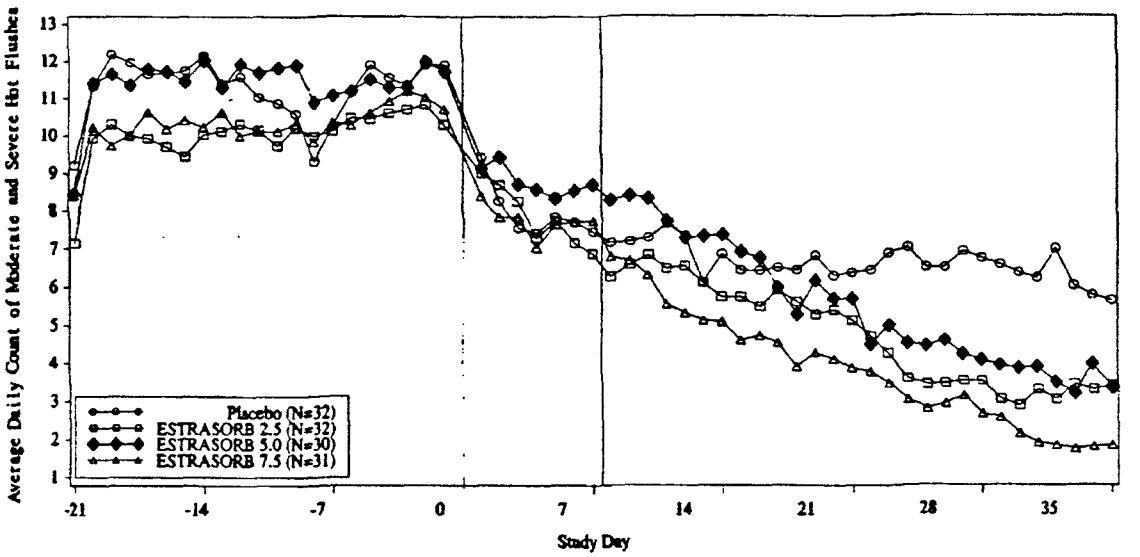


Figure 20. Change From Baseline For the Mean Daily Count of Hot Flushes For Week 3 and Week 4

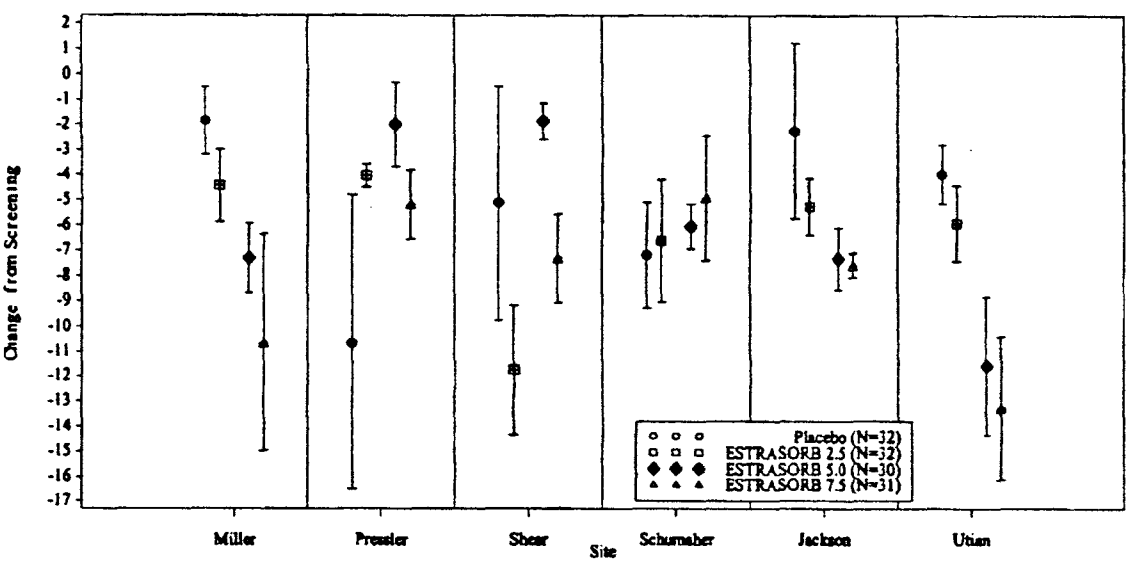


Figure 21. Relationship Between Estradiol Trough Serum Concentration and Hot Flush Count (R= 0.6302 and $R^2 = 0.3971$)

