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APPENDICES

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APPENDIX A

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APPENDIX B

INDIVIDUAL STUDY REVIEW

BIOEQUIVALENCE STUDIES

Study: Z/SEL/94/030: Open label, randomized pharmacokinetic study to establish the bioequivalence of two oral forms of selegiline hydrochloride

This study compares Zydis® selegiline to a German product at a strength higher (8 times) than proposed to-be-marketed and as such would not be a relevant comparison for a proposed US product. This study has been reviewed to assess the relative bioavailability of selegiline at equal doses with a Zydis® and conventional formulation

The study design is as follows:

Study Design	Open label, single dose, 2-way crossover
Study Population	N=24 healthy subjects Gender:16M &8F, Ages: 45-75 yrs (mean 53.1 yrs), Weight: 50-100 kg (mean 75.7 kg): males weight 69.2-100 kg, females weight 50-65.6 kg Race: NA
Treatment Group	A: Zydis® Selegiline (T) B: Morvergan® Selegiline (R) (German product)
Dosage and Administration	A: 10 mg (2 x 5 mg) single dose (T) to be placed on tongue, 150 ml water before dosing, batch 94J01SE B: 10 mg (2 x 5 mg) single dose (R) to be swallowed with 150 ml water, batch 084114 Administered after overnight fast, and 4 hours fast post dose Wash out period 2 weeks
Sampling: Blood	For selegiline (SEL), N-desmethyl-selegiline (NDMS), L-methamphetamine (L-MA) and L-amphetamine (L-AMP): At predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 48, 72 and 96 hours postdose.
Urine	none
Feces	none
Analysis	GCMS method for selegiline and N-desmethyl-selegiline GLC for methamphetamine and amphetamine Lower Limits of Quantitation Plasma Selegiline 0.01 ng/mL N-desmethyl-selegiline 0.04 ng/mL L-Amphetamine 0.1 ng/mL L-Methamphetamine 0.1ng/mL Assay validation complete and acceptable
PK Assessment	AUC0-t, AUC0-∞,Cmax, Tmax, t1/2
PD Assessment	None

Criteria for Evaluation:

Statistical Analysis:

The objective of this study was to show that the Zydis® formulation is equivalent to the Movergan formulation with respect to AUC and Cmax for the major metabolite (N-desmethyl-selegiline (NDMS), as it was expected that the plasma selegiline (SEL) levels would be low. However, if the plasma SEL levels were detectable, bioequivalence could also be based on the parent. Equivalence in terms of amphetamine (L-AMP) and methamphetamine (L-MA) was also determined.

ANOVA Tests/Acceptance Criteria

- Two one-sided tests procedure was performed for AUC and Cmax.
- 90% CI to fall between 0.80-1.25
- Effects of sequence, subject-within-sequence, period and formulation evaluated

Pharmacokinetic Results:

The mean (SD) pharmacokinetic parameters are shown in the following Table:

Treatment	Moiety	AUC0-∞ (ng.h/ml)	Cmax (ng/ml)	Tmax (h)	T1/2 (h)
Zydis (2 x 5 mg)	SEL	6.92 (5.70)	5.17 (3.04)	0.33 (0.12)	7.61 (6.43)
	NDMS	36.58 (15.01)	14.47 (4.53)	0.71 (0.16)	8.64 (3.10)
	L-AMP	104.85 (28.65)	3.01 (0.83)	5.40 (3.20)	19.40 (4.14)
	L-MA	215.43 (65.70)	8.90 (2.29)	2.40 (1.15)	16.22 (4.53)
Movergan (2 x 5 mg)	SEL	0.83 (0.75)	0.86 (0.94)	0.58 (0.12)	3.45 (3.33)
	NDMS	35.60 (14.62)	17.36 (5.87)	0.72 (0.15)	7.12 (1.39)
	L-AMP	108.01 (27.63)	3.54 (1.16)	4.16 (2.97)	17.55 (4.17)
	L-MA	23.91 (77.14)	10.59 (2.76)	2.16 (1.06)	15.37 (3.70)

The assessment of bioequivalence can be determined from the following Table:

Parameter	SEL	NDMS	L-AMP	L-MA
Ratio AUC_Z/AUC_M	**8.87**	1.03	0.97	0.93
90% CI	**[6.69-11.76]**	[0.96-1.11]	[0.89-1.05]	[0.85-1.01]
%CV	60.2	15.7	17.2	16.8
Ratio $Cmax_Z/Cmax_M$	**7.60**	0.84	0.86	0.84
90% CI	**[5.52-10.46]**	[0.78-0.91]	[0.81-0.92]	[0.79-0.89]
%CV	69.7	15.6	13.5	11.6
Median $Tmax_Z$-$Tmax_M$	-0.25	0	1.19	0.25
90% CI	[-0.25, 0.125]	[-0.125, 0.125]	[0.25-2.25]	[-0.25, 0.75]

Conclusions:

- Basing bioequivalence assessment on selegiline, the Zydis® formulation is not bioequivalent to the Movergan® formulation. Both AUC and Cmax for SEL were

significantly higher (6-8 fold) for the Zydis® formulation. These would also suggest buccal absorption and decreased conversion of selegiline to metabolites via first pass hepatic metabolism.

