Mean (%CV) Pharmacokinetic Parameters

Pharmacokinetic Parameter	Treatment[a]	Selegiline Mean (%CV)	N-desmethylselegiline Mean (%CV)	L-amphetamine Mean (%CV)	L-methamphetamine Mean (%CV)	Alprazolam Mean (%CV)
$AUC_{(0-\tau)}$ (pg*hr/mL)	Sel	68594.2 (16)	33292.5 (34)	63646.7 (28)	161494.9 (31)	-
	Sel + A	59160.3 (18)	31641.8 (34)	61543.1 (30)	156621.2 (34)	141.43[b] (22)
	A	-	-	-	-	143.54[b] (15)
AUCT M/P	Sel	-	0.5 (30)	0.9 (26)	2.4 (30)	-
	Sel + A	-	0.5 (28)	1.0 (26)	2.7 (31)	-
	A	-	-	-	-	-
C_{max} (pg/mL)	Sel	3857.3 (23)	1721.4 (36)	3111.0 (28)	7964.4 (30)	-
	Sel + A	3151.4 (23)	1601.2 (33)	3047.1 (28)	8040.9 (34)	22.69[c] (22)
	A	-	-	-	-	22.98[c] (19)
C_{min} (pg/mL)	Sel	2066.2 (20)	1026.9 (36)	2138.4 (33)	5336.3 (37)	-
	Sel + A	1708.3 (16)	974.9 (32)	2027.0 (35)	5024.6 (40)	13.29[c] (24)
	A	-	-	-	-	13.55[c] (18)
C_{ss} (pg/mL)	Sel	2857.5 (16)	1387.0 (34)	2651.7 (28)	6728.0 (31)	-
	Sel + A	2465.0 (18)	1318.4 (34)	2564.3 (30)	6525.9 (34)	17.65[c] (22)
	A	-	-	-	-	17.94[c] (15)
CL (L/hr)[d]	Sel	298.4 (16)	-	-	-	-
	Sel + A	347.7 (17)	-	-	-	3.69 (22)
	A	-	-	-	-	3.55 (14)
T_{max} (hr)	Sel	7.17 (59)	9.50 (39)	9.88 (64)	10.33 (44)	-
	Sel + A	6.02 (50)	7.51 (62)	9.68 (50)	11.01 (39)	1.38 (35)
	A	-	-	-	-	1.34 (53)
Fluctuation %	Sel	90.91 (53)	69.66 (45)	48.68 (38)	52.95 (40)	-
	Sel + A	86.18 (42)	64.41 (25)	53.36 (28)	63.52 (33)	72.26 (18)
	A	-	-	-	-	70.49 (26)
MRT (hr)[e]	Sel	11.67 (4)	11.98 (3)	12.15 (3)	12.08 (3)	-
	Sel + A	11.68 (4)	11.90 (4)	11.97 (4)	11.90 (5)	3.72 (2)
	A	-	-	-	-	3.72 (2)
$T_{½}$ (hr)[f]	Sel	-	-	-	-	-
	Sel + A	-	-	-	-	10.00 (33)
	A	-	-	-	-	9.18 (35)
K_{el} (hr)[f]	Sel	-	-	-	-	-
	Sel + A	-	-	-	-	0.0756 (29)
	A	-	-	-	-	0.0824 (28)

[a]Treatments were Sel=Selegiline (STS 20mg/20cm^2) alone; Sel + A=Selegiline (STS 20mg/20cm^2) + Alprazolam; A=Alprazolam alone

[b]Units for Alprazolam are ng*hr/mL

[c]Units for Alprazolam are ng/mL

[d]Apparent plasma clearance of the metabolites could not be calculated, as the metabolites were not dosed separately.

[e]MRT for metabolites are uncorrected values (uncorrected for parent selegiline).

[f]Calculated for Alprazolam only

$AUC_{(0-\tau)}$=area under the concentration-time curve calculated by the trapezoidal rule (over tau, the dosing interval); AUCT=area under the concentration-time curve; CL=total clearance; C_{max}= maximum concentration over the entire sampling phase; C_{min}=minimum concentration over the dosing interval tau; C_{ss}=concentration at steady-state; CV=coefficient of variation; K_{el}=apparent elimination rate constant; M/P=metabolite to parent; MRT=mean residence time; T_{max}=time to attain C_{max}; $T_{½}$=apparent elimination half-life calculated as $0.693/K_{el}$

Note: R(-)-N-desmethylselegiline, R(-)-amphetamine, and R(-)-methamphetamine are interchangeable terms for N-desmethylselegiline, L-amphetamine, and L-methamphetamine.

Data Source: Appendix C.1

Study #13

Title: Steady-state pharmacokinetic drug interaction study between risperidone and selegiline transdermal system in healthy volunteers (Study #S9303-P9921).

This was an open-label, randomized, 3 period, 3-treatment, 6-way latin square crossover study in 12 subjects (6 males and 6 females, 18-41 years of age). Six groups of subjects (2 each group) were randomized to one of six treatment sequences of three treatments for 7 days each (3 weeks total):
Treatment A : STS 20 mg/20 cm^2 alone.
Treatment B : STS 20 mg/20 cm^2 + risperidone
Treatment C : Risperidone alone.

Selegiline was administered once daily for 7 days for treatment A and B and 1 mg risperidone tablets three times daily for seven days for treatments B and C. Blood samples were collected at predose and on day 7 at regular intervals till 24 hours for the determination of selegiline and its metabolites as well as risperidone and its metabolite 9-OH risperidone.

The results of the study indicated that risperidone did not alter the steady state pharmacokinetics of STS. Furthermore, STS produced no effect on the pharmacokinetics of risperidone.

Pharmacokinetic Parameters of Selegiline and Metabolites (All Subjects)

		Selegiline		N-desmethylselegiline		L-amphetamine		L-methamphetamine	
Parameter	Treatment	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
AUC(0-τ) (pg*hr/mL)	Sel	57155	24	31090	40	56404	43	133078	40
	Sel + R	53244	28	30750	40	61118	56	139135	45
AUC(0-τ) M/P	Sel	-	-	0.55	33	0.97	28	2.30	28
	Sel + R	-	-	0.58	34	1.12	35	2.60	33
C_{max} (pg/mL)	Sel	2984.5	27	1595.6	39	2778.4	41	6506.5	39
	Sel + R	2826.7	33	1562.7	39	3055.7	57	6883.6	47
C_{min} (pg/mL)	Sel	1726.1	22	950.3	39	1800.4	46	4317.8	45
	Sel + R	1586.0	23	972.8	39	1886.1	46	4385.1	40
C_{ss} (pg/mL)	Sel	2387.3	24	1298.5	40	2357.6	43	5560.4	40
	Sel + R	2226.1	28	1285.8	40	2553.3	56	5816.6	45
CL (L/hr)	Sel	368	23	-	-	-	-	-	-
	Sel + R	398	23	-	-	-	-	-	-
T_{max} (hr)	Sel	8.50	27	9.83	27	14.33	35	11.33	41
	Sel + R	8.56	73	8.59	42	16.33	24	13.75	38
Fluct C_{min}%	Sel	74.87	52	69.69	37	57.49	34	53.67	29
	Sel + R	77.66	41	63.25	50	58.16	30	55.56	36
Fluct C_{trough}%	Sel	50.60	68	39.45	36	17.16	60	21.66	39
	Sel + R	60.27	74	49.14	67	28.92	84	29.30	80
MRT^{ss} (hr)	Sel	11.74	3	12.02	3	12.52	3	12.36	2
	Sel + R	11.67	4	11.79	3	12.26	4	12.17	4

Pharmacokinetic Parameters of Risperidone and 9-OH Risperidone

		Risperidone N=12		9-OH Risperidone N=12		Risperidone* N=11		9-OH Risperidone* N=11	
Parameter	Treatment	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
$AUC_{(0-\tau)}$ (pg•hr/mL)	Ris	54.26	166	147.55	24	28.58	47	151.15	23
	Sel + R	56.78	171	150.16	30	29.18	55	151.94	31
$AUC_{(0-\tau)}$ M/P	Ris	-	-	5.45	43	-	-	5.92	30
	Sel + R	-	-	5.33	40	-	-	5.78	26
C_{max} (pg/mL)	Ris	10.73	98	15.87	25	7.80	39	16.29	24
	Sel + R	10.66	106	15.52	29	7.57	48	15.83	29
C_{min} (pg/mL)	Ris	1.87	286	8.78	27	0.33	87	8.89	28
	Sel + R	1.67	284	9.14	32	0.30	86	9.18	34
C_{ss} (pg/mL)	Ris	4.52	166	12.30	24	2.38	47	12.60	23
	Sel + R	4.73	171	12.51	30	2.43	55	12.66	31
CL (L/hr)	Ris	38.30	52	-	-	41.51	41	-	-
	Sel + R	39.49	57	-	-	42.82	48	-	-
T_{max} (hr)	Ris	1.46	40	3.09	70	1.50	39	2.82	73
	Sel + R	1.25	50	3.13	55	1.27	51	3.36	47
Fluct C_{min}%	Ris	2350.59	75	84.17	36	2597.46	65	87.52	33
	Sel + R	2237.87	59	73.32	28	2467.90	47	76.30	24
Fluct C_{trough}%	Ris	1884.24	78	56.81	64	2046.77	70	60.28	60
	Sel + R	1326.12	75	44.51	45	1450.27	65	48.08	34
MRT (hr)	Ris	3.67	21	5.71	4	3.53	18	5.69	4
	Sel + R	3.57	17	5.68	3	3.43	11	5.67	3
$T_{½}$ (hr)	Ris	3.98	83	28.55	83	3.04	16	22.06	38
	Sel + R	4.58	114	25.93	41	3.08	13	25.93	41
K_{el} (hr)	Ris	0.2186	30	0.0340	51	0.2340	17	0.0365	44
	Sel + R	0.2131	30	0.0311	42	0.2294	14	0.0311	42

%CV=coefficient of variance; $AUC_{(0-\tau)}$=area under the concentration-time curve calculated by the trapezoidal rule; Sel=Selegiline monotherapy; Sel + R=Selegiline + Risperidone; M/P=metabolite-to-parent drug ratio; C_{max}=maximum concentration over the entire sampling phase; C_{min}=pre-dose concentrations (trough levels) for assessment of steady-state attainment; C_{ss}=concentration at steady-state; CL=total clearance; T_{max}= time to attain C_{max}; Fluct C_{min} %=the percent fluctuation (relative to C_{min}); C_{trough}=pre-dose concentration prior to the last three consecutive morning doses; Fluct C_{trough} %= the percent fluctuation (relative to C_{trough}); MRT=mean residence time, $T_{½}$= apparent elimination half-life; K_{el}=apparent elimination rate constant
Data from Subject #10 were deleted because this subject was determined to be a slow metabolizer based on cytochrome P450-2D6 genotyping results.
Data Source: Appendix C.1

Study #14

Title: Steady-state pharmacokinetic drug interaction study between olanzapine and selegiline transdermal system in healthy volunteers (Study #S9303-P9922).

This was an open-label, randomized, 3 period, 3-treatment, 6-way latin square crossover study in 12 subjects (5 males and 7 females, 20-43 years of age). Six groups of subjects (2 each group) were randomized to one of six treatment sequences of three treatments for 10 days each:
Treatment A : STS 20 mg/20 cm^2 alone.
Treatment B : STS 20 mg/20 cm^2 + olanzapine
Treatment C : Olanzapine alone.

Selegiline was administered once daily for 10 days for treatment A and B and 5 mg olanzapine tablets once daily for ten days for treatments B and C. Blood samples were collected at predose and on day 10 at regular intervals till 24 hours for the determination of selegiline and its metabolites as well as olanzapine and its metabolite desmethylolanzapine.

The results of the study indicated that olanzapine did not alter the steady state pharmacokinetics of the STS.
90% confidence interval for selegiline (natural log transformed) is as follows:
AUC = 85.6-102.3
Cmax = 84.7-101.1

The STS produced no effect on the pharmacokinetics of olanzapine.