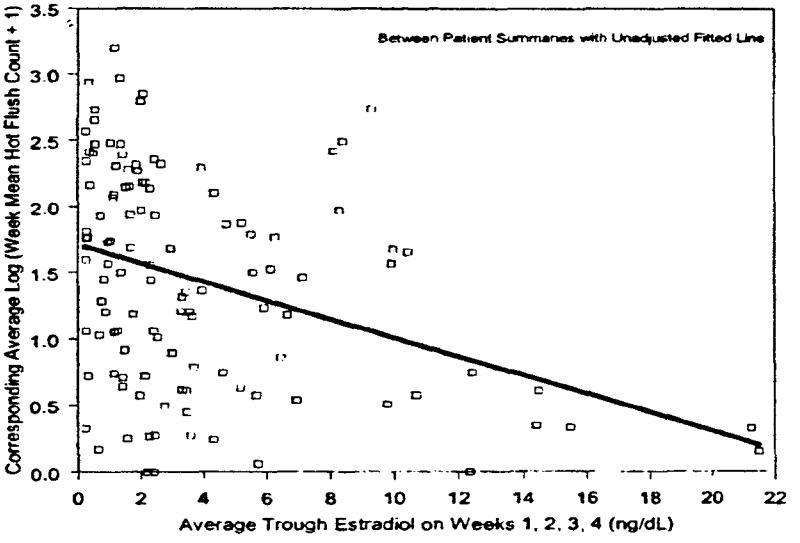


Figure 22. Relationship Between Estrone Trough Serum Concentration and Hot Flush Count (R= 0.5392 and $R^2 = 0.2907$)

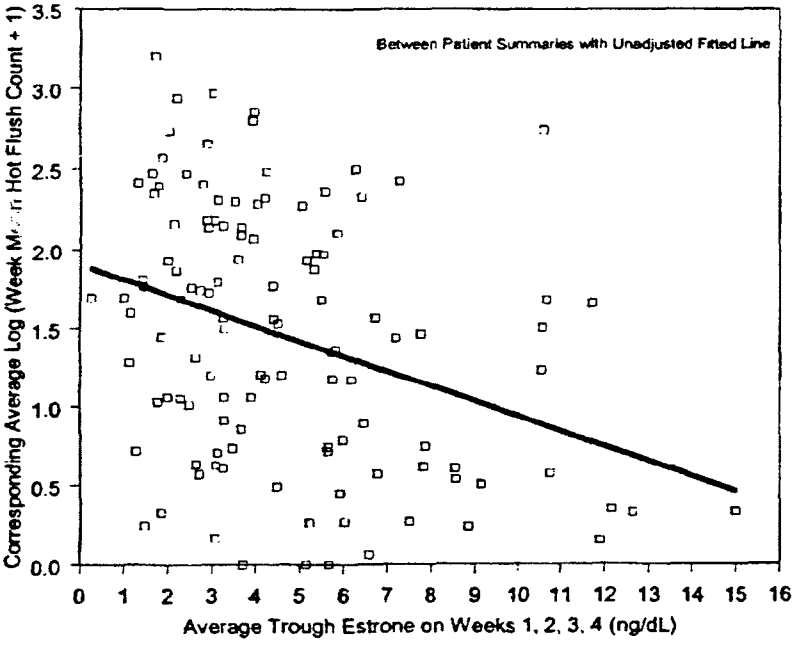
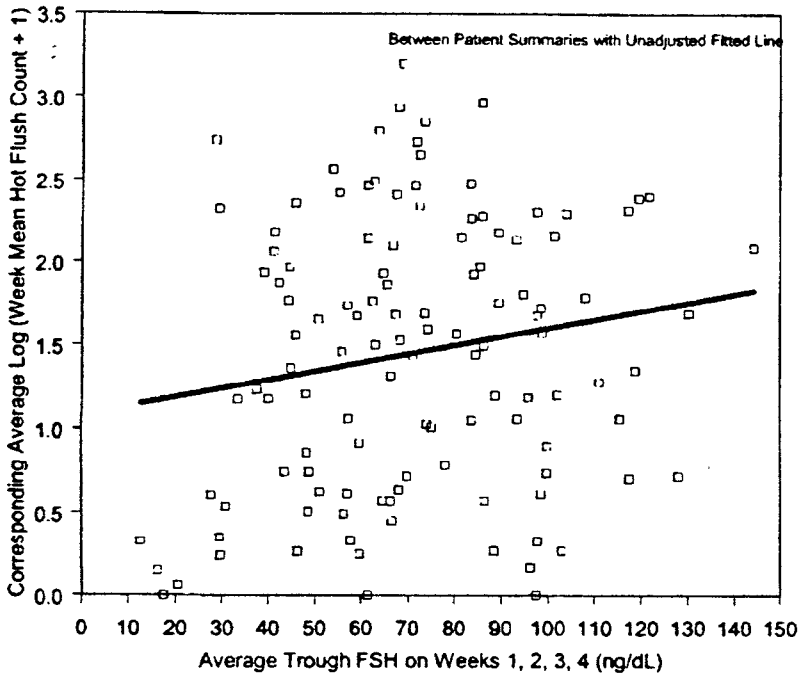