- Basing bioequivalence assessment on the primary metabolite NDMS, the Zydis® formulation is not bioequivalent to the Movergan® formulation. The two formulations are equivalent in terms of extent of absorption (AUC) for NDMS, but not in terms of rate of absorption (Cmax), suggesting the production of this metabolite was decreased with the Zydis® formulation.
- Between subject variability was extremely high for both treatments (% CV from 65-110%)
- The t1/2 of the metabolites were not affected by the formulation of selegiline. The plasma concentrations were close to the limit of quantitation in case of Movergan®, hence, reliable estimates of t1/2 of selegiline from this formulation cannot be made.
- Overall, it can be concluded that equal doses of selegiline in the Zydis® formulation compared to the conventional tablets produce approximately similar concentrations of the metabolites, however, selegiline concentrations are 6-8 fold higher.

Study: Z/SEL/95/023: Open label, randomized pharmacokinetic study to establish the bioequivalence of Zydis® selegiline and conventional tablet of selegiline

This study evaluates the relative bioavailability of selegiline from the Zydis® formulation at a dose 8 times lower (1.25 mg) than the conventional selegiline tablet dose of 10 mg. When comparing equidoses of the Zydis® and the conventional formulation in Study Z/SEL/94/030, the exposure from the Zydis® formulation was 6-8 fold higher than the conventional formulation.

The study design is as follows:

Study Design	Open label, single dose, 2-way crossover
Study Population	N=24 healthy subjects Gender: 13M &11F, Age: 45-70 yrs (mean 54.1 yrs), Weight: 51-100 kg (mean 73.2 kg) females weight 51-79 kg (mean 63), males weight 68-100 kg (mean 81.8 kg) Race: NA
Treatment Group	A: Zydis® Selegiline (T) B: Eldepryl® Selegiline (R) (US product)
Dosage and Administration	A: 1.25 mg single dose (T) to be placed on tongue, batch 95K03US B: 10 mg (2 x 5 mg) single dose (R) to be swallowed with 150 ml water, batch VEA07A No water allowed 30 minutes before and after dosing Administered after overnight fast, and 4 hours fast post dose Wash out period 2 weeks
Sampling: Blood	For selegiline (SEL), N-desmethyl-selegiline (NDMS), L-methamphetamine (L-MA) and L-amphetamine (L-AMP): At predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 48, 72 and 96 hours postdose.
Urine	For selegiline, N-desmethyl-selegiline, L-methamphetamine and L-amphetamine and Phenylethylamine (PEA): In 6 hourly fractions from 24 hour predose to 24 hours post dose and then up to 96 hours in 24 hour fractions.
Feces	none
Analysis	GC/MS method for selegiline and N-desmethyl-selegiline in plasma GLC method for methamphetamine and amphetamine in plasma GLC/MS method for selegiline, N-desmethyl-selegiline, methamphetamine and amphetamine and PEA in urine Lower Limits of Quantitation Selegiline: Plasma 0.01 ng/mL; Urine 1.0 ng/mL N-desmethyl-selegiline: Plasma 0.04 ng/mL; Urine 1.0 ng/mL L-Amphetamine: Plasma 0.1 ng/mL; Urine 1.0 ng/mL

	L-Methamphetamine 0.1ng/mL 1.0 ng/mL Phenylethylamine 1.38 ng/mL Assay validation complete and acceptable
PK Assessment	AUC0-t, AUC0-∞, Cmax, Tmax, t1/2
PD Assessment	• Excretion of PEA was used as a biomarker for the inhibition of MAO-B. Amount of PEA excreted in each period was determined from the measured concentration and the appropriate urine volume; cumulative 24 hour urine excretions of PEA were calculated

Criteria for Evaluation:

Statistical Analysis:

The objective of this study was to show that the Zydis® formulation was equivalent to the Eldepryl® formulation with respect to AUC and Cmax of plasma selegiline (SEL).

ANOVA Tests/Acceptance Criteria

- Two one-sided tests procedure was performed for AUC and Cmax.
- 90% CI to fall between 0.80-1.25
- Effects of sequence, subject-within-sequence, period and formulation evaluated

Pharmacokinetic Results:

The mean (SD) pharmacokinetic parameters are shown in the following Table:

Treatment	Moiety	AUC0-∞ (ng.h/ml)	Cmax (ng/ml)	Tmax (h)	T1/2 (h)
Zydis (1.25 mg)	SEL	0.525 (0.252)	1.12 (0.768)	0.236 (0.093)	0.848 (0.425)
	NDMS	1.649 (0.719)	1.19 (1.779)	0.927 (0.26)	1.613 (0.878)
	L-AMP	7.61 (2.27)	0.23 (0.10)	3.5 (2.7)	24.4 (8.9)
	L-MA	17.02 (9.26)	0.68 (0.31)	3.1 (2.4)	14.4 (3.2)
Eldepryl (2 x 5 mg)	SEL	0.37(0.28)	0.456 (0.488)	0.685 (0.284)	1.294 (0.547)
	NDMS	35.168 (11.062)	16.345 (4.11)	0.823 (0.26)	5.828 (2.014)
	L-AMP	94.33 (23.59)	3.44 (0.89)	4.10 (2.4)	16.3 (5.8)
	L-MA	226.64 (63.39)	10.49 (2.27)	2.4 (1.3)	15.5 (4.9)