Mean (%CV) Pharmacokinetic Parameters of Selegiline and Metabolites

Pharmacokinetic Parameter	N=12 Treatment [a]	Selegiline Mean (%CV)	R(-)-N-desmethylselegiline Mean (%CV)	R(-)-amphetamine Mean (%CV)	R(-) methamphetamine Mean (%CV)
$AUC_{(0\text{-}tau)}$ (pg*hr/mL)	Sel	72998.46 (18)	43901.91 (31)	70632.26 (30)	172931.65 (39)
	Sel + O	69419.83 (26)	43289.93 (31)	74062.03 (37)	177527.40 (40)
$AUC_{(0\text{-}tau)}$ M/P	Sel	-	0.61 (31)	0.96 (20)	2.33 (29)
	Sel + O	-	0.64 (31)	1.07 (25)	2.56 (30)
CL (L/hr)[b]	Sel	281.02 (16)	-	-	-
	Sel + O	304.76 (23)	-	-	-
C_{max} (pg/mL)	Sel	3911.86 (17)	2222.6 (29)	3474.4 (30)	8518.0 (39)
	Sel + O	3635.10 (27)	2132.8 (31)	3587.5 (35)	8952.7 (43)
C_{min} (pg/mL)	Sel	2251.2 (20)	1336.0 (30)	2309.0 (34)	5627.9 (43)
	Sel + O	2098.7 (29)	1392.2 (39)	2402.0 (39)	5383.7 (37)
C_{ss} (pg/mL)	Sel	3041.3 (18)	1829.1 (31)	2942.9 (30)	7205.1 (39)
	Sel + O	2892.5 (26)	1803.7 (31)	3085.9 (37)	7397.0 (40)
Fluct C_{min} %	Sel	75.57 (26)	68.30 (29)	53.90 (35)	54.83 (35)
	Sel + O	75.89 (39)	58.43 (39)	54.06 (45)	67.87 (68)
Fluct C_{trough}%	Sel	58.94 (29)	46.57 (40)	25.15 (74)	28.92 (63)
	Sel + O	55.47 (35)	32.76 (37)	20.44 (84)	28.63 (61)
MRT (hr)[c]	Sel	11.52 (3)	11.91 (2)	12.28 (4)	12.18 (4)
	Sel + O	11.81 (2)	12.04 (2)	12.27 (3)	12.19 (3)
T_{max} (hr)	Sel	6.00 (49)	7.83 (43)	11.75 (59)	12.38 (54)
	Sel + O	9.67 (45)	9.50 (34)	13.04 (55)	11.85 (42)

Mean (%CV) Pharmacokinetic Parameters of Olanzapine and Desmethylolanzapine

Pharmacokinetic Parameter	N=12 Treatment[a]	Olanzapine Mean (%CV)	Desmethylolanzapine Mean (%CV)
$AUC_{(0\text{-}tau)}$ (ng*hr/mL)	Sel + O	352.73 (29)	55.70 (43)
	O	374.37 (27)	62.97 (36)
$AUC_{(0\text{-}tau)}$ M/P	Sel + O	-	0.16 (29)
	O	-	0.17 (24)
CL (L/hr)[b]	Sel + O	15.63 (37)	-
	O	14.16 (25)	-
C_{max} (ng/mL)	Sel + O	20.48 (23)	2.73 (43)
	O	21.28 (26)	3.00 (36)
C_{min} (ng/mL)	Sel + O	9.11 (44)	1.88 (47)
	O	10.28 (36)	2.12 (37)
C_{ss} (ng/mL)	Sel + O	14.70 (29)	2.32 (43)
	O	15.60 (27)	2.62 (36)
Fluct C_{min} %	Sel + O	196.90 (119)	50.56 (42)
	O	116.82 (39)	42.18 (20)
Fluct C_{trough} %	Sel + O	93.76 (71)	27.66 (36)
	O	80.74 (56)	22.14 (39)
MRT (hr)[c]	Sel + O	11.41 (3)	12.11 (2)
	O	11.30 (4)	12.04 (2)
T_{max} (hr)	Sel + O	5.17 (35)	9.00 (38)
	O	5.67 (36)	12.67 (28)

Study #15

Title: Steady-state pharmacokinetic drug interaction study between levothyroxine and selegiline transdermal system in healthy volunteers (Study #S9303-P9925).

This was a single-center, open-label drug interaction study in 10 subjects (6 males and 4 females, 18-35 years of age). Subjects received a single oral dose of levothyroxine (150 μg) on day 1. Subjects then received STS once daily (20 mg/20 cm^2) for 13 consecutive days starting on day 4. On day 14, a single dose of levothyroxine was given in the presence of STS. STS dosing continued till day 16.

Blood samples were collected for 72 hours for the determination of levothyroxine. From day 9 to 12, blood samples were collected for the determination of trough levels of selegiline. On day 13, blood samples were collected at regular intervals for 24 hours for the determination of selegiline and its metabolites. For the next 72 hours (day 17), blood samples were collected at regular intervals for determination of selegiline and thyroxine.

The results of the study indicated that thyroxine did not alter the steady state pharmacokinetics of the STS. 90% confidence interval for selegiline (natural log transformed):
AUC = 86.4-101.6
Cmax = 82.5-102.1

The STS produced no effect on the pharmacokinetics of thyroxine but the Tmax of thyroxine prolonged in the presence of STS. The Tmax of T3 was 43.6 hours (range: 1-72) in the presence of STS as compared to 16.9 hours (range: 1-60) when thyroxine was given alone. The Tmax of T4 was 14 hours (range: 2-72) in the presence of STS as compared to 4.7 hours (range: 1-14) when thyroxine was given alone.

Pharmacokinetic Parameter	Treatment[a] (N=10)	Selegiline		N-desmethylselegiline		L-amphetamine		L-methamphetamine	
		Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
AUCτ (pg*hr/mL)	Sel	76704.64	36	35569.88	46	76060.52	25	203385.45	24
	Sel + L	70895.93	30	33371.26	43	77693.39	21	205702.93	20
AUCτ M/P	Sel	-	-	0.47	38	1.05	29	2.79	22
	Sel + L	-	-	0.48	35	1.17	35	3.07	28
CL (L/hr)[b]	Sel	290.50	33	-	-	-	-	-	-
	Sel + L	307.25	32	-	-	-	-	-	-
C_{max} (pg/mL)	Sel	4089.2	32	1919.7	45	3938.8	25	10443.7	24
	Sel + L	3793.7	34	1670.3	40	3792.1	22	10113.7	21
C_{min} (pg/mL)	Sel	2333.9	34	1117.7	50	2333.9	31	6345.1	27
	Sel + L	2359.3	27	1073.3	45	2426.6	25	6557.1	24
C_{ss} (pg/mL)	Sel	3196.0	36	1482.1	46	3169.2	25	8474.4	24
	Sel + L	2954.0	30	1390.5	43	3237.2	21	8571.0	20
Fluctuation C_{min} %	Sel	77.41	23	77.75	34	73.14	37	67.12	36
	Sel + L	58.56	40	57.66	27	58.08	24	55.77	24
Fluctuation C_{trough} %	Sel	43.60	29	55.78	46	35.54	74	37.94	69
	Sel + L	50.21	52	45.53	41	21.04	68	28.60	58
MRT (hr)[c]	Sel	11.72	3	11.66	2	12.17	3	12.14	3
	Sel + L	11.53	4	11.79	3	12.35	4	12.18	3
T_{max} (hr)	Sel	5.2	37	8.6	16	10.0	46	9.4	40
	Sel + L	5.1	72	11.0	30	13.4	23	10.6	42

[a]*Sel=Selegiline (STS [20mg/20cm^2]) alone; Sel + L=Selegiline (STS [20mg/20cm^2]) + Levothyroxine*
[b]Apparent plasma clearance of the metabolites could not be calculated, as the metabolites were not dosed separately.
[c]MRT for metabolites are uncorrected values (uncorrected for parent selegiline).
AUCτ=area under the concentration-time curve over tau, the dosing interval; CL=total clearance; C_{max}=maximum concentration over the dosing interval tau$_{(\tau)}$; CV=coefficient of variation; C_{min}=minimum plasma concentration over the dosing interval tau$_{(\tau)}$; C_{ss}=steady-state concentration of drug; M/P=metabolite/parent; MRT=mean residence time; T_{max}=time to attain C_{max}
Data Source: Appendix C.1

The *following table presents* the mean (%CV) non-compartmental pharmacokinetic parameters for T_3 and T_4, after levothyroxine was given alone and concomitantly with selegiline.

Pharmacokinetic Parameter	Treatment[a] (N=10)	T3		T4	
		Mean	%CV	Mean	%CV
AUCT (ng*hr/mL)	L	96.10	9	557.53[b]	10
	Sel + L	86.67	4	556.28[b]	11
C_{max} (ng/mL)	L	1.603	16	9.44[c]	9
	Sel + L	1.453	9	9.34[c]	11
MRT (hr)	L	36.01	2	35.27	2
	Sel + L	36.18	2	35.36	3
T_{max} (hr)	L	16.9	108	4.7	87
	Sel + L	43.6	84	14.0	148

[a]Sel + L=Selegiline (STS [20 mg/20 cm^2]) + Levothyroxine; L=Levothyroxine alone
[b]mcg*hr/dL
[c]mcg/dL

Study #16

Title: Steady-state pharmacokinetic drug interaction study between ibuprofen and selegiline transdermal system in healthy volunteers (Study #S9303-P9926).

This was a single-center, open-label drug interaction study in 10 subjects (7 males and 3 females, 19-44 years of age). Subjects received a single oral dose of ibuprofen (800 mg) on day 1. Subjects then received STS once daily (20 mg/20 cm^2) for 11 consecutive days. On day 12, a single dose of ibuprofen was given in the presence of STS. STS dosing continued till day 13.

Blood samples were collected at regular intervals till 24 hours for the determination of ibuprofen. From day 7 to 10, blood samples were collected for the determination of trough levels of selegiline. On day 11, blood samples were collected at regular intervals for 24 hours for the determination of selegiline and its metabolites. For the next 24 hours (day 12), blood samples were collected at regular intervals for determination of selegiline and ibuprofen.

The results of the study indicated that ibuprofen did not alter the steady state pharmacokinetics of the STS. 90% confidence interval for selegiline (natural log transformed):
AUC = 86.6-103.6
Cmax = 85.2-98.1

STS produced no effect on the pharmacokinetics of ibuprofen.

Pharmacokinetic Parameter	N=10 Treatment[a]	Selegiline Mean (%CV)	N-desmethylselegiline Mean (%CV)	L-amphetamine Mean (%CV)	L-methamphetamine Mean (%CV)	Ibuprofen Mean (%CV)
AUC(0-tau) (pg*hr/mL)[b]	Sel	49490 (27)	30924 (60)	52500 (30)	121900 (25)	-
	Sel + I	47048 (28)	28535 (66)	47075 (32)	107133 (25)	-
	I	-	-	-	-	-
AUC(0-tau) M/P	Sel		0.60 (45)	1.13 (43)	2.69 (48)	-
	Sel + I	-	0.57 (42)	1.03 (32)	2.42 (39)	-
	I	-	-	-	-	-
AUCI (mcg*hr/mL)	Sel	-	-	-	-	-
	Sel + I	-	-	-	-	254.53 (22)
	I	-	-	-	-	264.14 (17)
AUCT (mcg*hr/mL)	Sel	-	-	-	-	-
	Sel + I	-	-	-	-	248.93 (21)
	I	-	-	-	-	258.13 (17)
Cmax (pg/mL)[c]	Sel	2712.7 (24)	1583.9 (56)	2577.7 (29)	6091.5 (23)	-
	Sel + I	2486.1 (24)	1410.4 (62)	2341.0 (31)	5359.8 (27)	58.7 (13)
	I	-	-	-	-	63.7 (15)
Cmin (pg/mL)	Sel	1536.6 (39)	1009.3 (73)	1781.9 (32)	4104.6 (27)	-
	Sel + I	1472.1 (29)	883.4 (67)	1590.4 (35)	3609.8 (26)	-
	I	-	-	-	-	-
Css (pg/mL)	Sel	2062.1 (27)	1288.5 (60)	2187.5 (30)	5079.2 (25)	-
	Sel + I	1957.6 (28)	1186.7 (66)	1958.6 (32)	4458.7 (25)	-
	I	-	-	-	-	-
CL (L/hr)	Sel	434.26 (30)	-	-	-	-
	Sel + I	453.01 (25)	-	-	-	3.27 (19)
	I	-	-	-	-	3.10 (16)
Tmax (hr)	Sel	6.95 (95)	10.20 (52)	8.51 (54)	6.95 (66)	-
	Sel + I	6.25 (93)	9.06 (72)	10.28 (61)	10.18 (69)	1.80 (44)
	I	-	-	-	-	2.00 (71)
Fluct Cmin%	Sel	107.94 (105)	82.83 (98)	46.27 (26)	50.70 (36)	-
	Sel + I	72.74 (41)	64.17 (50)	49.91 (48)	50.09 (49)	-
	I	-	-	-	-	-
Fluct Ctrough%	Sel	48.57 (67)	50.48 (51)	35.73 (62)	41.98 (60)	-
	Sel + I	47.66 (27)	31.30 (37)	34.68 (71)	33.47 (74)	-
	I	-	-	-	-	-
MRT[d] (hr)	Sel	11.84 (3.5)	11.83 (3.3)	11.88 (3.2)	11.85 (3.2)	-
	Sel + I	11.92 (2.2)	12.13 (2.5)	11.96 (3.9)	11.96 (4.0)	3.80 (12)
	I	-	-	-	-	3.93 (17)
T½ (hr)	Sel	-	-	-	-	-
	Sel + I	-	-	-	-	2.33 (15)
	I	-	-	-	-	2.30 (14)
Kel (hr)	Sel	-	-	-	-	-
	Sel + I	-	-	-	-	0.3045 (15)
	I	-	-	-	-	0.3048 (13)

[a]Treatments were Sel=Selegiline (STS 20 mg/20 cm^2) alone; Sel + I= Selegiline (STS 20 mg/20 cm^2) + ibuprofen; I=ibuprofen alone

[b]Units for Ibuprofen are mcg*hr/mL

[c]Units for Ibuprofen are mcg/mL

[d]Uncorrected MRT for metabolites

$AUC_{(0-tau)}$=area under the concentration curve, over tau [τ] the dosing interval; AUCI=area under the concentration-time curve to infinity; AUCT=area under the concentration time curve; CL=total clearance; C_{max}=maximum concentration over the entire sampling phase; C_{min}=minimum plasma concentration over the dosing interval tau; C_{ss}=concentration at steady-state; Fluct C_{min}%= the percent fluctuation (relative to C_{min}) calculated as $(C_{max}-C_{min})/C_{min}$ *100; Fluct C_{trough} %= the percent fluctuation (relative to C_{trough}) calculated as $(C_{max}-C_{trough})/C_{trough}$ *100; CV=coefficient of variation; K_{el}=apparent elimination rate constant; MRT=mean residence time; T_{max}=time to attain C_{max}; $T_{½}$=apparent elimination half-life

Note: *R(-)-N-desmethylselegiline, R(-)-amphetamine, and R(-)-methamphetamine are interchangeable terms for N-desmethylselegiline, L-amphetamine, and L-methamphetamine, respectively.*

Study #17

Title: Pharmacokinetic/pharmacodynamic drug interaction study between alcohol and selegiline transdermal system in healthy volunteers (Study #S9303-P9927).