Figure 23. Relationship Between FSH Trough Serum Concentration and Hot Flush Count (R= 0.6535 and $R^2 = 0.4271$)



Comments and Conclusions:

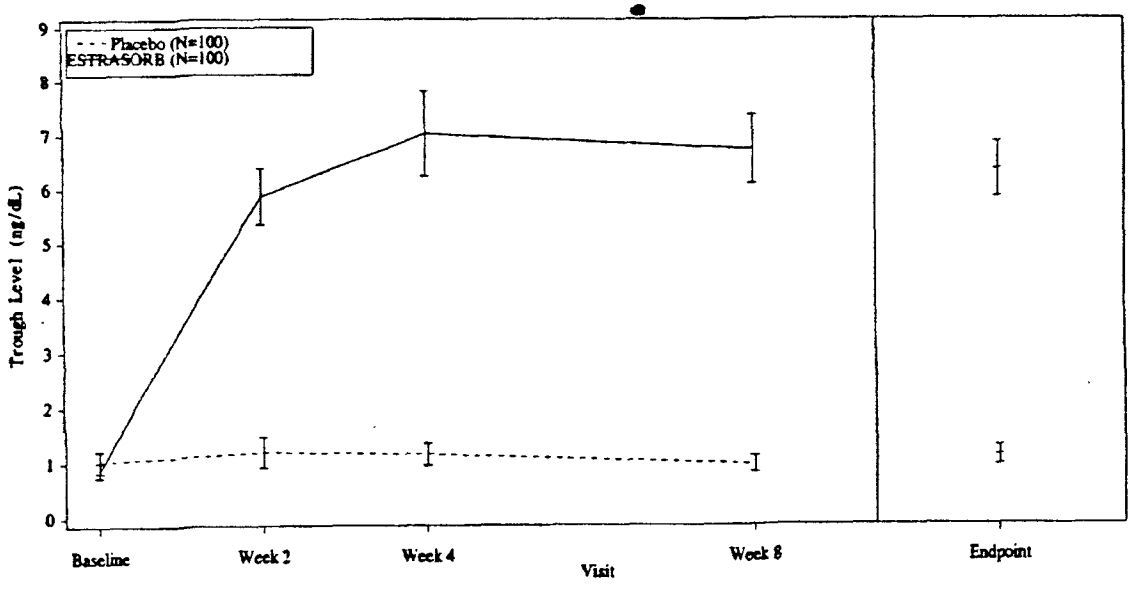
There is some correlation between trough estradiol and estrone serum levels and hot flushes counts ($R^2 = 0.3971$ and 0.2907, respectively). As trough hormone concentrations increases the score for hot flushes decreases. In addition, there some positive correlation between FSH serum trough levels and hot flushes counts ($R^2 = 0.4271$). As serum FSH level increases hot flushes counts increases.

Phase III Pivotal Study (#E99-1):

This is a pivotal Phase III clinical trail in women with symptomatic post-menopausal syndrome. The objectives of this study were to investigate the safety and efficacy of Estrasorb following daily application at a dose of 7.5 mg (3 gram of Estrasorb) for 12 weeks. Estrasorb was applied to the anterior of each thigh and calf (split-dose) as either three doses of 1.15 g each of active Estrasorb or three 1.15 g foil-laminated pouches of placebo. This was a double blind, placebo controlled, parallel group trail were all subjects continued on placebo for additional one-week period following the 12 weeks treatment. The primary efficacy parameters for hot flushes were monitored on Weeks 4 and 12. Trough serum estradiol, estrone, and FSH levels were measured on Days 1 (prior to treatment) at the end of the placebo run-in period, and at the end of Day 14, 28, 56, and 84 (i.e., weeks 2, 4, 8, and 12). Estradiol, estrone, and FSH levels in the placebo treatment group remained relatively unchanged during the active treatment period. A total of 200 subjects enrolled in this trial in which 100 received active treatments and 100 received placebo.