- Despite the 8-fold reduction in dose with the Zydis® formulation, it was not equivalent to Eldepryl®. The exposure was 58% higher and Cmax was more than 2 fold higher with Zydis® selegiline.

The assessment of equivalence can be determined from the following Table:

Parameter	SEL	NDMS	L-AMP	L-MA
Ratio AUC_Z/AUC_{M*} 90% CI %CV	1.58 [1.07-2.31] 73.2	ND	ND	ND
Ratio $Cmax_Z/Cmax_M$ 90% CI	2.85 [2.00-4.85]	ND	ND	ND
Median $Tmax_Z$-$Tmax_M$ 90% CI	-0.42 [-0.54, -0.29]	ND	ND	ND

ND=not determined

- The half-life of NDMS seems to be shorter for the Zydis formulation. The plasma concentrations were low to be able to adequately evaluate the terminal phase.

Urinary Recovery of parent/metabolites:

The selegiline concentrations were measurable in the urine of only 6/24 subjects for Zydis® and 7/12 subjects for Eldepryl®, but NDMS urine concentrations were measured in 23/24 subjects and the other metabolites in all subjects.
The mean recoveries expressed as percentage of the dose calculated for selegiline and the three metabolites are given in the following Table. In order to assess the percentage of the dose recovered in the urine, the amount of the three metabolites were corrected into "selegiline equivalents": this correction was carried out by multiplying the amounts excreted with a factor (Mol. Wt. Selegiline/Mol. Wt. Metabolite). The molecular weights used were:

187.3 for selegiline
173.3 for NDMS, giving a correction factor of 1.08
135.2 for L-AMT, giving a correction factor of 1.39
149.2 for L-MA, giving a correction factor of 1.26

Compound	With Zydis Administration	With Eldepryl Administration
SEL	0.05%	0.01%
NDMS	0.37%	0.9%
L-AMP	9.8%	13.4%
L-MA	22.4%	29.9%

From this data it is again demonstrated that higher percentage (5-fold) of the selegiline dose reaches systemic circulation and lower percentage of the metabolites are excreted with the Zydis® formulation, which is consistent with the plasma concentrations of these moieties.

Pharmacodynamic Assessments:

The excretion of PEA was measured in urine as a biomarker for the inhibition of

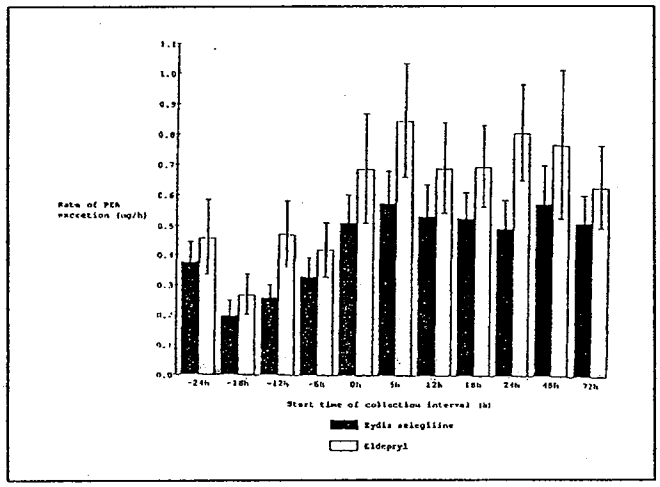
MAO-B. PEA is a specific endogenous substrate of MAO-B and is found in trace amounts in the brain. The hypothesis regarding PEA as a marker for evaluating MAO-B inhibition is that when MAO-B is inhibited, concentration of PEA in the brain rises rapidly. When metabolism of PEA in the brain is inhibited, a greater amount of PEA enters the systemic circulation, where it is excreted unchanged in the urine. Therefore if SEL inhibits brain MAO-B, the urinary excretion of PEA increases. This excretion of PEA in the urine is used as a biomarker for assessing MAO-B inhibition. Although PEA is used as a marker for MAO-B inhibition, it is not a sensitive marker.

The mean amounts of PEA excreted at each interval for the Zydis® and Eldepryl® formulations are shown in the following Table:

Collection Interval	Mean (SD) PEA in µg for Zydis®	Mean (SD) PEA in µg for Eldepryl®
-24-0h	7.04 (5.59)	9.72 (9.02)
0-24h	12.6 (8.87)	17.6 (17.32)
24-48h	11.93 (10.76)	19.47 (18.54)
48-72h	13.94 (14.41)	18.58 (28.88)
72-96h	12.4 (10.61)	15.27 (15.97)

- The post-dose mean amounts of PEA are higher than the pre-dose PEA amounts in both formulations
- The increase in PEA is maintained at 72-96 hours post dose in both formulations
- Eldepryl® has higher concentrations of PEA excreted in the urine as compared to Zydis®.
- The percent increase in PEA at 72 hours post dose as compared to pre-dose was similar for both formulations.