This was a single-center, open-label drug interaction study in 15 male subjects (21-44 years of age). Subjects received a single oral dose of alcohol or placebo on two separate occasions, days 1 and 2. Subjects then received STS once daily (20 mg/20 cm^2) for 10 consecutive days. On days 11 and 12, subjects received alcohol in combination with STS. Alcohol was given in the form of commercially available Everclear (0.75 g/kg) mixed in grape juice (20% v/v) and was ingested on two separate days (days 1 or 2 and days 11 or 12). Behaviour and mood assessment tests were performed and compared with STS + placebo or STS + alcohol.

On days 1 and 2 blood samples were collected at regular intervals till 8 hours for the determination of alcohol. From day 7 to 10, blood samples were collected for the determination of trough levels of selegiline. On days 11-13 blood samples were collected at regular intervals for the determination of selegiline and its metabolites and alcohol. The results of the study indicated that alcohol did not alter the steady state pharmacokinetics of STS. STS produced no effect on the pharmacokinetics of alcohol.
90% confidence interval for selegiline (natural log transformed):
AUC = 98.2 - 120.1
Cmax = 98.5 - 133.6

The combination of the STS and alcohol did not produce any significant effect on memory, learning, psychomotor performance as compared to alcohol given alone.

Pharmacokinetic Parameters of Selegiline and Selegiline Metabolites

N=15		Selegiline		R(-)-N-desmethylselegiline		R(-)-amphetamine		R(-)-methamphetamine	
Parameter	Treat-ment[a]	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
$AUC_{(0\text{-}tau)}$ (pg*hr/mL)	Sel	80391.21	25	42076.04	44	72739.42	41	197051.02	33
	Sel + A	87869.72	26	44501.88	41	69642.41	34	193423.36	24
$AUC_{(0\text{-}tau)}$ M/P	Sel	-	-	0.52	31	0.90	31	2.51	33
	Sel + A	-	-	0.50	29	0.82	33	2.35	35
C_{trough}	Sel	2696.61	21	1434.33	41	2914.39	46	7791.32	37
	Sel + A	2662.65	23	1493.29	44	2700.71	39	7392.83	28
CL/F (L/hr)	Sel	263.39	24	-	-	-	-	-	-
	Sel + A	243.43	28	-	-	-	-	-	-
C_{max} (pg/mL)	Sel	4600.4	25	2210.6	44	3777.4	40	10335.8	33
	Sel + A	5347.6	28	2515.1	40	3663.8	36	10193.1	25
C_{min} (pg/mL)	Sel	2391.9	28	1225.7	44	2332.4	40	6275.4	32
	Sel + A	2395.4	19	1279.8	41	2324.7	37	6427.6	30
C_{ss} (pg/mL)	Sel	3349.6	25	1753.2	44	3030.8	41	8210.5	33
	Sel + A	3661.2	26	1854.2	41	2901.8	34	8059.3	24
T_{max} (hr)	Sel	7.85	60	7.93	49	11.78	56	11.52	51
	Sel + A	6.62	47	8.45	22	8.36	45	8.21	61
Fluct C_{min}%	Sel	98.09	45	81.93	38	63.88	56	65.64	39
	Sel + A	124.48	48	99.77	35	60.28	37	63.30	41
Fluct C_{trough} %	Sel	73.16	51	54.24	47	34.96	82	36.85	66
	Sel + A	105.87	63	71.77	29	38.14	66	41.36	59
MRT (hr)[b]	Sel	11.46	5	11.65	3	12.17	4	12.17	4
	Sel + A	10.95	8	11.24	7	11.77	7	11.80	7

Pharmacokinetic Parameters of Alcohol (N=15)

Parameter	Treatment[a]	Mean	%CV
$AUC_{(0\text{-}inf)}$ (mcg*hr/mL)	Selegiline + Alcohol	4002.42	15
	Alcohol	4019.83	16
$AUC_{(0\text{-}t)}$ (mcg*hr/mL)	Selegiline + Alcohol	3935.06	16
	Alcohol	3913.51	17
CL/F (L/hr)	Selegiline + Alcohol	15.02	15
	Alcohol	14.87	14
C_{max} (mcg/mL)	Selegiline + Alcohol	979.46	19
	Alcohol	1096.97	26
$T_{½}$ (hr)	Selegiline + Alcohol	0.78	31
	Alcohol	0.85	31
K_{el} (1/hr)	Selegiline + Alcohol	0.9527	23
	Alcohol	0.8787	25
MRT (hr)	Selegiline + Alcohol	2.92	8
	Alcohol	2.88	11
T_{max} (hr)	Selegiline + Alcohol	1.02	47
	Alcohol	1.23	42

[a]Selegiline=STS ($20mg/20cm^2$)

Study #18

Title: Steady-state pharmacokinetic/pharmacodynamic drug interaction study between pseudoephedrine and selegiline transdermal system in healthy volunteers (Study #S9303-P9928).

This was a single-center, open-label drug interaction study in 12 subjects (9 males and 3 females, 19-27 years of age). Subjects received pseudoephedrine or STS (20 mg/20 cm^2) according to the following schedule:

	Treatment Period				
	1 (Days 1-3)		2 (Day 4-10)	3 (Days 11-13)	
	Day 1	Days 2 and 3	Days 4-10	Day 11	Days 12 and 13
All Subjects[a]	Single Dose Pseudoephedrine (60 mg)	Multiple Dose Pseudoephedrine (60 mg TID)	STS (20 mg/20 cm^2) applied daily	Single Dose Pseudoephedrine (60 mg) + STS (20 mg/20 cm^2) applied daily	Multiple Dose Pseudoephedrine (60 mg TID) + STS (20 mg/20 cm^2) applied daily

On day 1, blood samples were collected at regular intervals till 24 hours and on days 2 and 3 at 1 and 6 hours after each pseudoephedrine dosing for the determination of pseudoephedrine. From day 5 to 10, blood samples were collected for the determination of trough levels of selegiline. On day 11, blood samples were collected at regular intervals till 24 hours for the determination of pseudoephedrine and selegiline and its metabolites. On days 12 and 13, sampling occured pre-dose and at 1 and 6 hours after each pseudoephedrine dosing for the determination of selegiline and pseudoephedrine concentrations.

The results of the study indicated that STS produced no effect on the pharmacokinetics of pseudoephedrine. 90% confidence interval for pseudoephedrine (natural log transformed) is as follows:

AUC = 90.4 - 111.3

Cmax = 90 – 110

Effect of pseudoephedrine on the steady state pharmacokinetics of STS was not determined.

The following Table summarizes the pharmacokinetic parameters of pseudoephedrine given with and without selegiline.

N=10		Selegiline		N-desmethylselegiline		L-amphetamine		L-methamphetamine		Pseudoephedrine	
Parameter	Treat-ment[a]	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
$AUC_{(0\rightarrow 24hr)}$ M/P	Sel + P	-	-	0.65	38	1.16	24	3.0	37	-	-
$AUC_{(0\text{-}inf)}$ (ng*hr/mL)	Sel + P	-	-	-	-	-	-	-	-	1970.39	26
	P	-	-	-	-	-	-	-	-	1979.67	28
$AUC_{(0\rightarrow 24hr)}$ (pg*hr/mL)[b]	Sel + P	52651.42	23	34634.92	54	62283.27	40	158547.88	51	1773.60	32
	P	-	-	-	-	-	-	-	-	1779.41	33
C_{max} (pg/mL)[c]	Sel + P	2845.3	19	1786.7	49	3136.5	37	8319.8	46	224.1	20
	P	-	-	-	-	-	-	-	-	226.1	23
C_{min} (pg/mL)	Sel + P	1803.1	24	1130.7	58	2123.2	46	5144.5	55	-	-
C_{ss} (pg/mL)	Sel + P	2193.8	23	1443.1	54	2595.1	40	6606.2	51	-	-
CL (L/hr)	Sel + P	400.61	25	-	-	-	-	-	-	31.92	20
	P	-	-	-	-	-	-	-	-	32.34	26
t_{max} (hr)	Sel + P	3.69	195	8.79	19	7.99	23	8.60	25	2.19	28
	P	-	-	-	-	-	-	-	-	2.31	41
Fluct C_{min}%	Sel + P	61.12	38	62.01	44	51.54	31	65.39	29	-	-
Fluct C_{trough}%	Sel + P	49.91	58	57.60	55	43.89	43	57.52	41	-	-
MRT (hr)[c]	Sel + P	11.46	4	11.28	4	11.60	2	11.49	3	8.49	19
	P	-	-	-	-	-	-	-	-	8.44	12
T½ (hr)	Sel + P	-	-	-	-	-	-	-	-	5.12	30
	P	-	-	-	-	-	-	-	-	4.89	13
Kel (1/hr)	Sel + P	-	-	-	-	-	-	-	-	0.1438	24
	P	-	-	-	-	-	-	-	-	0.1440	13

N-desmethylselegiline=R(-)-N-desmethylselegiline; L-amphetamine=R(-)-amphetamine;
L-methamphetamine=R(-)-methamphetamine;
[a]Sel + P=selegiline (STS (20 mg/20 cm^2)) + pseudoephedrine; P=pseudoephedrine monotherapy
[b]ng*hr/mL for pseudoephedrine
[c]ng/mL for pseudoephedrine

No statistically significant differences were observed for maximum changes in SBP within 90 minutes of dosing with pseudoephedrine in the absence or presence of selegiline. No trends were observed among subjects in maximum changes in systolic blood pressure after single dose pseudoephedrine with respect to time of occurrence after dosing, plasma concentration, the value of the change, or the effect of concomitant selegiline.

For medical reviewer: Please evaluate if changes in blood pressure following the administration of pseudoephedrine or pseudoephedrine with the STS are indeed of no clinical significance as claimed by the Sponsor.

APPEARS THIS WAY
ON ORIGINAL

Study #19

Title: Steady-state pharmacokinetic drug interaction study between ketoconazole and selegiline transdermal system in healthy volunteers (Study #S9303-P9931).

This was a single-center, open-label drug interaction study in 10 subjects (5 males and 5 females, 20-43 years of age). Subjects received STS (20 mg/20 cm^2) for 7 consecutive days once daily. From day 8 to 14, ketoconazole (200 mg once daily) was given orally with STS. Pre-dose blood samples (30 minutes prior to dosing) were taken on days 1 to 7 and days 9 to 14. On days 7 and 14, blood samples were taken at regular intervals for 24 hours to determine the concentrations of selegiline and its metabolites as well as ketoconazole.

The results of the study indicated that ketoconazole produced no effect on the pharmacokinetics of the STS. Ketoconazole, however, increased the AUC of selegiline metabolites by 30%. The failure of ketoconazole to produce any effect on the pharmacokinetics of selegiline indicates that selegiline may not be metabolized by 3A4 or only a small fraction of selegiline is metabolized by 3A4.

90% confidence interval for selegiline and its metabolites: (natural log transformed) is as follows:

	90% Confidence Interval	
	ln AUC(0-tau) (pg*hr/mL)	ln Cmax (pg/mL)
Selegiline	92.19 – 125.54	87.60 – 122.42
R(-)-N-desmethylselegiline	115.72 – 163.96	106.90 – 156.44
R(-)-amphetamine	111.98 – 147.69	111.38 – 151.25
R(-)-methamphetamine	104.66 – 143.36	26.98 – 158.08

APPEARS THIS WAY
ON ORIGINAL

Pharmacokinetic values for selegiline, its metabolites, and ketoconazole are summarized in the following table.