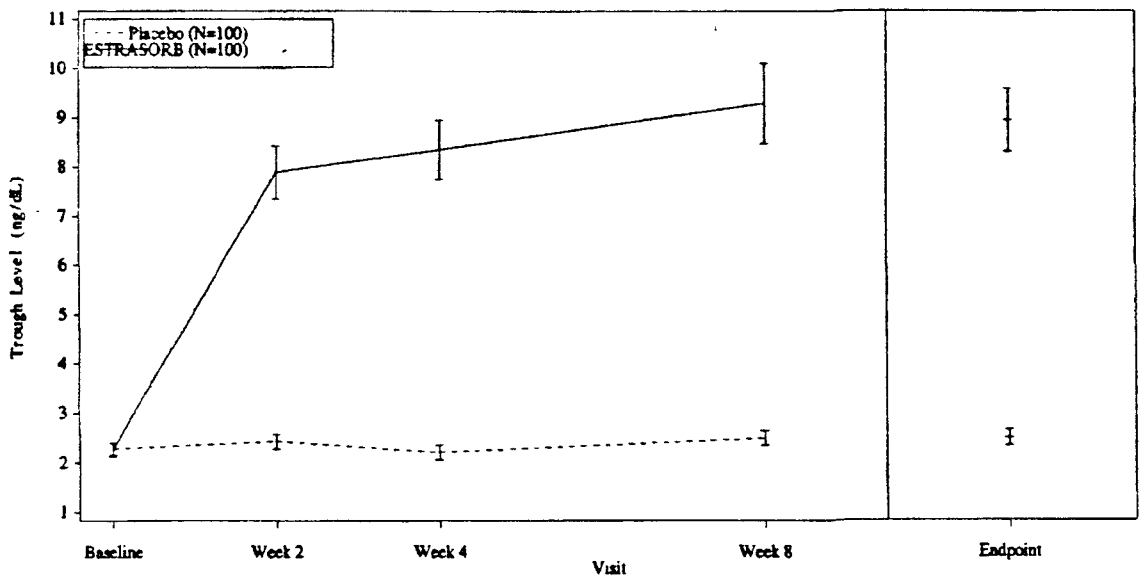
No further increase was noted in mean trough serum levels of estradiol and estrone after the 4th week of treatment (**Figures 24-25**). Similarly, the reduction in serum FSH levels almost reached the plateau by 4th week (**Table 12 and Figures 26-29**). The data shows a relatively good relationship between hot flushes count and serum trough concentrations for estradiol, estrone, and FSH, respectively (**Figures 29-31**). The data clearly show significant reduction in hot flushes count following Estrasorb application compared to placebo.

Figure 24 Mean (±SE) of Estradiol Serum Levels By Visit and Treatment Group (study # E99-1)



APPEARS THIS WAY
ON ORIGINAL

Figure 25. Mean (±SE) of Estrone Serum Levels By Visit and Treatment Group (study # E99-1)



APPEARS THIS WAY
ON ORIGINAL

Table 12. Summary of Change From Screening for the Average daily Hot Flush Count (study E99-1)

Time Point	Statistic	Treatment Group		P-value
		Placebo	ESTRASORB	
Total Number of Subjects in the ITT Population	N	100	100	
Screening (Observed value)	n	100	100	ND
	Mean (S.D.)	13.63 (5.48)	13.05 (5.78)	
	Median	11.7	11.5	
	Min, Max			
Week -1 (Placebo Period)	n	99	99	ND
	Mean (S.D.)	-2.34 (3.91)	-1.75 (3.77)	
	Median	-2.0	-1.3	
	Min, Max			
Week 4	n	97	96	<0.001**
	Mean (S.D.)	-5.97 (4.76)	-8.56 (6.19)	
	Median	-6.6	-8.8	
	Min, Max			
Week 8	n	94	91	<0.001**
	Mean (S.D.)	-6.67 (5.26)	-10.74 (6.99)	
	Median	-7.2	-9.9	
	Min, Max			
Week 12	n	90	90	<0.001**
	Mean (S.D.)	-7.20 (5.39)	-11.11 (6.84)	
	Median	-7.7	-10.3	
	Min, Max			

*Significant at the 0.050 level; **significant at the 0.010 level.
ND = Not Done.
Note: P-values for treatment group comparisons are obtained from an ANCOVA model including effects for treatment, screening average daily count of moderate and severe hot flushes, and stratum (intact uterus vs hysterectomy).
Note: This table includes imputed data as described in the statistical methods section of the study report.
Source: Table 7.0