The PEA excretion rates at the various time intervals are shown in the following Figure:



Conclusions:

- Although this study cannot be truly called a bioequivalence study as the sponsor describes it, the bioavailability of 1.25 mg selegiline from the Zydis® formulation is not comparable to the 10 mg selegiline from the Eldepryl®, although the previous study showed that at equal doses the bioavailability from the Zydis® formulation was 8-fold higher than the conventional formulation.
- Inspite of the 8-fold reduction in dose with the Zydis formulation, the AUC (58% ↑) and Cmax (> 2-fold ↑) were higher with the Zydis formulation and the Tmax was shorter. This may be attributed to substantial pre-gastric absorption with the Zydis® formulation.
- In contrast to Eldepryl®, the plasma concentrations of the three metabolites were lower after the administration of the Zydis® formulation, which may be probably due to decreased conversion of selegiline to metabolites via first-pass hepatic metabolism because there is pre-gastric absorption as well.
- The inter-subject variability was lower with the Zydis formulation (%CV: 48-75% for selegiline), as compared to Eldepryl® (% CV: 75-106%), probably because the fast dissolving tablet escapes the first-pass metabolism.

SINGLE DOSE PHARMACOKINETICS IN HEALTHY SUBJECTS

Study: Z/SEL/95/003: Open randomized study to assess the pharmacokinetics of three doses of selegiline administered in Zydis® dosage form compared with a standard tablet.

The study design is as follows:

Study Design	Open label, randomized, single dose, 4-treatment, balanced incomplete block, each subject receiving two of the 4 possible treatments
Study Population	N=23 healthy subjects Gender: 9M & 14F, Ages: 40-67 yrs (mean 50.9 yrs), Mean age of females 53.5, Mean age of males 46.7, Weight: 40-95 kg(mean 67.8 kg), Race: All White
Treatment Group	A: Zydis® 1.25 mg B: Zydis® 2.5 mg C: Zydis® 5 mg D: Eldepryl ® Selegiline 10 mg
Dosage and Administration	A: Zydis® 1.25 mg, one quarter x 5 mg tablet and three quarter placebo B: Zydis® 2.5 mg, one half x 5 mg tablet and one half placebo, placebo batch 12425B029 C: Zydis® 5 mg, one tablet, batch 94J01SE These treatments to be placed on tongue and allowed to dissolve without water, no water allowed 30 minutes before and after dosing D: Eldepryl ® (UK) 10 mg (2 x 5 mg) swallowed with 150 ml water, batch UHB50A All treatments administered after overnight fast, and 4 hours fast post dose Wash out period 2 weeks
Sampling: Blood	For selegiline, N-desmethyl-selegiline, L-methamphetamine and L-amphetamine: At predose and 0.08, 0.17, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 12 24, 48, 72 and 96 hours post-dose.
Urine	For Phenylethylamine (PEA) and 5-hydroxyindole acetic acid (5-HIAA): At pre-dose and post-dose from 0-12 and 12-24 hours
Feces	none
Analysis	GC/MS method for selegiline and N-desmethyl-selegiline in plasma GLC method for methamphetamine and amphetamine in plasma GLC/MS method for selegiline, N-desmethyl-selegiline, methamphetamine and amphetamine and PEA in urine HPLC with electrochemical detection for 5-HIAA GC with electrochemical detection for selegiline in saliva and mouth rinsings

	Lower Limits of Quantitation Plasma / Urine Selegiline 0.01 ng/mL N-desmethyl-selegiline 0.04 ng/mL L-Amphetamine 0.1 ng/mL L-Methamphetamine 0.1ng/mL Phenylethylamine 1.38 ng/mL 5-HIAA 1 ng/mL Assay validation complete and acceptable
PK Assessment	AUC0-t, AUC0-∞, Cmax, Tmax, t1/2 of selegiline and three metabolites, and total urinary excretion of PEA and 5-HIAA
PD Assessment	• Excretion of PEA was used as a biomarker for the inhibition of MAO-B. Amount of PEA excreted in each period was determined from the measured concentration and the appropriate urine volume; 24 hour urine excretions of PEA were calculated • Excretion of 5-HIAA was used as a biomarker for inhibition of MAO-A

Pharmacokinetic Results:

Mean (SD) pharmacokinetic parameters for the selegiline and its metabolite are as follows:

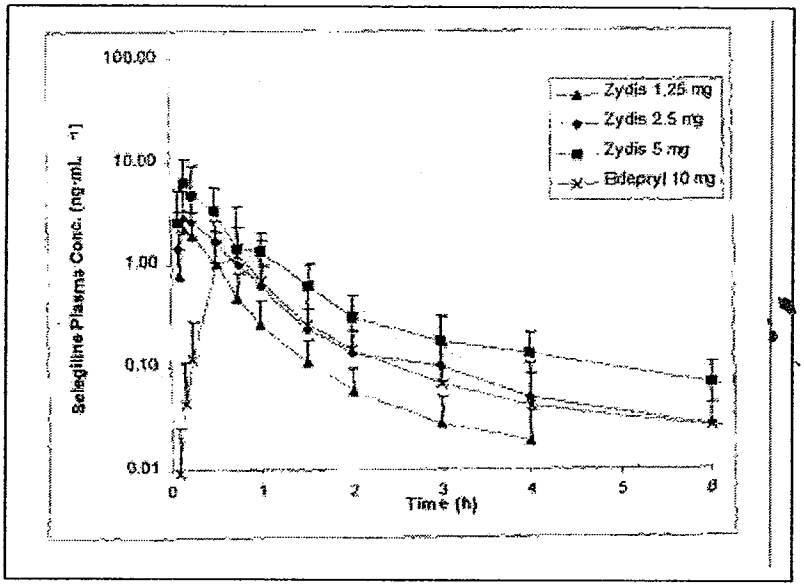
Selegiline (SEL)

Parameter	Treatment			
	Zydis 1.25 mg	Zydis 2.5 mg	Zydis 5 mg	Eldepryl 10 mg
AUC0-∞ (ng.h/ml)	1.31 (0.66)	2.29 (1.16)	4.88 (2.68)	1.42 (1.99)
Dose normalized AUC0-∞ (ng.h/ml)	5.2	4.6	4.88	
Cmax (ng/ml)	2.36 (1.14)	3.38 (2.44)	6.43 (4.42)	1.50 (2.38)
Tmax (h)*	0.17 (0.17-0.25)	0.17 (0.08-0.75)	0.21 (0.17-0.50)	0.63 (0.25-1.0)
T1/2 (h)	1.5 (0.7)	4.0 (4.4)	3.7 (1.7)	1.9 (1.7)

*median (range)

- There was no statistical difference between the Zydis® 1.25 mg and Eldepryl® 10 mg mean AUC, although Cmax was higher with the Zydis® formulation.
- Cmax and AUC0-∞ appeared to be linear with dose for the Zydis® formulation, although no statistical tests were done (see dose normalized mean AUC0-∞ in the Table), as there is another study evaluating dose proportionality.
- T1/2 calculations may not be very accurate since in some cases fewer time points were used in the calculation.

The mean (SD) plasma concentration profiles for the 4 treatments are shown in the following Figure:



Metabolites:

NDMS

Parameter	Treatment			
	Zydis 1.25 mg	Zydis 2.5 mg	Zydis 5 mg	Eldepryl 10 mg
AUC0-∞ (ng.h/ml)	2.4 (0.8)	7.6 (3.0)	14.5 (6.8)	47.8 (23.8)
Cmax (ng/ml)	1.19 (0.49)	2.94 (1.09)	5.58 (2.73)	18.37 (9.13)
Tmax (h)	0.88 (0.5-2)	1 (0.5-2)	1 (0.5-2)	0.75 (0.5-1.5)
T1/2 (h)	2.8 (1.4)	5.2 (2.3)	5.6 (2.9)	7.1 (3.0)

L-AMP

Parameter	Treatment			
	Zydis 1.25 mg	Zydis 2.5 mg	Zydis 5 mg	Eldepryl 10 mg
AUC0-∞ (ng.h/ml)	8.9 (6.6)	22.4 (11.5)	43.1 (20.4)	113.6 (27.8)
Cmax (ng/ml)	0.34 (0.21)	0.78 (0.51)	1.26 (0.53)	3.6 (0.92)
Tmax (h)	3.5 (1-12)	5 (0.5-12)	3.0 (1.5-6)	4 (1.5-6)
T1/2 (h)	21.8 (14.3)	20.9 (5.6)	23.0 (7.3)	17.8 (2.0)

L-MA

Parameter	Treatment			
	Zydis 1.25 mg	Zydis 2.5 mg	Zydis 5 mg	Eldepryl 10 mg
AUC0-∞ (ng.h/ml)	20.0 (6.8)	51.7 (14.3)	103.2 (47.2)	288.4 (67.3)
Cmax (ng/ml)	0.93 (0.39)	2.03 (0.68)	4.69 (1.89)	12.92 (3.95)
Tmax (h)	2 (0.5-3)	3 (0.5-6)	1.5 (1-6)	2 (0.8-6)
T1/2 (h)	17.4 (5.3)	17.4 (4.5)	15.8 (3.3)	14.9 (1.8)

- Following Eldepryl® 10 mg, the plasma concentrations of all the three metabolites were about 3-fold higher as compared to the Zydis® 5 mg formulation.