N=10		Selegiline		N-desmethylselegiline		L-amphetamine		L-methamphetamine		Ketoconazole	
Parameter	Treatment	Mean	CV%	Mean	CV%	Mean	CV%	Mean	CV%	Mean	CV%
$AUC_{(0\text{-}tau)}$ (pg*hr/mL)	Sel	65197.6	41	31037.7	60	51760.6	40	117396.0	31	-	-
	Sel + K	68148.0	26	39846.0	31	66046.6	38	149308.0	44	26.68[a]	42
$AUC_{(0\text{-}tau)}$ M/P	Sel	-	-	0.46	21	0.81	24	1.90	29	-	-
	Sel + K	-	-	0.58	18	0.98	30	2.22	36	-	-
C_{max} (pg/mL)	Sel	3587.2	40	1732.1	61	2732.2	48	5915.0	36	-	-
	Sel + K	3662.6	30	2084.1	36	3442.4	36	8338.6	35	5.00[b]	36
C_{min} (pg/mL)	Sel	1922.3	31	910.2	43	1654.0	31	3879.9	26	-	-
	Sel + K	1970.6	30	1190.4	29	2025.4	41	4707.0	40	0.00[b]	-
C_{ss} (pg/mL)	Sel	2716.6	41	1293.2	60	2156.7	40	4891.5	31	-	-
	Sel + K	2839.5	26	1660.2	31	2751.9	38	6221.2	44	1.11[b]	42
CL (L/hr)	Sel	341.3	29	-	-	-	-	-	-	-	-
	Sel + K	312.2	26	-	-	-	-	-	-	9.13	57
T_{max} (hr)	Sel	6.80	37	8.25	43	11.00	33	10.65	55	-	-
	Sel + K	8.60	43	8.90	48	12.25	65	13.6	35	2.50	66
Fluct C_{min} %	Sel	89.27	50	82.78	45	61.83	50	50.29	43	-	-
	Sel + K	89.40	47	73.54	44	74.95	41	82.27	46	-	-
Fluct C_{trough} %	Sel	64.54	51	56.98	49	39.87	81	27.44	62	-	-
	Sel + K	51.01	50	47.70	57	44.80	76	42.34	80	-	-
MRT (hr)	Sel	11.57	3	-	-	-	-	-	-	-	-
	Sel + K	11.80	4	-	-	-	-	-	-	4.56	21
Uncorrected MRT (hr)	Sel	-	-	11.67	2	12.15	3	12.17	4	-	-
	Sel + K	-	-	11.90	4	12.29	5	11.75	9	-	-
CLr (L/hr)	Sel	0.57	137	0.89	60	8.44	30	9.29	26	-	-
	Sel + K	0.45	102	0.70	47	6.32	36	7.49	41	-	-
%Fe	Sel	0.16	109	0.14	60	2.89	38	6.80	40	-	-
	Sel + K	0.16	103	0.15	47	2.70	31	6.30	30	-	-
$T_{1/2}$ (hr)	Sel	-	-	-	-	-	-	-	-	-	-
	Sel + K	-	-	-	-	-	-	-	-	2.35	25
K_{el} (1/hr)	Sel	-	-	-	-	-	-	-	-	-	-
	Sel + K	-	-	-	-	-	-	-	-	0.3115	25

Sel = Selegiline monotherapy; Sel + K = Selegiline + Ketoconazole; N-desmethylselegiline=R(-)-N-desmethylselegiline; L-amphetamine= R(-)-amphetamine; L-methamphetamine= R(-)-methamphetamine

[a] units for Ketoconazole are mcg*hr/mL

[b] units for Ketoconazole are mcg/mL

Study #20

Title: Single dose pharmacokinetic drug interaction study between carbamazepine and selegiline transdermal system in healthy volunteers (Study #S9303-P9933).

This was a phase I, single-sequence, three-treatment drug interaction study in 10 subjects (7 males and 3 females, 19-45 years of age). Subjects received a single dose of STS (20 mg/20 cm^2) on day 1 and removed 24 hours later. Carbamazepine 200 mg bid) was given orally for the next 13 days starting on day 4. On day 17, STS was given with carbamazepine and was removed 24 hours later. Blood samples were taken at regular intervals till 72 hours for determination of selegiline and its metabolites on days 1 and 17. Pre-dose blood samples were taken from day 6 to 16 for the measurement of carbamazepine. The results of the study indicated that carbamazepine increased the AUC and Cmax of STS by 92% and 71%, respectively. The AUC of desmethylselegiline was lower by 28% but amphetamine and methamphetamine AUCs increased by 100% and 52%, when selegiline was given with carbamazepine as compared to selegiline given alone. 90% confidence interval for selegiline (natural log transformed) is as follows:
AUC = 165.2 - 242.5
Cmax = 138.5 - 226.0
The STS did not alter the pharmacokinetics of carbamazepine.

The results of the study are rather surprising as carbamazepine is an enzyme inducer and it should decrease selegiline levels. No explanation was provided by the Sponsor for this contrasting effect of carbamazepine on STS.

Single Dose Pharmacokinetic Parameters of Selegiline and Metabolites

Pharmacokinetic	(N =9)	Selegiline		N-desmethylselegiline		L-amphetamine		L-methamphetamine	
Parameters	Treatment	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
AUC(0-inf) (pg*hr/mL)	Sel	22757.62	57	15350.09	55	31379.62	48	71319.36	38
	Sel + C	43987.13	57	11427.38	85	62519.15	49	109756.54	50
AUC(0-24) (pg*hr/mL)	Sel	13732.38	54	7121.03	39	4844.13	41	17318.55	33
	Sel + C	28908.38	63	6305.34	61	15736.48	52	30843.22	49
AUC(0-t) (pg*hr/mL)	Sel	21337.74	58	13480.00	52	21377.46	42	59973.05	35
	Sel + C	41558.98	59	9743.25	79	51503.86	47	92784.15	47
AUCI M/P	Sel	-	-	0.75	48	1.53	35	3.75	48
	Sel + C	-	-	0.26	51	1.45	11	2.58	20
AUCT M/P	Sel	-	-	0.71	53	1.16	43	3.36	42
	Sel + C	-	-	0.24	53	1.29	12	2.33	15
AUC(0-24) M/P	Sel	-	-	0.59	47	0.40	49	1.44	39
	Sel + C	-	-	0.23	40	0.57	18	1.12	11
CL (L/hr)	Sel	1176.34	55	-	-	-	-	-	-
	Sel + C	553.85	38	-	-	-	-	-	-
CLr (L/hr)	Sel	0.74	102	0.83	40	6.84	37	8.03	31
	Sel + C	0.29	93	0.52	57	5.35	39	5.48	34
C_{max} (pg/mL)	Sel	1053.5	51	559.0	41	576.9	37	1810.4	30
	Sel + C	1802.3	57	391.0	59	1296.7	43	2332.6	41
% Fe	Sel	0.07	80	0.07	59	1.39	49	3.44	36
	Sel + C	0.06	83	0.03	83	2.30	71	3.67	61
$T_{½}$ (hr)	Sel	17.92	52	14.01	60	33.62	90	21.12	26
	Sel + C	21.10	34	13.04	71	22.12	22	20.81	24
K_{el} (hr)	Sel	0.0477	44	0.0687	59	0.0275	34	0.0349	27
	Sel + C	0.0359	32	0.0724	47	0.0326	20	0.0352	26
MRT (hr)	Sel	27.01	24	30.02	29	65.08	67	44.47	18
	Sel + C	26.35	18	26.24	34	45.98	15	42.95	17
T_{max} (hr)	Sel	19.78	24	24.00	10	27.56	9	26.67	7
	Sel + C	16.67	33	12.89	27	25.78	27	23.33	20

Sel=Selegiline [STS (20mg/20cm^2)] alone; Sel + C=Selegiline [STS (20mg/20cm^2)] + carbamazepine

Steady-State Pharmacokinetic Parameters of Carbamazepine and Carbamazepine-10, 11-Epoxide

Pharmacokinetic Parameters	(N=9) Treatment	Carbamazepine Mean	Carbamazepine %CV	Carbamazepine-10, 11-Epoxide Mean	Carbamazepine-10, 11-Epoxide %CV
AUC(0-inf) (mcg*hr/mL)	*Sel + C*	*318.05*	*47*	*37.26*	*38*
	C	.	.	.	.
AUC(0-t) (mcg*hr/mL)	Sel + C	260.21	36	33.72	35
	C	.	.	.	.
AUC(0-10) (mcg*hr/mL)	Sel + C	60.20	28	7.99	35
	C	59.90	26	8.02	33
AUC(0-10) M/P	Sel + C	-	-	0.14	29
	C	-	-	0.14	32
CL (L/hr)	*Sel + C*	*3.54*	*26*	-	-
	C	3.51	22	-	-
C_{max} (mcg/mL)	Sel + C	6.424	26	0.8547	35
	C	6.437	23	0.8677	33
C_{min} (mcg /mL)	Sel + C	5.627	30	0.7489	36
	C	5.660	28	0.7451	34
C_{ss} (mcg/mL)	Sel + C	6.019	28	0.7987	35
	C	5.984	26	0.8008	33
Fluct Cmin %	*Sel + C*	*15.61*	*54*	*14.59*	*59*
	C	15.01	47	17.16	46
Fluct Ctrough %	Sel + C	8.30	58	9.66	76
	C	10.06	65	11.77	53
$T_{½}$ (hr)	Sel + C	25.67	30	18.78	21
	C	.	.	.	.
K_{el} (hr)	Sel + C	0.0296	35	0.0385	23
	C	.	.	.	.
T_{max} (hr)	*Sel + C*	*8.45*	*59*	*6.78*	*93*
	C	5.22	72	3.78	86

Sel=Selegiline [STS (20mg/20cm^2)] alone; Sel + C=Selegiline [STS (20mg/20cm^2)] + carbamazepine

Study #21

Title: Pharmacokinetic interaction between the selegiline transdermal system and cocaine (Study #98-2).

The objectives of this study were to evaluate the effect of STS (20 mg/cm^2) administered once daily for 10 days (7 days pre-cocaine and 3 days post) on the pharmacokinetics of cocaine and its inactive metabolite benzoylecgonine (BE) as well as effect of single dose cocaine (10 days apart) on the pharmacokinetics of selegiline.

This was a single-center, open-label drug interaction study in 12 subjects (11 males and 1 female, 21-45 years of age). A single dose of cocaine (0.5 mg/kg over 10 minutes followed by 2 mg/kg over 4 hours) was intravenously infused to experienced, nondependent cocaine users. STS (20 mg/20 cm^2) was administered on day 4 and continued through day 12, patches being removed every 24 hours. The second cocaine infusion took place 2 hours after the administration of STS on day 11. Blood samples were taken at regular intervals till 45 hours for determination of cocaine and its metabolite. Blood samples were also taken for the measurement of selegiline and its metabolite concentrations on days 4 through 9 (pre-dose) and on day 11 at regular intervals till 48 hours. Pharmacodynamic parameters such as systolic and diastolic blood pressure, heart rate, respiration rate and rate pressure product were measured.

The results of the study indicated that the STS produced no effect on the pharmacokinetics of cocaine or its metabolite. Single dose cocaine did not effect the trough levels of selegiline and desmethylselegiline. The effect of the STS on the pharmacokinetics of cocaine has been summarized in the Tables below.

Table II. Summary of session 1 and 2 plasma cocaine pharmacokinetic parameters (mean ± SD) and their statistical comparisons (p-values between treatments) (a)

Subject	Cmax (ng/mL)	Tmax (hrs)	AUC(0-t) (ng*h/mL)	λz (1/hrs)	T-1/2 (hrs)	AUC(0-∞) (ng*h/mL)	AUCext (%)	CL (mL/min/kg)	Vz (L/kg)
Session 1									
Mean	721	2.66	2642	0.453	1.71	2675	1.40	18.3	2.49
SD	773	1.74	1470	0.126	0.808	1471	1.03	6.17	0.885
Session 2									
Mean	640	2.27	2359	0.456	1.57	2398	1.78	18.0	2.44
SD	332	2.04	499	0.087	0.30	487	1.87	3.34	0.640
Friedman Test p-Values Between Sessions									
	0.248	0.999	0.564	0.564	0.564	0.564	ND	0.564	0.999

Table III. Summary of plasma BE pharmacokinetic parameters (mean ± SD) from sessions 1 and 2, and their statistical comparisons (p-values between treatments) (a)

Subject	Cmax (ng/mL)	Tmax (hrs)	AUC(0-t) (ng*h/mL)	λz (1/hrs)	T-1/2 (hrs)	AUC(0-∞) (ng*h/mL)	AUCext (%)
Session 1							
Mean	1045	4.79	13028	0.0928	8.63	13649	3.45
SD	180	0.496	3028	0.0229	5.36	3817	6.45
Session 2							
Mean	957	5.04	12879	0.0971	7.52	13238	2.21
SD	184	0.653	3757	0.0237	1.82	4181	2.24
Friedman Test p-Values Between Sessions							
	0.564	0.157	0.9999	0.9999	0.9999	0.9999	ND

Table V. Mean ± SD selegiline and metabolite trough (prepatch) plasma concentrations (ng/mL) on Days 11, 12 and 13, and p-values associated with their differences.

DRUG	DAY 11	DAY 12	DAY 13	p-value
Selegiline	1.43 ± 0.79	1.44 ± 1.02	1.86 ± 0.61	0.054
R(-)-N-Desmethylselegiline	0.854 ± 0.669	0.982 ± 0.770	0.992 ± 0.618	0.26
R(-)-Methamphetamine	3.52 ± 1.11	4.38 ± 1.98	5.46 ± 1.97	0.038 (Day 13>11)
R(-)-Amphetamine	1.50 ± 0.56	1.72 ± 0.78	2.27 ± 0.91	0.047 (Day 13>11)

Cocaine infusion led to a clinically acceptable increase in systolic blood pressure but not in diastolic blood pressure. With cocaine infusion, the subject's skin temperature decreased by 5.4 ± 2.7 ^{0}C but returned to normal within 2.5 hours. No difference in any pharmacodynamic parameter of cocaine was found when given with or without the STS.