APPEARS THIS WAY
ON ORIGINAL

Figure 26. Mean (±SE) of FSH Serum Levels By Visit and Treatment Group (study # E99-1)

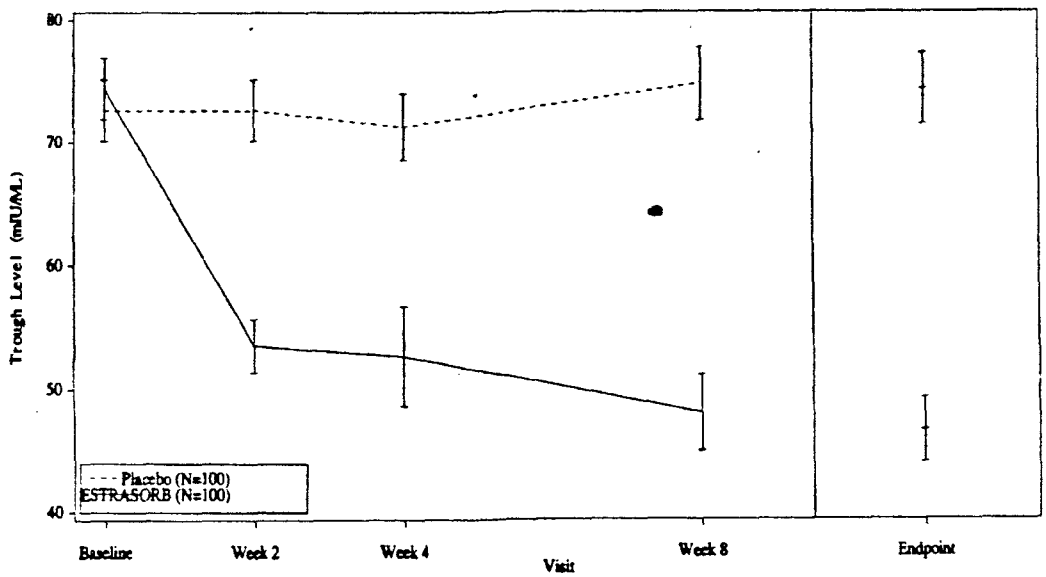


Figure 27. Average Daily Count of Hot Flushes by Week and Treatment Group (study # E99-1)

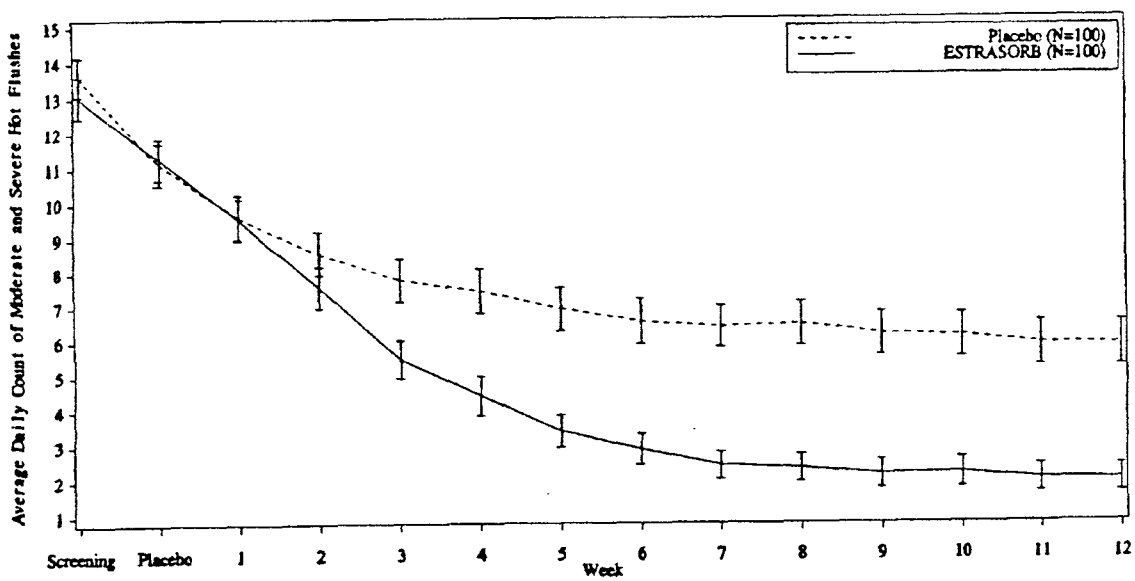


Figure 28. Average Daily Count of Hot Flushes by Study Day and Treatment Group (study # E99-1)