Pharmacodynamic Assessment:

Urinary Excretion of PEA:

This excretion of PEA in the urine is used as a marker for assessing MAO-B inhibition. Although PEA is used as a marker for MAO-B inhibition, it is not a sensitive marker as it is known that MAO-B activity is 95-100% inhibited within 4-8 hours after oral administration of SEL. It is also known that as the dose of SEL is increased, the amount of PEA excreted is also increased. Therefore, there is some degree of uncertainty regarding the degree of MAO-B inhibition in the brain using PEA as a marker.

	Treatment			
	Zydis 1.25 mg	Zydis 2.5 mg	Zydis 5 mg	Eldepryl 10 mg
-12-0 h (µg)	4.0 (3.9)	2.2 (2.6)	4.1 (3.4)	2.5 (1.8)
0-12 h (µg)	9.0 (11.0)	13.3 (10.2)	34.7 (20.5)	9.1 (14.7)
12-24 h (µg)	7.8 (5.8)	12.7 (8.9)	31.0 (23.9)	11.1 (18.1)

- The excretion of PEA increased as the dose of Zydis® selegiline increased.
- The between subject variability in PEA excretion was extremely high.
- PEA excretion increases in the 12 hour collection in all treatments as compared to the pre-dose PEA levels in the urine.
- The amount of PEA excreted at post dosing was similar with Zydis® 1.25 mg (16.8 µg) and Eldepryl® 10 mg (20.2 µg)
- Pearson correlation showed that there was a significant (r=0.0001) correlation between urinary excretion of PEA and log-transformed AUC of selegiline but not of NDMS.

Urinary Excretion of 5-HIAA:

5-hydroxy indole acetic acid (5-HIAA) is used as a marker for assessing MAO-A inhibition. 5-hydroxytryptamine is metabolized to 5-HIAA by MAO-A. Therefore, inhibition of MAO-A leads to decrease in urinary concentrations of 5-HIAA.

	Treatment			
	Zydis 1.25 mg	Zydis 2.5 mg	Zydis 5 mg	Eldepryl 10 mg
-12-0 h (mg)	1.7 (0.7)	1.7 (0.9)	1.7 (0.5)	1.7 (0.7)
0-12 h (mg)	2.0 (0.7)	1.5 (0.6)	2.0 (0.8)	2.0 (0.9)
12-24 h (mg)	2.0 (0.7)	1.6 (0.5)	1.8 (0.9)	2.0 (0.8)

- The urinary excretion of 5-HIAA was not affected by the dose of selegiline.
- The urinary excretion of 5-HIAA was not affected by treatment with either Zydis® selegiline or Eldepryl®.

Conclusions:

- The Zydis® 1.25 mg formulation yields similar exposure to Eldepryl 10 mg, although Cmax is higher with the Zydis formulation.
- The Zydis® 5 mg formulation yields 3-fold higher concentrations of selegiline, and 2.4-3.2 fold lower concentrations of the metabolites as compared to a 10 mg Eldepryl®. This is most likely due to selegiline being absorbed pre-gastrically from the Zydis formulation, avoiding first pass metabolism. The relative bioavailability of selegiline from Zydis® formulation administered on the tongue without water is about 700% when compared to Eldepryl® formulation swallowed normally.
- The pharmacokinetics of selegiline and its metabolites appeared to be linear with the dose in the range 1.25-5 mg, although no statistical tests were done and the inter-subject variability was very high.
- The amount of PEA excreted after Zydis® 1.25 mg administration was similar to that excreted after Eldepryl® 10 mg administration.
- The amount of 5-HIAA excreted was unchanged with the change in formulation or increase in selegiline dose.

Study: Z/SEL/96/008: Open randomized comparative pharmacokinetic study of Zydis® selegiline (5 mg) and Eldepryl® Syrup (10 mg).

This study has not been reviewed as Eldepryl® Syrup is not marketed in the US, hence, the comparison between Zydis® selegiline and the syrup formulation is irrelevant for this application. The 5 mg Zydis® selegiline will not be the marketed strength in US.

Study: Z/SEL/95/001: Open randomized study to assess buccal absorption of Selegiline in Zydis® dosage form.

The study design is as follows:

Study Design	Open label, randomized, single dose, 3-way crossover
Study Population	N=12 healthy male and female subjects Gender: 6M & 6F, Ages: 45-70 yrs (mean 52.8 yrs) Mean age of females 50.3 Mean age of males 55.3 Weight: 58-92 kg (mean 75.9 kg), Race: 11 White and 1 Black
Treatment Group	A: Zydis® selegiline swallowed (SW) B: Zydis® selegiline not swallowed (NS) C: Eldepryl ® (US product)
Dosage and Administration	A: 10 mg (2 x 5 mg) single dose to be placed on tongue to allow to be dissolved in the saliva, resulting solution brought to the front of the mouth and swirled in the mouth every 2 seconds for a minute and then swallowed, batch 94J01SE B: 10 mg (2 x 5 mg) single dose to be placed on tongue to allow to be dissolved in the saliva, resulting solution swirled in the mouth every 2 seconds for a minute, without swallowing. The solution spat out into a collection container. The mouth then rinsed three times with 25 ml water and spat out into the collection container. batch 94J01SE C: 10 mg (2 x 5 mg) swallowed with 150 ml water, batch 38009A Administered after overnight fast, and 4 hours fast post dose Wash out period 2 weeks
Sampling: Blood	For selegiline (SEL), N-desmethyl-selegiline (NDMS), L-methamphetamine (L-MA) and L-amphetamine (L-AMP): At predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 12 and 24 hours post-dose. For Zydis® NS treatment, concentration of selegiline determined in two 15 ml aliquots of the collection container as well
Urine	For selegiline, N-desmethyl-selegiline, L-methamphetamine and L-amphetamine, PEA and 5-hydroxyindoleacetic acid (5-HIAA): At pre-dose and post-dose from 0-2, 2-4, 4-6, 6-12 and 12-24 hours
Feces	none
Analysis	GC/MS method for selegiline and N-desmethyl-selegiline in plasma GLC method for methamphetamine and amphetamine in plasma GLC/MS method for selegiline, N-desmethyl-selegiline, methamphetamine and amphetamine and PEA in urine HPLC with electrochemical detection for 5-HIAA GC with electrochemical detection for selegiline in saliva and mouth rinsings

	Lower Limits of Quantitation Plasma / Urine / Saliva Selegiline 0.01 ng/mL / 1.0 ng/mL / 10µg/mL N-desmethyl-selegiline 0.04 ng/mL / 1.0 ng/mL L-Amphetamine 0.1 ng/mL / 1.0 ng/mL L-Methamphetamine 0.1ng/mL / 1.0 ng/mL Phenylethylamine / 1.38 ng/mL 5-HIAA / 1 ng/mL Assay validation complete and acceptable
PK Assessment	AUC0-t, AUC0-∞, Cmax, Tmax, t1/2, cumulative and total urinary excretion of selegiline and three metabolites
PD Assessment	• Excretion of PEA was used as a marker for the inhibition of MAO-B. Amount of PEA excreted in each period was determined from the measured concentration and the appropriate urine volume; cumulative 24 hour urine excretions of PEA were calculated • Excretion of 5-HIAA was used as a marker for inhibition of MAO-A

Pharmacokinetic Results:

Mean (SD) pharmacokinetic parameters are as follows:

Compound	Zydis SW				Zydis NS				Eldepryl			
	AUC0-t ng.h/ml	Cmax ng/ml	Tmax h	t1/2 h	AUC0-t ng.h/ml	Cmax ng/ml	Tmax h	t1/2 h	AUC0-t ng.h/ml	Cmax ng/ml	Tmax h	t1/2 h
SEL	17.63 (12.40)	12.79 (8.82)	0.32 (0.18)	5.39 (1.08)	5.71 (7.12)	4.25 (3.53)	0.23 (0.11)	5.14 (1.14)	1.11 (1.01)	0.97 (0.85)	0.73 (0.33)	5.34 (2.14)
NDMS	42.48 (17.97)	15.14 (6.53)	0.95 (0.33)	6.36 (2.08)	2.59 (3.02)	0.79 (0.67)	1.18 (0.25)	5.80 (2.67)	45.83 (20.56)	19.05 (6.73)	0.91 (0.32)	5.35 (1.83)
L-AMP	48.42 (15.99)	2.60 (0.70)	5.83 (3.21)	40.47 (17.6)	6.38 (3.54)	0.34 (0.17)	11.36 (6.92)	93.24 (54.75)	58.11 (16.60)	3.11 (0.79)	4.58 (3.79)	31.63 (14.13)
L-MA	136.31 (38.12)	8.64 (2.03)	3.08 (1.16)	18.34 (5.36)	12.09 (8.77)	0.69 (0.47)	4.36 (1.63)	25.38 (7.67)	172.40 (43.16)	11.48 (2.37)	2.63 (1.38)	16.30 (4.95)

SEL:

- Highest AUC and Cmax of SEL were seen with Zydis® SW and lowest with Zydis® NS.
- Exposure from Zydis® SW was 16-fold higher than after Eldepryl®.
- Highest Tmax was observed with Eldepryl®
- t1/2 were comparable between treatments.

Metabolites:

- Highest AUC and Cmax of NDMS, L-AMP and L-MA were seen with Eldepryl® and lowest with Zydis® NS.
- Tmax and t1/2 were comparable, however, plasma levels of L-AMP were very low after the Zydis® NS treatment.