PHARMACOKINETIC INTERACTIONS BETWEEN THE SELEGILINE TRANSDERMAL SYSTEM AND COCAINE
Protocol ISEL C19803 (Study 98-2)

Subjective Measures — Summary of Peak Changes (Mean ± SD for 12 Subjects)

Measures	Session 1		Session 2	
	Peak Mean ± SD	Peak Time (Hr Postdose)	Peak Mean ± SD	Peak Time (Hr Postdose)
Physiologic Measures				
Systolic Blood Pressure (mmHg)	17 ± 8	2.2 ± 1.9	17 ± 9	1.9 ± 1.7
Diastolic Blood Pressure (mmHg)	10 ± 5	2.8 ± 2.4	12 ± 6	2 ± 2
Heart Rate (beats/min)	26 ± 10	0.8 ± 0.9	27 ± 12	0.9 ± 1.7
Rate Pressure Product (sbp*hr)	4224 ± 1638	1.4 ± 1.5	4437 ± 2333	0.9 ± 1.6
Respiration Rate (inhal/min)	3.8 ± 4	0.9 ± 1.3	3.8 ± 3.6	0.4 ± 0.3
Skin Temperature (°C)	-5.4 ± 2.7	0.8 ± 0.4	-5 ± 3.2	1.0 ± 1.2
Core Temperature (°C)	0.7 ± 0.2	4.5 ± 1.6	0.7 ± 0.5	4.2 ± 1.9
Subjective Measures				
VA - Good Drug Effect (0-100)	66 ± 23	0.9 ± 1.5	60 ± 21	1 ± 1.3
VA - Bad Drug Effect(0-100)	46 ± 31	1.9 ± 2.3	55 ± 25	1.4 ± 1.9
VA - Desire for Cocaine (0-100)	35 ± 18	1.8 ± 2.3	31 ± 27	0.7 ± 0.9
Global Intoxication (0-100)	57 ± 27	0.7 ± 1	53 ± 23	0.6 ± 0.9
Cocaine Craving (0-100)	33 ± 25	1.1 ± 1.3	20 ± 21	0.6 ± 0.7
Monetary Value ($)	38 ± 44	1 ± 1.2	33 ± 23	0.7 ± 0.9
POMS Scales				
Tension (0-28)	7.5 ± 6.1	1 ± 0	4.8 ± 3.9	1 ± 0
Depression (0-64)	3 ± 6.5	3 ± 0	1.5 ± 2.4	3 ± 0
Anger (0-28)	2.8 ± 6.4	6 ± 0	-2.1 ± 5.7 *	6 ± 0
Vigor (0-32)	-3.6 ± 3.4	6 ± 0	-3.9 ± 6.1	6 ± 0
Confusion (0-20)	2.5 ± 2.8	6 ± 0	2.7 ± 4.7	3 ± 0
Fatigue (0-28)	5.9 ± 5.9	6 ± 0	2.8 ± 5.3	6 ± 0

* Significantly different from session 1 ($p<0.03$).
Session 1: First cocaine infusion, performed on day 1, before selegiline administration.
Session 2: Second cocaine infusion, performed on day 11, following one week of selegiline administration by STS patch (20 mg/day). Infusion began 2 hours after application of the selegiline daily patch.

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Study #22

Title: Steady-state pharmacokinetic and pharmacodynamic drug interaction study between phenylpropanolamine and selegiline transdermal system in healthy volunteers (Study #S9303-P0046).

This was a single-center, open-label drug interaction study in 11 male subjects (20-44 years of age). Subjects received phenylpropanolamine or STS (20 mg/20 cm^2) according to following schedule:

Treatment Period				
I (Days 1 through 3)		II (Days 5 through 11)	III (Days 12 through 14)	
Day 1	Day 2 to 3	Days 5 through 11	Day 12	Day 13 to 14
Single Dose phenylpropanolamine (25 mg)	Multiple Dose (6) phenylpropanolamine (25 mg q4h)[a]	STS (20mg/20cm^2) applied daily	Single Dose phenylpropanolamine (25 mg) + STS (20mg/20cm^2) Applied daily	Multiple Dose (6) phenylpropanolamine (25 mg q4h)[a]

[a]Last two doses of multiple dosing occurred on Days 3 and 14, respectively, for Treatment Periods I and III.
q4h = every 4 hours

On day 1, blood samples were collected at regular interevals till 24 hours and on days 2 and 3 at 1 and 4 hours after each phenylpropanolamine dosing for the determination of phenylpropanolamine. From day 8 to 11, blood samples were collected for the determination of trough levels of selegiline. On day 12, blood samples were collected at regular intervals till 24 hours for the determination of phenylpropanolamine and selegiline and its metabolites. On days 13 and 14, sampling occured pre-dose and at 1 and 4 hours after each phenylpropanolamine dosing for the determination of selegiline and phenylpropanolamine concentrations. Blood pressure was measured 30 minutes before each dose of phenylpropanolamine on days 1,2, 3, 12, 13, and 14. On days 1, 2, 3, 12, 13, and 14 blood pressure was measured every 10 minutes for 2 hours after dosing.

Eleven subjects completed the study. The results of the study indicated that STS produced no effect on the pharmacokinetics of phenylpropanolamine. 90% confidence interval for phenylpropanolamine (natural log transformed) is as follows:
AUC = 88 – 107; Cmax = 90 - 109

Effect of phenylpropanolamine on the steady state pharmacokinetics of the STS was not determined.
The following Table summarizes the pharmacokinetic parameters of phenylpropanolamine with and without the STS.

		N = 11								N = 10[b]	
		Selegiline		R(-)-N-desmethylselegiline		R(-)-amphetamine		R(-)-methamphetamine		Phenylpropanolamine	
Parameter	Treat-ment[a]	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
$AUC_{(0\text{-}tau)}$ (pg*hr/mL)	Sel + P	69821.63	25	38633.13	39	67729.27	47	168675.45	33	-	-
$AUC_{(0\text{-}tau)}$ M/P	Sel + P	-	-	0.55	26	0.95	24	2.40	18	-	-
$AUC_{(0\text{-}inf)}$ (ng*hr/mL)	Sel + P	-	-	-	-	-	-	-	-	489.89	28
	P	-	-	-	-	-	-	-	-	515.95	37
$AUC_{(0\text{-}t)}$ (ng*hr/mL)	Sel + P	-	-	-	-	-	-	-	-	408.80	30
	P	-	-	-	-	-	-	-	-	412.11	27
$AUC_{(24\text{-}48)}$ (ng*hr/mL)	Sel + P	-	-	-	-	-	-	-	-	1927.65	18
	P	-	-	-	-	-	-	-	-	1996.87	14
Avg C_{trough} (pg/mL)	Sel + P	2304.93	23	1272.84	46	2524.3	53	5981.01	36	-	-
C_{max} (pg/mL)[c]	Sel + P	3795.9	27	2080.4	38	3433.6	49	8503.4	35	79.59	27
	P	-	-	-	-	-	-	-	-	80.70	28
C_{min} (pg/mL)	Sel + P	2154.3	21	1180.4	41	2207.3	45	5337.7	33	-	-
C_{ss} (pg/mL)	Sel + P	2909.2	25	1609.7	39	2822.1	47	7028.1	33	-	-
C_{last} (ng/mL)	Sel + P	-	-	-	-	-	-	-	-	11.65	34
	P	-	-	-	-	-	-	-	-	13.18	50
CL (L/hr)[d]	Sel + P	303.34	25	-	-	-	-	-	-	55.02	30
	P	-	-	-	-	-	-	-	-	54.34	35
T_{max} (hr)	Sel + P	5.89	47	8.80	29	8.98	27	8.07	33	1.60	51
	P	-	-	-	-	-	-	-	-	1.60	60
Fluct C_{min} %	Sel + P	75.37	34	79.72	34	54.67	33	59.20	28	-	-
Fluct C_{trough} %	Sel + P	65.27	44	69.07	43	38.98	59	43.63	47	-	-
MRT (hr)[e]	Sel + P	11.26	3	11.25	3	11.74	3	11.66	3	7.30	25
	P	-	-	-	-	-	-	-	-	7.52	30
$T_{1/2}$ (hr)	Sel + P	-	-	-	-	-	-	-	-	4.69	31
	P	-	-	-	-	-	-	-	-	4.70	40
K_{el} (1/hr)	Sel + P	-	-	-	-	-	-	-	-	0.1609	30
	P	-	-	-	-	-	-	-	-	0.1689	38

No statistically significant differences were observed for maximum mean changes in SBP or DBP after dosing with phenylpropanolamine in the absence or presence of selegiline. Although a statistically significant increase in mean maximum heart rate was observed on Day 3 after dose 6 (p=0.0246), this maximum mean change in heart rate was not considered clinically significant by the Sponsor.

No mean changes in vital signs and individual subject changes were considered clinically significant by the Sponsor. No subject experienced an increase from baseline in SBP of>60

mmHg. Four subjects experienced an isolated protocol-defined, endpoint pressor response [three (3) consecutive SBP measurements ->30 mmHg above the previous baseline].

For medical reviewer: Please evaluate if changes in blood pressure following the administration of phenylpropanolamine or phenylpropanolamine with the STS are indeed of no clinical significance as claimed by the Sponsor.

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Study #23

Title: Pharmacokinetics of selegiline in patients with depression.

In order to evaluate the pharmacokinetics of selegiline via the STS in patients with major depression, trough blood samples were obtained in Phase Ill efficacy studies (20 mg/20 cm^2). A total of 177 patients participated in the study. Eighty-eight were on placebo and 89 on STS (20 mg/20 cm^2) for a 6-week period. Blood samples were obtained at baseline and at the week 6 visit in all cases. Of the 82 patients for whom data were available 6 patients were excluded from the database because of compliance issues.

Considerable fluctuations in selegiline trough concentrations occurred over the 6-week treatment period. A 2-fold variation in steady-state trough selegiline concentrations is apparently not uncommon in these patients; with some patients exhibiting far greater changes. It is likely that patient compliance issues compromise the accuracy and reliability of the data but the overall mean values were actually quite similar to the theoretical value of 1.0. Thus, it appears that a 2- to 3-fold fluctuation in selegiline trough plasma concentration falls within the normal clinical variability seen with the STS.

Comparison of the results from this trial to those generated in the Phase I steady-state studies, where subject compliance and sample processing were better controlled, reveals fairly good general agreement. The average trough concentration in patients, using the 6-week data generated in 73 patients, was approximately 2800 pcg/mL (CV 39.5 %). For comparison, the average trough concentration 24 hours after the last patch application in 11 male volunteers based on the S9303-P9923, was 2449 pcg/mL (CV 18.9%). The overall similarity in the data generated in the major depression patients to that seen in the healthy volunteer program for STS, demonstrates that no major differences exist between the patients and the healthy volunteer population in the pharmacokinetics of transdermally administered selegiline via the STS (20 mg/20 cm2).

Table 30. Trough Plasma Concentrations (pg/mL) for Selegiline and its Metabolites Obtained During the Conduct of Study S9303-E106-96B

	Week 1 (N=16)	Week 3 (N=27)	Week 6 (N=73)	Ratio wk 1/wk 6	Ratio wk 3/wk 6
Selegiline	3151	2995	2829	1.1	1.1
N-Desmethylselegiline	1617	1660	1502	1.1	1.1
Amphetamine	2370	2565	2530	0.94	1.0
Methamphetamine	5653	5422	5450	1.0	1.0

Study #24

IDENTIFICATION OF THE PRINCI PAL HUMAN LIVER MICROSOMAL CYTOCHROME P450 ISOENZYMES INVOLVED IN THE METABOLISM OF SELEGILINE, N-DESMETHYL SELEGILINE, AMPHETAMINE AND METHAMPHETAMINE IN VITRO

This study was conducted to identify the principal human liver cytochrome P450 isoenzymes involved in the metabolism of selegiline, N-desmethylselegiline, amphetamine and methamphetamine. This study was conducted at [redacted] Selegiline HCl Lot No. 9803007 and N--desmethylselegiline HCl Lot No. 245-C-R1-01-21-0 were used in this study.

An [redacted] liquid chromatography/tandem mass spectrometry [redacted] LC/MS/MS) method was used to profile the in vitro metabolism of selegiline, N-desmethylselegiline, amphetamine and methamphetamine by human liver microsomes.

A preliminary experiment was conducted with selegiline, desmethylselegiline, amphetamine and methamphetamine to optimize the in vitro incubation conditions. Based upon the results of this study (no metabolism of amphetamine or methamphetamine was detected over the concentration range of 0.015 to 1.5 pM), a correlation analysis [redacted] reaction phenotyping program; [redacted] was carried out using human liver microsomes from 15 individual donors. Microsomes, were incubated with selegiline or N-desmethylselegiline at 0.5 and 5 microM in the presence of an NADPH-regenerating system.

From these data a chemical inhibition study was also conducted to determine whether the rate of metabolism of selegiline and N-desmethylselegiline at 0.5 or 5 microM was decreased in the presence of CYP isoform-selective substrates or inhibitors.

Results of the study indicated that CYP2B6, CYP2C9 and CYP3A/5 appeared to be the major contributing CYP enzymes in the formation of methamphetamine from selegiline with CYP2A6 having a minor role. CYP2B6 and CYP3A4/5 appeared to contribute to the formation of amphetamine from selegiline and N-desmethylselegiline.

Under the experimental conditions, no CYP enzyme could be clearly identified as having a significant role in the formation of N-desmethylselegiline from selegiline. The possible involvement of CYP2D6 was indicated but only at the high selegiline concentration of 5 microM. The correlation coefficient, however, was relatively weak at 0.62 and N-desmethylselegiline formation was not inhibited by I microM quinidine (a

selective and potent inhibitor of CYP2D6). Although not supported by the correlation analysis, the results of the chemical inhibition study suggested that CYP2B6, CYP2C9 and CYP3A4/5 might be involved in the formation of N-dcsmethylselegiline from selegiline.

Conclusion:

The results of the correlation study combined with those from the chemical inhibition study indicated that CYP2B6, CYP2C9 and CYP3A/5 appeared to be the major contributing CYP enzymes in the formation of methamphetamine from selegiline with CYP2A6 having a minor role. CYP2B6 and CYP3A4/5 appeared to contribute to the formation of amphetamine from N-desmethylselegiline.