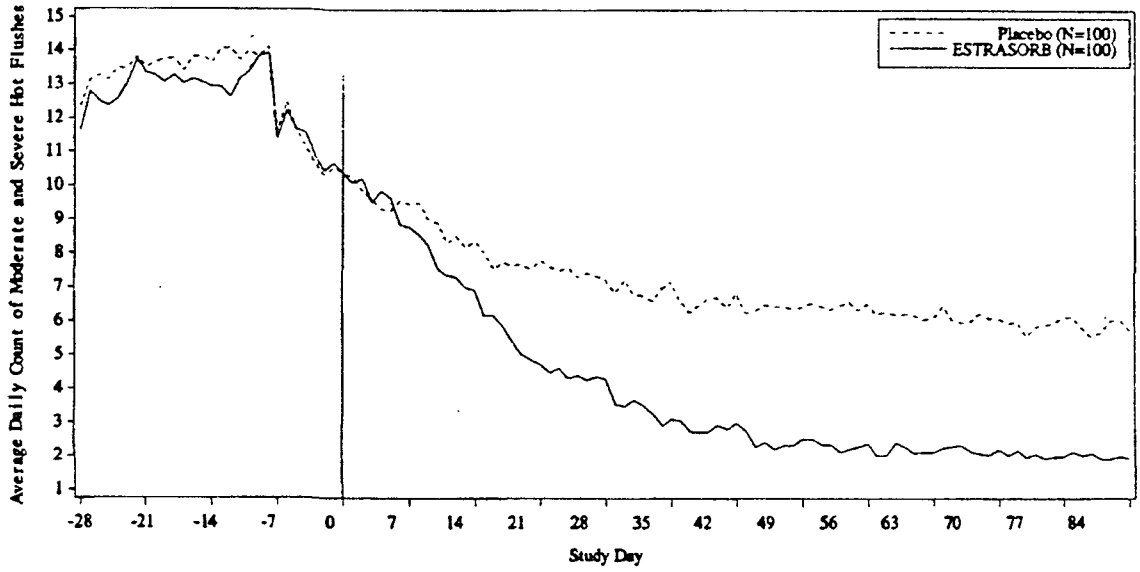


Figure 29. % of Subjects With a Clinical Respnse By Week and Treatment Group (study # E99-1)

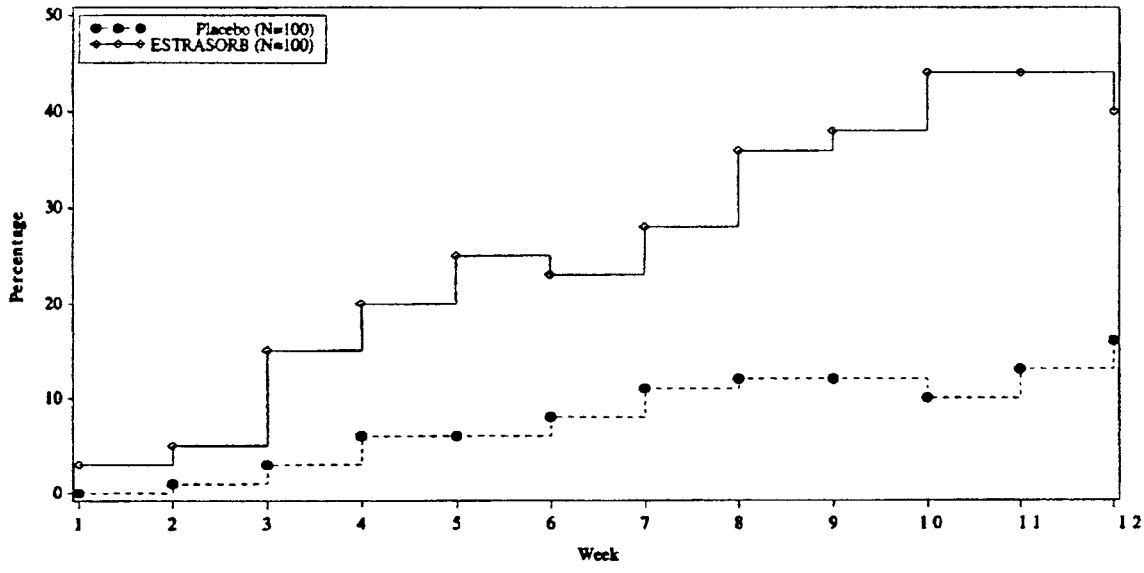


Figure 30. Relationship Between Estradiol Trough Serum Concentration and Hot Flush Count Following Daily Application of Estrasorb for 12 Weeks at Estradiol Dose of 7.5 mg (study # 99-1) ($R^2 = 0.1205$)

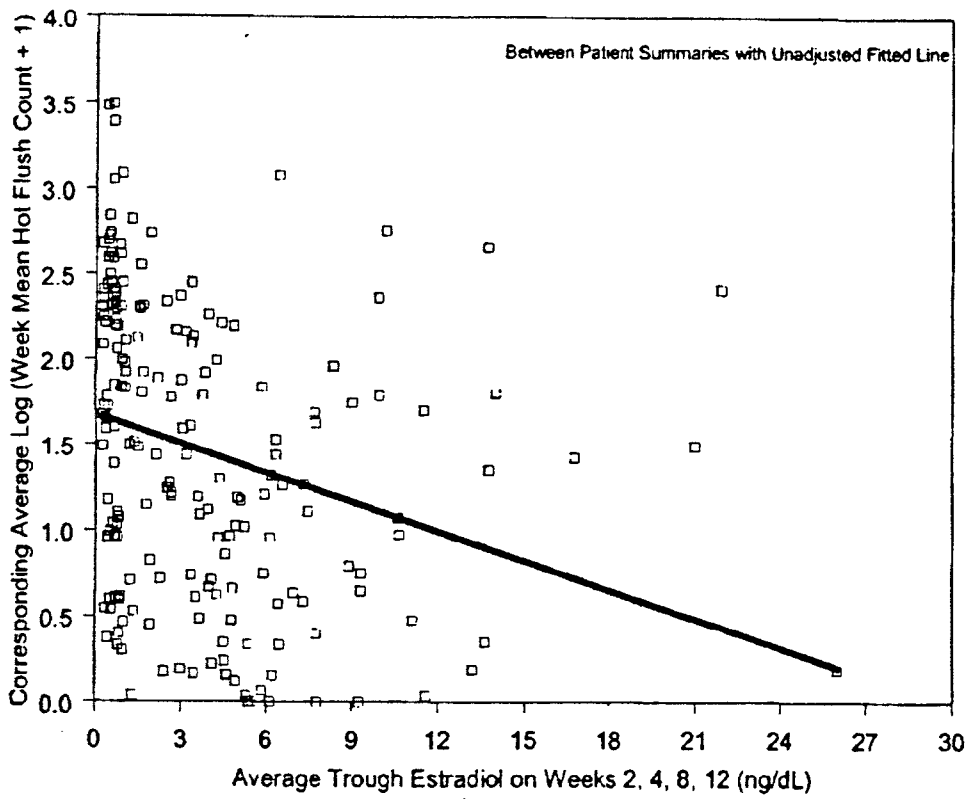
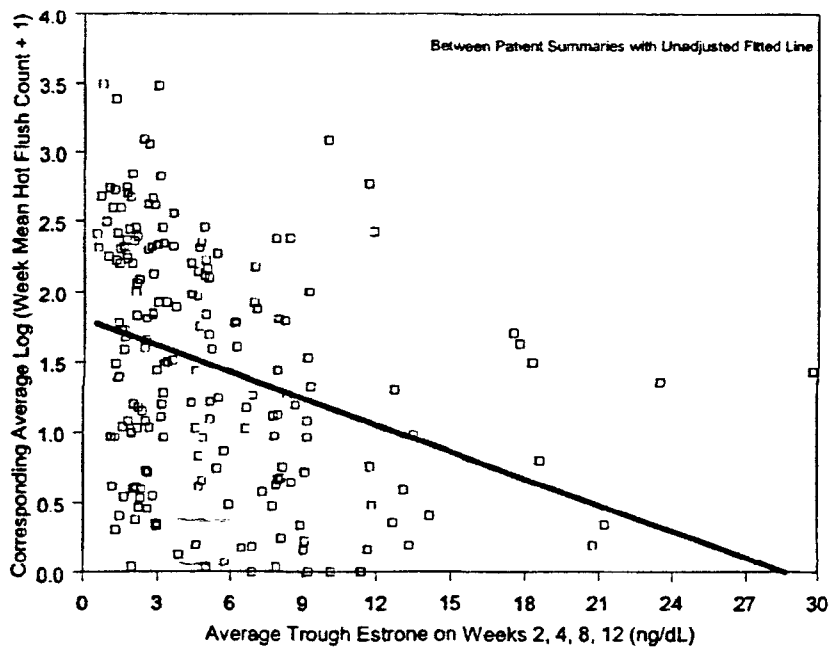
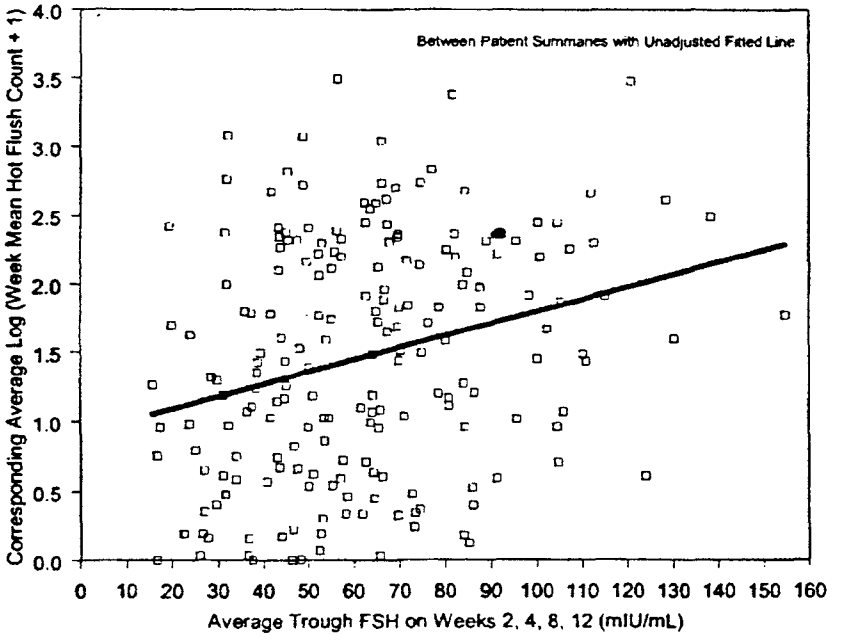