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INHIBITION OF SELEGILINE METABOLISM IN HUMAN LIVER MICROSOMES BY ENZYME-SELECTIVE CHEMICAL SUBSTRATES OR INHIBITORS (N-DESMETHYLSELEGILINE FORMATION)

SUBSTRATE	CHEMICAL INHIBITORS							
	Conc.	100 μM EFC* **CYP2B6**	100 μM Erythromycin **CYP3A4**	100 μM TAO** **CYP3A4/5**	100 μM Nicotine **CYP2A6**	20 μM Sulfaphenazole **CYP2C9**	400 μM S-mephenytoin **CYP2C19**	1 μM Quinidine **CYP2D6**
SELEGILINE	0.5 μM †	**57.3**	**NI**	**NI**	**NI**	NI	**NI**	N/A
	5 μM †	**58.3**	**19.0**	**22.7**	**8.9**	**32.5**	**NI**	**NI**

† 0.5 and 5 μM selegiline = ~93 and 933 ng/mL

Values are expressed as percent inhibition

* 7-ethoxy-4-fluoromethylcoumarin

** Troleandomycin

NI : no inhibition

N/A : not applicable

APPEARS THIS WAY
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INHIBITION OF SELEGILINE METABOLISM IN HUMAN LIVER MICROSOMES BY ENZYME-SELECTIVE CHEMICAL SUBSTRATES OR INHIBITORS (METHAMPHETAMINE FORMATION)

SUBSTRATE	CHEMICAL INHIBITORS							
	Conc.	100 μM EFC* **CYP2B6**	100 μM Erythromycin **CYP3A4**	100 μM TAO** **CYP3A4/5**	100 μM Nicotine **CYP2A6**	20 μM Sulfaphenazole **CYP2C9**	400 μM S-mephenytoin **CYP2C19**	1 μM Quinidine **CYP2D6**
SELEGILINE	0.5 μM †	**29.6**	**NI**	**NI**	**NI**	**NI**	**NI**	N/A
	5 μM †	**50.4**	**19.7**	**28.1**	**8.7**	**37.5**	**NI**	**11.0**

† *0.5 and 5 μM selegiline = ~93 and 933 ng/mL*

Values are expressed as percent inhibition.

* 7-ethoxy-4-fluoromethylcoumarin
** Troleandomycin
NI : no inhibition
N/A : not applicable

APPEARS THIS WAY
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INHIBITION OF SELEGILINE AND N-DESMETHYLSELEGILINE METABOLISM IN HUMAN LIVER MICROSOMES BY ENZYME-SELECTIVE CHEMICAL SUBSTRATES OR INHIBITORS (AMPHETAMINE FORMATION)

SUBSTRATES	CHEMICAL INHIBITORS							
	Conc.	*100 μM* EFC* **CYP2B6**	*100 μM* Erythromycin **CYP3A4**	*100 μM* TAO** **CYP3A4/5**	*100 μM* Nicotine **CYP2A6**	*20 μM* Sulfaphenazole **CYP2C9**	*400 μM* S-mephenytoin **CYP2C19**	*1 μM* Quinidine **CYP2D6**
SELEGILINE	0.5 μM †	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	5 μM †	**55.5**	**4.8**	**25.7**	**12.0**	**NI**	**NI**	**8.2**
N-DESMETHYL SELEGILINE	0.5 μM †	**38.4**	**12.7**	**11.0**	**NI**	**14.0**	**2.7**	**N/A**
	5 μM †	**11.1**	**23.5**	**41.5**	**8.7**	**NI**	**NI**	**N/A**

† 0.5 and 5 μM selegiline = ~93 and 933 ng/mL
0.5 and 5 μM N-desmethylselegiline = ~86.7 and 867 ng/mL

Values are expressed as percent inhibition.

* 7-ethoxy-4-fluoromethylcoumarin
** Troleandomycin
NI : no inhibition
N/A : not applicable
ND : No metabolites were detected

CORRELATION OF THE SAMPLE-TO-SAMPLE VARIATION BETWEEN METABOLITE FORMATION AND CYTOCHROME P450 ENZYME ACTIVITIES AT 0.5 μM *(~93 NG/ML)* SELEGILINE AND 0.5 μM *(~86.7 NG/ML)* N-DESMETHYLSELEGILINE

Reaction / CYP450	Selegiline						N-Desmethylselegiline	
	N-Desmethylselegiline [1]		Amphetamine [1]		Methamphetamine [1]		Amphetamine [2]	
Caffeine *N3*-demethylation CYP1A2	0.3633 *	*(0.1872)***	0.1083	*(0.7065)*	0.2908	*(0.2997)*	0.1577	*(0.5817)*
Coumarin 7-hydroxylation CYP2A6	0.3774	*(0.1691)*	**0.7431**	***(0.0009)***	0.5156	*(0.0482)*	**0.8272**	***(0.0001)***
S-Mephenytoin *N*-demethylation CYP2B6	0.2588	*(0.3590)*	**0.9796**	***(0.0000)***	**0.7113**	***(0.0021)***	**0.9767**	***(0.0000)***
Tolbutamide methylhydroxylation CYP2C9	0.4898	*(0.0635)*	**0.6083**	***(0.0144)***	**0.6734**	***(0.0047)***	0.5860	*(0.0200)*
S-Mephenytoin 4-hydroxylation CYP2C19	0.4448	*(0.0976)*	0.5875	*(0.0196)*	0.2774	*(0.3237)*	0.5917	*(0.0185)*
Dextromethorphan O-demethylation CYP2D6	0.4081	*(0.1333)*	0.0947	*(0.7421)*	0.5401	*(0.0363)*	0.1324	*(0.6446)*
Chlorzoxazone 6-hydroxylation CYP2E1	0.3550	*(0.1986)*	0.5677	*(0.0257)*	0.5679	*(0.0256)*	0.5429	*(0.0351)*
Dextromethorphan *N*-demethylation CYP3A4	-0.2710	*(0.3356)*	**0.9572**	***(0.0000)***	**0.7057**	***(0.0023)***	**0.9583**	***(0.0000)***
Testosterone 6β-hydroxylation CYP3A4/5	-0.1907	*(0.5036)*	**0.8277**	***(0.0001)***	**0.7096**	***(0.0021)***	**0.8447**	***(0.0000)***
Lauric acid 12-hydroxylation CYP4A11	0.5505	*(0.0320)*	0.1060	*(0.7125)*	0.2696	*(0.3384)*	0.1118	*(0.6973)*

[1] Metabolites formed using 0.5 μM (~93 ng/mL) selegiline as substrate.

[2] *Metabolite formed using 0.5 μM (~86.7 ng/mL) N-desmethylselegiline as substrate.*

* Coefficient of correlation

** *(p-value)*

Note: The result is statistically significant when p-value is less than 0.05

CORRELATION OF THE SAMPLE-TO-SAMPLE VARIATION BETWEEN METABOLITE FORMATION AND CYTOCHROME P450 ENZYME ACTIVITIES AT 5 μM *(~933 NG/ML)* SELEGILINE AND 5 μM *(~867 NG/ML)* N-DESMETHYLSELEGILINE

Reaction / CYP450	Selegiline						N-Desmethylselegiline	
	N-Desmethylselegiline [1]		Amphetamine [1]		Methamphetamine [1]		Amphetamine [2]	
Caffeine *N3*-demethylation CYP1A2	0.2951 *	*(0.2920)***	0.0734	*(0.7990)*	0.2923	*(0.2969)*	0.1408	*(0.6234)*
Coumarin 7-hydroxylation CYP2A6	-0.3094	*(0.2678)*	**0.8159**	***(0.0001)***	**0.6333**	***(0.0097)***	**0.8299**	***(0.0000)***
S-Mephenytoin *N*-demethylation CYP2B6	-0.2012	*(0.4798)*	**0.9864**	***(0.0000)***	**0.8209**	***(0.0001)***	**0.9769**	***(0.0000)***
Tolbutamide methylhydroxylation CYP2C9	0.2256	*(0.4265)*	0.4967	*(0.0591)*	**0.6409**	***(0.0085)***	0.5882	*(0.0194)*
S-Mephenytoin 4-hydroxylation CYP2C19	-0.4440	*(0.0983)*	**0.6724**	***(0.0048)***	0.4376	*(0.1040)*	0.5842	*(0.0205)*
Dextromethorphan *O*-demethylation CYP2D6	**0.6161**	***(0.0128)***	-0.0059	*(0.9837)*	0.3514	*(0.2035)*	0.1318	*(0.6462)*
Chlorzoxazone 6-hydroxylation CYP2E1	0.1476	*(0.6066)*	0.4707	*(0.0767)*	0.5385	*(0.0370)*	0.5265	*(0.0426)*
Dextromethorphan *N*-demethylation CYP3A4	-0.2202	*(0.4381)*	**0.9680**	***(0.0000)***	**0.7986**	***(0.0002)***	**0.9595**	***(0.0000)***
Testosterone 6β-hydroxylation CYP3A4/5	-0.1382	*(0.6299)*	**0.8281**	***(0.0001)***	**0.7313**	***(0.0013)***	**0.8447**	***(0.0000)***
Lauric acid 12-hydroxylation CYP4A11	0.2524	*(0.3715)*	0.0213	*(0.9411)*	0.2235	*(0.4309)*	0.1113	*(0.6987)*

[1] Metabolites formed using 5 μM (~933 ng/mL) selegiline as substrate.

[2] Metabolite formed using 5 μM (~867 ng/mL) N-desmethylselegiline as substrate.

* Coefficient of correlation

** *(p-values)*

The result is statistically significant when p-value is less than 0.05

Study #25

DETERMINATION OF THE POTENTIAL FOR SELEGILINE AND N-DESMETHYLSELEGILINE TO INHIBIT CYTOCHROME P450 ENZYMES (CYP2C9, CYP2CI 9, CYP2B6, CYP2D6, CYP3A4/5 AND CYP2A6) IN VITRO

This study was conducted to evaluate the potential for selegiline and N-desmethylselegiline to inhibit human liver microsomal P450 activities. This study was conducted at [redacted]
Selegiline HCl Lot No. 9803007 and N-desmethylselegiline HCl Lot No. 245-C-R1-01-21-0 were used in this study.

The effect of selegiline and N-desmethylselegiline on CYP2C9 (tolbutamide methyl-hydroxylation), CYP2C19 (S-mephenytoin 4'-hydroxylation), CYP2B6 (S-mephenytoin N-demethylation), CYP2D6 (dextromethorphan o-demethylation), CYP3A4/5 (testosterone 6β-hydroxylation) and CYP2A6 (coumarin 7-hydroxylation) enzyme activities was assessed in pooled human liver microsomes over a concentration range of 2.5 to 250 microM. Known CYP isoform-selective substrates or inhibitors were used as positive controls.

Selegiline and N-desmethylselegiline caused a concentration-dependent inhibition of CYP2D6 activity at 10-250 microM. Selegiline and N-desmethylselegiline caused a concentration-dependent inhibition of CYP3A4/5 activity at 10-250 microM and 25-250 microM, respectively. CYP2C19 and CYP2B6 activities were inhibited by selegiline and N-desmethylselegiline, but only at high concentrations (100-250 microM). There was no significant inhibitory effect on CYP2A6 or CYP2C9 activities by selegiline or N-desmethylselegiline. Positive control incubations showed moderate to complete inhibition of the appropriate enzyme activities using the CYP isoform-selective substrates and inhibitors.

The cytochrome P450 enzyme activities were inhibited by selegiline and N-desmethylselegiline, at concentrations that were several orders of magnitude higher than are observed in humans at steady-state (0.01 microM) following daily application of the Selegiline Transdermal System. Consequently. it would not be expected that thc inhibitory effects observed in vitro by selegiline and N-demethylselegiline would translate into any clinically significant drug-drug interactions.

TABLE 1

THE EFFECT OF SELEGILINE AND N-DESMETHYLSELEGILINE ON TOLBUTAMIDE METHYL-HYDROXYLATION (CYP2C9) ACTIVITY IN POOLED HUMAN LIVER MICROSOMES

Test Article Concentrations (μM)	Test Articles			
	Selegiline		N-Desmethylselegiline	
0	24.9	*(100)*	25.1	*(100)*
2.5	28.1	*(112.9)*	23.7	*(94.4)*
10	27.0	*(108.4)*	26.4	*(104.9)*
25	29.3	*(117.5)*	25.4	*(101.1)*
100	25.3	*(101.4)*	25.6	*(102.0)*
250	27.9	*(112.1)*	22.3	*(88.7)*

Tolbutamide methyl-hydroxylation activity was assessed at a final tolbutamide concentration of 50 µM.
The activity is expressed in pmol/mg protein/min.
The values in parentheses indicate the percent of tolbutamide methyl-hydroxylation activity in the presence of Selegiline or N-Desmethylselegiline.

TABLE 2

THE EFFECT OF SELEGILINE AND N-DESMETHYLSELEGILINE ON S-MEPHENYTOIN 4'-HYDROXYLATION (CYP2C19) ACTIVITY IN POOLED HUMAN LIVER MICROSOMES

Test Article Concentrations (μM)	Test Articles			
	Selegiline		N-Desmethylselegiline	
0	147.5	*(100)*	147.8	*(100)*
2.5	147.3	*(99.6)*	163.1	*(110.4)*
10	141.6	*(95.8)*	146.6	*(99.2)*
25	144.9	*(98.1)*	157.7	*(106.7)*
100	76.1	*(51.5)*	94.2	*(63.8)*
250	56.6	*(38.3)*	72.5	*(49.1)*

S-mephenytoin 4'-hydroxylation activity was assessed at a final *S*-mephenytoin concentration of 50 µM.
The activity is expressed in pmol/mg protein/min.
The values in parentheses indicate the percent of *S*-mephenytoin 4'-hydroxylation activity remaining in the presence of Selegiline or N-Desmethylselegiline.