Figure 31. Relationship Between Estrone Trough Serum Concentration and Hot Flush Count Following Daily Application of Estrasorb for 12 Weeks at Estradiol Dose of 7.5 mg (study # 99-1) ($R^2 = 0.1512$)



C:\dmautop\te

Figure 32. Relationship Between FSH Trough Serum Concentration and Hot Flush Count Following Daily Application of Estrasorb for 12 Weeks at Estradiol Dose of 7.5 mg (study # 99-1) (R^2 = 0.1095)



Comments and Conclusions:

The data from this study are similar to those observed in study # E98-2. Therefore, it can be concluded that there was a some PK/PD relationship between trough estradiol and estrone serum levels and hot flushes counts (R^2 = 0.1205 and 0.1512, see Figures 30 and 31).

Phase I Residual Study (#E2000-1):

This is a skin residual study in 12 symptomatic post-menopausal women following application of 1.15 g foil-laminated pouch of Estrasorb (2.5 mg of estradiol per g) on each thigh at either two or eight hours post application. The objective of this study was to investigate the amount of dose remaining on skin following application. Residual estradiol levels and the percent of residual estradiol on the skin for the left anterior thigh at 2 hours post dose, the right anterior thigh at 8 hours post-dose, and the left and right anterior thighs post-washing at 8 hours were determined in this study. Based on the data, virtually no residual estradiol was detected on the skin after washing with soap (**Tables 9 and 10**).

Redacted 2

page(s) of trade secret and/or confidential commercial information (b4)

ClinPharm/Biopharm Briefing on: March , 2002.

Briefing Attendees: Drs. Henry Malinowski, Shiew Mei Huang, John Hunt, Ameeta Parekh, and Sayed Al Habet

Reviewed by:

Sayed Al-Habet, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

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

cc: NDAs # 21-319: HFD-580, HFD-860 (Al-Habet, Parekh, and Malinowski), and Drug files (Biopharm File, CDR).

Appendix I

Sponsor's Proposed Original Label

28 pages redacted from this section of the approval package consisted of draft labeling

---

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

/s/

Sayed Al-Habet
10/8/03 09:21:16 AM
BIOPHARMACEUTICS

Ameeta Parekh
10/8/03 03:59:02 PM
BIOPHARMACEUTICS

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE

APPLICATION NUMBER(S)

21-371

ADMINISTRATIVE/CORRESPONDENCE

Redacted 6

page(s) of trade secret and/or confidential commercial information (b4)