TABLE 3

THE EFFECT OF SELEGILINE AND N-DESMETHYLSELEGILINE ON S-MEPHENYTOIN-N-DEMETHYLATION (CYP2B6) ACTIVITY IN POOLED HUMAN LIVER MICROSOMES

Test Article Concentration (μM)	Test Articles			
	Selegiline		N-Desmethylselegiline	
0	63.4	*(100)*	63.4	*(100)*
2.5	62.5	*(98.6)*	71.2	*(112.4)*
10	58.1	*(91.8)*	60.0	*(94.5)*
25	59.0	*(93.1)*	62.4	*(98.4)*
100	39.1	*(61.8)*	42.9	*(67.7)*
250	38.9	*(61.3)*	35.0	*(55.2)*

S-mephenytoin N demethylation activity was assessed at a final *S*-mephenytoin concentration of 50 µM.
The activity is expressed in pmol/mg protein/min.
The values in parentheses indicate the percent of *S*-mephenytoin N demethylation activity remaining in the presence of Selegiline or N-Desmethylselegiline.

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TABLE 4

THE EFFECT OF SELEGILINE AND N-DESMETHYLSELEGILINE ON DEXTROMETHORPHAN *O*-DEMETHYLATION (CYP2D6) ACTIVITY IN POOLED HUMAN LIVER MICROSOMES

Test Article Concentrations (μM)	Test Articles			
	Selegiline		N-Desmethylselegiline	
0	216.5	*(100)*	241.8	*(100)*
2.5	207.7	*(95.9)*	225.3	*(93.2)*
10	193.1	*(89.2)*	207.2	*(85.7)*
25	183.8	*(84.9)*	168.2	*(69.6)*
100	118.3	*(54.6)*	77.1	*(31.9)*
250	60.8	*(28.1)*	35.4	*(14.6)*

Dextromethorphan *O*-demethylation activity was assessed at a final dextromethorphan concentration of 25 μM.
The activity is expressed in pmol/mg protein/min.
The values in parentheses indicate the percent of dextromethorphan *O*-demethylation activity remaining in the presence of Selegiline or N-Desmethylselegiline.

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TABLE 5

THE EFFECT OF SELEGILINE AND N-DESMETHYLSELEGILINE ON TESTOSTERONE 6β-HYDROXYLATION (CYP3A4/5) ACTIVITY IN POOLED HUMAN LIVER MICROSOMES

Test Article Concentrations (μM)	Test Articles			
	Selegiline		N-Desmethylselegiline	
0	4484.6	*(100)*	4107.5	*(100)*
2.5	4531.7	*(101.1)*	4035.8	*(98.3)*
10	4096.9	*(91.4)*	3641.9	*(88.7)*
25	3989.7	*(89.0)*	3613.5	*(88.0)*
100	3128.5	*(69.8)*	3051.5	*(74.3)*
250	2316.0	*(51.6)*	2113.1	*(51.4)*

Testosterone 6β-hydroxylation activity was assessed at a final testosterone concentration of 50 μM.
The activity is expressed in pmol/mg protein/min.
The values in parentheses indicate the percent of Testosterone 6β-hydroxylation activity remaining in the presence of Selegiline or N-Desmethylselegiline.

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TABLE 6

THE EFFECT OF SELEGILINE AND N-DESMETHYLSELEGILINE ON COUMARIN 7-HYDROXYLATION (CYP2A6) ACTIVITY IN POOLED HUMAN LIVER MICROSOMES

Test Article Concentrations (μM)	Test Articles			
	Selegiline		N-Desmethylselegiline	
0	1439.3	*(100)*	1439.3	*(100)*
2.5	1450.2	*(100.8)*	1337.6	*(92.9)*
10	1386.9	*(96.4)*	1277.7	*(88.8)*
25	1310.2	*(91.0)*	1322.2	*(91.9)*
100	1193.4	*(82.9)*	1184.8	*(82.3)*
250	1127.8	*(78.4)*	1174.9	*(81.6)*

Coumarin 7-hydroxylation activity was assessed at a final coumarin concentration of 25 μM.
The activity is expressed in pmol/mg protein/min.
The values in parentheses indicate the percent of coumarin 7-hydroxylation activity remaining in the presence of Selegiline or N-Desmethylselegiline.

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TABLE 7

EFFECTS OF INHIBITORS ON CYP2C9, CYP2C19, CYP2B6, CYP2D6, CYP3A4/5 AND CYP2A6 ACTIVITIES IN POOLED HUMAN LIVER MICROSOMES (POSITIVE CONTROLS)

Enzyme Sample	Sulfaphenazole (20 μM)	Omeprazole (10 μM)	EFC (100 μM)	Quinidine (1 μM)	TAO (100 μM)	8-Methoxypsoralen (2.5 μM)
CYP2C9	100.0	n/t	n/t	n/t	n/t	n/t
CYP2C19	n/t	61.8	n/t	n/t	n/t	n/t
CYP2B6	n/t	n/t	38.8	n/t	n/t	n/t
CYP2D6	n/t	n/t	n/t	82.2	n/t	n/t
CYP3A4/5	n/t	n/t	n/t	n/t	69.9	n/t
CYP2A6	n/t	n/t	n/t	n/t	n/t	95.4

Values are expressed as percent inhibition.

TAO, Troleandomycin, and 8-Methoxypsoralen (non-competitive inhibitors) were pre-incubated for ~15 min at 37°C with microsomes in the presence of NADPH, *prior to incubation with the substrate.*
EFC: 7-ethoxy-4-trifluoromethyl coumarin.
n/t: Not tested.

Analytical Method

For the simultaneous quantification of selegiline, N-desmethylselegiline, amphetamine, and methamphetamine, the assay is a [redacted] extraction procedure coupled with a high performance liquid chromatographic mass spectrometric detection. The assay utilizes [redacted] as an internal standard (IS) [redacted]

. All the assays demonstrated acceptable within and between day accuracy and precision. The lower limit of quantification for selegiline, N-desmethylselegiline and amphetamine and methamphetamine was [redacted] respectively. The stability of extracted specimens for re-injection was at least 48 hours. Selegiline and its metabolites are stable for extended periods in the frozen state, irrespective of the assay employed, and stable for at least 5 freeze/thaw cycles. With respect to the [redacted] LC/MS/MS procedure, an extended stability program confirmed the freezer stability at -20 C for 830 days for selegiline, N.desmethylselegiline and amphetamine. Stability for methamphetamine could only be demonstrated for 278 days.

The following Table summarizes the linearity, recovery, inter-and intra-day accuracy and precision of selegiline and its metabolites analytical method.

Protein binding and plasma/red blood cell partitioning

Protein binding of selegiline was determined in the absence and presence of selegiline metabolites. Heparinized human plasma was fortified with selegiline or R-desmethylseligiline at 2, 10, 100 and 500 ng/mL. Human plasma was also fortified with selegiline (2 ng/mL) in the presence of desmethylselegiline (2 ng/mL), amphetamine (2 ng/mL) and methamphetamine (4 ng/mL). The concentrations of selegiline and its metabolites used in this study are the maximum concentrations observed following administration of 20 mg/cm^2 selegiline patch. The plasma samples were incubated for four hours at 37^o C prior to ultracentrifugation (centrifuged at 4300 rpm for 12 minutes). The results of the study indicated that selegiline and desmethylselegiline are 89-92% and 78-83% bound to human plasma proteins, respectively. Selegiline (90%) and desmethylselegiline (74%) were bound to plasma proteins to the same extent as that seen when evaluated separately. Amphetamine and methamphetamine were bound 79% and 28%, respectively to human plasma proteins.

Selegiline partitioned into red blood cells with a partition coefficient ranging from 0.54 to 1.59.

Dissolution

The Sponsor's proposed dissolution method for STS is as follows:

Apparatus: Apparatus 5 (paddle over disk)
Medium: 0.1 M Phosphate Buffer, pH = 5.0
Volume: 500 mL
Temprature: 32^0C
Paddle speed: 50 rpm
Specification:

1 hour: [redacted] (range: [redacted]
4 hours: [redacted] (range: [redacted]
8 hours: [redacted] (range: [redacted])
24 hours: NLT [redacted]

Sponsor's proposed dissolution method for STS is acceptable to the FDA

The multipoint drug release profile, effect of pH and paddle speed on drug release and the impact of various sizes of STS on in-vitro drug release and lot-to-lot QC comparison have been shown in the subsequent sections. The data indicate that the dissolution of STS is not affected between pH 3 to 6, and various paddle speeds.

DISSOLUTION PROFILE SUMMARY – Table I

Lot 26E007D
20 mg/20 cm² – 50 RPM

Time Point (hours)	Amount of Drug (mg)	% Drug Release	RSD	Range
1	6.05	30	2.9	
2	8.34	42	2.6	
4	11.20	56	2.2	
6	12.96	65	1.5	
8	14.18	71	1.6	
10	15.10	76	1.5	
12	15.78	79	1.1	
14	16.44	82	1.1	
16	16.88	85	1.1	
18	17.26	86	1.1	
20	17.65	88	0.9	
22	17.89	89	0.9	
24	18.23	91	0.9	

Lot 26E006L
20 mg/20 cm² – 50 RPM

Time Point (hours)	Amount of Drug (mg)	% Drug Release	RSD	Range
1	6.11	31	1.7	
2	8.39	42	1.6	
4	11.25	56	0.7	
6	12.99	65	0.0	
8	14.19	71	0.0	
10	15.07	75	0.7	
12	15.74	79	0.5	
14	16.36	82	0.5	
16	16.80	84	0.0	
18	17.15	86	0.7	
20	17.47	87	0.6	
22	17.73	89	0.6	
24	17.99	90	0.7	

LOT 28E007D

Sheet 28D007D Control PGK 1042 Dissolution.XLS
Samples 1-6

Sheet 28D007D Control PGK 1042 Dissolution#2.XLS
Samples 7-12

Amount of Drug Dissolved (mg)

Time Point (hrs)	1	2	3	4	5	6	7	8	9	10	11	12	Average	SD	%RSD
1													6.05	0.144	2.4
2													8.34	0.185	2.2
4													11.2	0.221	2.0
6													12.98	0.219	1.7
8													14.18	0.207	1.5
10													15.1	0.198	1.3
12													15.78	0.171	1.1
14													16.44	0.163	1.0
16													16.88	0.166	1.0
18													17.26	0.158	0.9
20													17.65	0.162	0.9
22													17.89	0.141	0.8
24													18.23	0.194	1.1

% Drug Release (based on 20 mg)

Time Point (hrs)	1	2	3	4	5	6	7	8	9	10	11	12	Average	RSD	Range
1													30	2.8	29 - 32
2													42	2.6	40 - 44
4													56	2.2	55 - 58
6													65	1.5	64 - 67
8													71	1.6	70 - 74
10													76	1.5	74 - 78
12													79	1.1	78 - 81
14													82	1.1	81 - 84
16													85	1.1	83 - 86
18													86	1.1	85 - 88
20													88	0.9	87 - 89
22													89	0.9	88 - 90
24													91	0.9	90 - 92

LOT 28E006L

Sheet dissolut_14pts.XLS
Samples 1-6

Sheet dissolut_14pts(2).XLS
Samples 7-12

Amount of Drug Dissolved (mg)

Time Point (hrs)	1	2	3	4	5	6	7	8	9	10	11	12	Average	SD	%RSD
1													6.11	0.096	1.6
2													8.39	0.097	1.2
4													11.25	0.067	0.6
6													12.99	0.05	0.4
8													14.19	0.052	0.4
10													15.07	0.053	0.4
12													15.74	0.079	0.5
14													16.36	0.065	0.4
16													16.8	0.063	0.4
18													17.15	0.091	0.5
20													17.47	0.082	0.5
22													17.73	0.082	0.5
24													17.99	0.099	0.6

% Drug Release (based on 20 mg.)

Time Point (hrs)	1	2	3	4	5	6	7	8	9	10	11	12	Average	RSD	Range
1													31	1.7	30 - 31
2													42	1.6	41 - 43
4													56	0.7	56 - 57
6													65	0.0	65 - 65
8													71	0.0	71 - 71
10													75	0.7	75 - 76
12													79	0.5	78 - 79
14													82	0.5	81 - 82
16													84	0.0	84 - 84
18													86	0.7	85 - 87
20													87	0.6	87 - 88
22													89	0.6	88 - 89
24													90	0.7	89 - 91

6.D.1.2 Multipoint Drug Release Data

Multipoint drug release profiles were obtained for two batches (26E007D and 26E006L) of the STS (20 mg/20 cm^2) using the proposed dissolution methodology. **Figure 3** displays the results for these two lots.

As shown, the drug release profile is well characterized, with 13 time points defining the curve. The release after 24 hours is ≥ 90%. The drug release profiles for the two lots are virtually identical with an RSD of less than 2% at each time point for both lots. The results for the two lots are virtually superimposable, confirming the drug release profile and appropriateness of the proposed test times (1, 4, 8 and 24 hours).

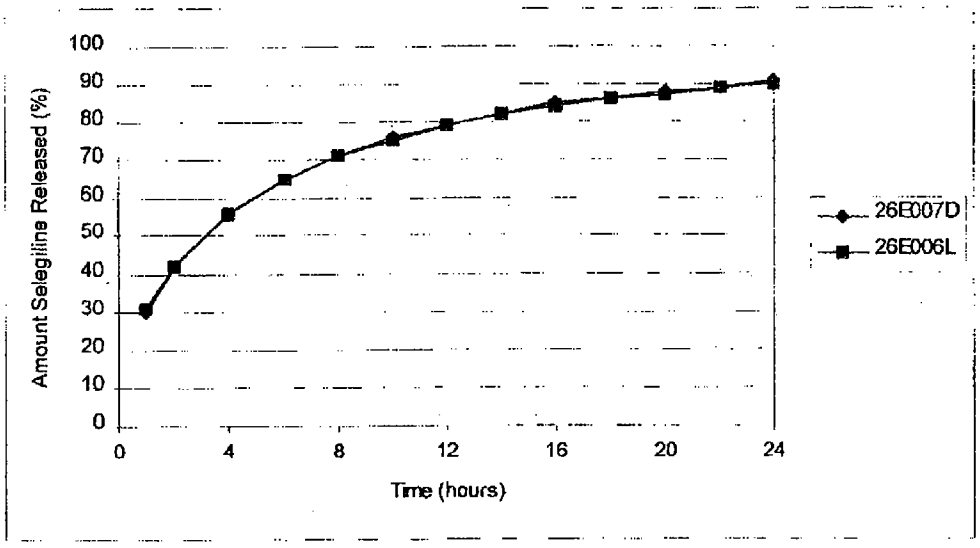

Figure 3. Multipoint Drug Release Profiles

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6.D.1.3 Effects of pH and Paddle Speed on Drug Release

The effects of pH and paddle speed on the drug release of selegiline from the STS was evaluated. The drug release profile was run over the range of pH from 3.0 to 7.0 at 50 RPM and at pH 5.0 at 100 RPM. **Figure 4** shows the results of these evaluations. These data demonstrate that the method is robust for both paddle speed and pH. The method produced identical results for 50 and 100 RPM. The results were also comparable between pH 3.0 and 6.0. The proposed method parameters of pH 5.0 and 50 RPM are well supported by these data.

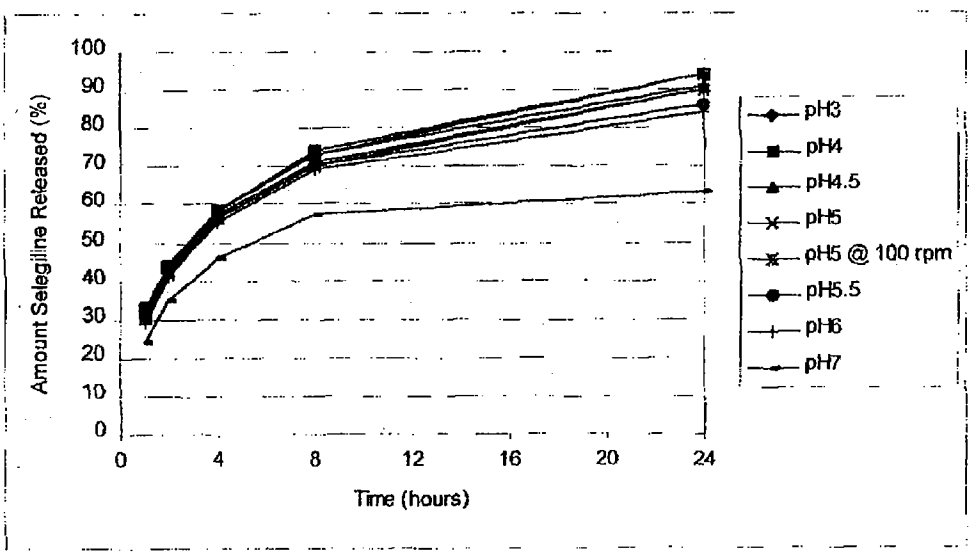

Figure 4. Effects of pH and RPM on Drug Release

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6.D.1.4 Drug Release Results for Various Sizes of STS

Figure 5 shows the drug release results for all batches of the current formulation and strength (1 mg/cm^2) and four patch sizes. As shown, the drug release results for all lots of drug product are comparable with between 91 and 96% of the drug released from all four sizes of the patch (5, 10, 15 and 20 cm^2) within 12 hours.

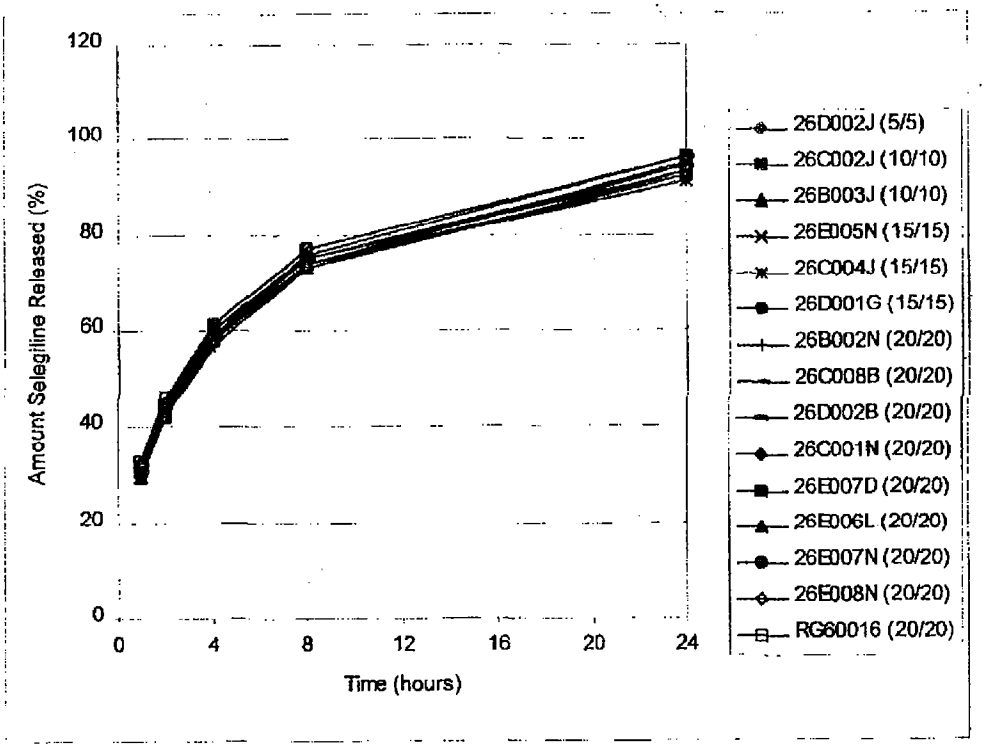

Figure 5. Summary of STS Drug Release Results For Various Sizes of the Proposed Market Formulation

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6.D.1.5 Lot-to-Lot QC Comparisons

Table 11 compares the assay and drug release results for all lots of the current STS formulation (20 mg/20 cm^2). As shown, the assay values for all batches of the proposed market formulation/size (20 mg/20 cm^2) are consistent, ranging from [redacted] mg/patch [redacted] to [redacted] mg/patch [redacted]. The drug release results at all time points show very high lot-to-lot reproducibility among all batches of the market formulation/size produced.

Table 11. Lot-to-Lot Comparison of the Assay and Drug Release Results

		Assay		Drug Released %/hr				
Lot No.	mg/cm^2	mg	%	1	2	4	8	24
26D002J	5/5	5.0						
26C002J	10/10	9.7						
26B003J	10/10	10.0						
26E005N	15/15	15.1						
26C004J	15/15	14.5						
26D001G	15/15	15.3						
26B002N	20/20	19.9						
26C008B	20/20	19.3						
26D002B	20/20	20.2						
26C001N	20/20	19.6						
26E007D	20/20	20.3						
26E006L	20/20	20.1						
26E007N	20/20	20.4						
26E008N	20/20	20.0						
RG60016	20/20	20.6						

For the proposed marketing product, the comparability of the drug release results was high across nine lots of product, as shown in **Table 12.**

Table 12. Comparison of the Drug Release Results for 9 Lots of Product

Time (hr)	Percent Released (range)
1	
2	
4	
8	
24	

6.C.4 Drug Formulation

The formulations of the pilot lots and proposed market product are shown in **Table 7.** The formulation of the pilot batches used in the bioavailability, pharmacokinetics and clinical trials supporting this NDA is the same as the proposed market formulation.

Table 7. Formulations of the Pilot Lots and Proposed Market Product

Component	Function	Quantity Per Batch		Quantity Per Finished System
		Pilot	Commercial	
Selegiline Base	Active			20 mg
Acrylic Adhesive	Adhesive			
	Release Liner			
	Backing Material			

The pilot batch size of most 20 mg/20m^2 lots used in the pharmacokinetics and clinical trials was —, which produces a maximum theoretical yield of — transdermal systems. The proposed maximum commercial batch size is —, which represents a — fold scale-up of the pilot lots.

The formulation — in order to maintain its transdermal flux for 24-hour dosing period.

Description of the Selegiline Transdermal System (STS):

The proposed STS market product consists of the Following components:

1. Backing film ([translucent]
2. Release liner (
3. Drug/Adhesive Matrix (selegiline base/acrylic adhesive
4. The STS is packaged in a paper/foil/ pouch stock.

The STS used in all clinical trials employed a pigmented backing film. Recently, non-pigmented backing material has been used resulting in a translucent patch.

Description of Patch Manufacturing:

Patch Performance

The STS monolithic technology is intended to disperse selegiline uniformly throughout the adhesive. The high drug content in the patch is required in order to maintain an adequate flux rate across the skin to achieve pharmacologically active concentrations of the drug during 24 hour dosing period. Like other transdermal products, the actual dose of selegiline administered from STS is significantly less than that actually contained in the patch. Therefore, residual selegiline concentrations in the patch have been measured to determine the actual delivered dose based on in-vivo performance. On average, the STS (20 mg/20 cm^2) delivered 5.12 mg of selegiline over the 24-hour application period.

Table 13. Amount of Selegiline Delivered (mg) from the STS (20 mg/20 cm^2) Following Dermal Application for 24 Hours

Study Number	Number of Patches	Lot Number	Mean Delivered Dose (mg)	CV (%)	Min-Max (mg)
S9303-031-95B	60	26C008B	4.35	14.8	
S9303-P9809	12	26E007D	4.78	22.0	
S9303-P9811	12	26E007D	4.01	23.1	
S9303-P9812	8	26E007D	3.96	20.0	
S9303-P9923	107	26E007N	4.64	22.3	
S9303-P9927	157	26E008N	5.75	22.3	
S9303-P9932	192	R6G0016	5.24	20.7	
S9303-P0045	131	R6G0016	4.86	38.3	
S9303-P0046	99	R6G0016	5.45	23.1	
ALL STUDIES	**778**	-	**5.12**	**26.4**	

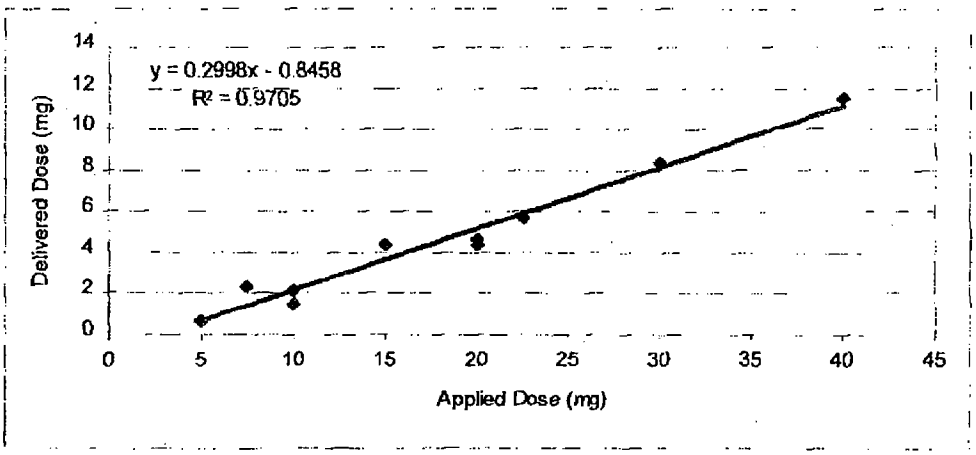

Figure 7. Relation between Applied Dose and Delivered Dose of Selegiline

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Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-336	Brand Name	Emsam
OCPB Division I	HFD-860	Generic Name	Selegiline
Medical Division	HFD-120	Drug Class	MAO inhibitor
OCPB Reviewer	Iftekhar Mahmood	Indication(s)	Depression
OCPB Team Leader	Raman Baweja	Dosage Form	Transdermal
		Dosing Regimen	20 mg/20 cm^2/day
Date of Submission	May 24, 2001	Route of Administration	Transdermal
Estimated Due Date of OCPB Review	January 2002	Sponsor	Somerset
PDUFA Due Date	March 24, 2002	Priority Classification	S
Division Due Date	January 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:	x	1	1	
Isozyme characterization:	X	2	2	
Blood/plasma ratio:	X	1	1	As one study
Plasma protein binding:	x	1	1	Part of a study
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	3	3	
multiple dose:	X	3	3	
Patients-				
single dose:				
multiple dose:		1	1	
Dose proportionality -				
fasting / non-fasting single dose:	x	1	1	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	12	12	
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	x	1	1	
geriatrics:	x	3	3	
renal impairment:	x	1	1	
hepatic impairment:	x	1	1	

PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	2	2	
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	x	1	1	
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	1	1	Part of absolute bioavailability study
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X	1	1	
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X	15		
Total Number of Studies		**34**	**34**	

Filability and QBR comments

	"X" if yes	**Comments**
Application filable ?	**X**	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 ?	**No**	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	**Iftekhar Mahmood**	
Secondary reviewer Signature and Date		

CC: NDA 21-336, HFD-850(Electronic Entry or Lee), HFD-120(Bates), HFD-860(Mahmood, Baweja, Mehta),

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Iftekhar Mahmood
2/28/02 01:04:35 PM
BIOPHARMACEUTICS

Raman Baweja
2/28/02 02:18:30 PM
BIOPHARMACEUTICS