Urinary Excretion:

The mean amounts (% or mg) recovered in the urine are as follows:

Compound	With Zydis SW Administration	With Zydis NS Administration	With Eldepryl Administration
SEL	0.08%	0.04%	0.00%
NDMS	0.45%	0.00%	0.60%
L-AMP	5.18%	2.42%	6.55%
L-MA	13.76%	5.96%	17.71%
PEA	0.1394 mg	0.0848 mg	0.0430 mg
5-HIAA	0.0047 g	0.0045 g	0.0047 g

- The concentrations of the parent drug as well as the metabolites in the urine were commensurate with the plasma concentrations observed in each treatment. Based on the urinary recovery of SEL and the metabolites, the total dose absorbed was 19.47% from Zydis® SW, 8.42% from Zydis® NS and 24.86% from Eldepryl®.
- The percent of SEL recovered in the urine was highest with the Zydis® SW treatment.
- The PEA concentrations with Zydis® SW were 3-fold higher than after Eldepryl® administration. This rank order in PEA concentrations also correlates to the plasma concentrations of SEL, which was highest in the Zydis® SW treatment group, although the exposure from Zydis® SW was 16-fold higher than that after Eldepryl®. The plasma metabolite concentrations had a different rank order as compared to the urinary excretion of PEA, suggesting SEL is the molecule more likely responsible to MAO-B inhibition in the brain.
- There was no difference in 5-HIAA excretion among treatment groups. 5-hydroxytryptamine is metabolized to 5-HIAA by MAO-A. Therefore, inhibition of MAO-A leads to decrease in urinary concentrations of 5-HIAA. From this study no conclusions can be drawn regarding MAO-A inhibition by the treatment group, as urinary excretion of MAO-A in the absence of treatment is unknown.

Selegiline in Saliva:

The mean concentrations of selegiline in saliva ranged from 65.00-86.70 µg/ml
The total amount of selegiline recovered from saliva\mouth rinsing was 3.916-6.936 mg. Therefore with a 10 mg initial dose, the mean amount of SEL absorbed or remaining to be absorbed in the mouth would range from 3.064-6.084 mg given a 10 mg initial dose.

The plasma concentrations from Zydis® NS formulation indicate that SEL can be absorbed without the need for swallowing it. Absorption of SEL can occur in the buccal cavity, pharynx and/or within the esophagus (pre-gastric)

Conclusions:

- Oral selegiline compared to Zydis® selegiline (both SW and NS) resulted in significantly lower mean AUC and Cmax values in plasma. The exposure from Zydis® was 16-fold higher than Eldepryl®.
- Compared to oral selegiline, Zydis® selegiline NS resulted in significantly lower metabolite concentrations, which is most likely due to differences in first-pass metabolism. Zydis® formulation undergoes buccal absorption, reducing the amount that would be subject to first-pass metabolism.
- Metabolite concentrations from Zydis® SW were lower than that from oral selegiline, but not drastically different as Zydis® SW would undergo both pre and post-gastric absorption, hence would be available for first pass metabolism as well.
- With Zydis® NS, that was not swallowed, about 60% of the dose was recovered in the saliva/mouth rinsings. Approximately, 40% of the starting dose was either absorbed from the oral mucosa or remained to be absorbed from the pre-gastric areas.
- The concentrations of the parent drug as well as the metabolites in the urine were commensurate with the plasma concentrations observed in each treatment.
- Although similar rank order was observed between the plasma SEL concentrations and that of PEA in the urine, no definite conclusions should be derived for the mechanism of inhibition. The degree of uncertainty regarding PEA data has been explained in the previous section.
- There was no difference in 5-HIAA excretion among treatment groups.

Study: Z/SEL/96/008: ***Open randomized study to compare the effect of food on the Pharmacokinetics of Zydis®selegiline (5 mg) and Eldepryl® (10 mg).***

The study design is as follows:

Study Design	Open label, randomized, single dose, 4-way crossover
Study Population	N=12 healthy male and female subjects Gender: 6M & 6F, Ages: 40-67 yrs (mean 50.9 yrs), Mean age of females 53.5, Mean age of males 46.7, Weight: 40-95 kg (mean 67.8 kg), Race: All White
Treatment Group	A: Zydis® Selegiline 5 mg fasted B: Zydis® Selegiline 5 mg fed C: Eldepryl ® 10 mg fasted D: Eldepryl ®10 mg fed
Dosage and Administration	A: Zydis® 5 mg, one tablet after an overnight fast, batch 95K02UV B Zydis® 5 mg, one tablet within 5 minutes of completing a FDA standard breakfast These treatments to be placed on tongue and allowed to dissolve without water, no water allowed 30 minutes before and after dosing C: Eldepryl ® (UK) 10 mg (2 x 5 mg) after an overnight fast D: Eldepryl ® (UK) 10 mg (2 x 5 mg) within 5 minutes of completion of breakfast These treatments swallowed with 150 ml water, batch VLA04A Treatment A &C administered after overnight fast, and 4 hours fast post- dose Wash out period 3 weeks FDA Diet: 2 eggs, 2 strips of bacon, 1 toast with butter, 2-4 oz hash brown, 1 glass of whole milk
Sampling: Blood	For selegiline, N-desmethyl-selegiline, L-methamphetamine and L-amphetamine: At predose and 0.08, 0.17, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 12, 24 hours post-dose.
Urine	For selegiline, N-desmethyl-selegiline, L-methamphetamine and L-amphetamine, Phenylethylamine (PEA) : At pre-dose and post-dose from 0-6, 6-12 and 12-18 and 18-24 hours
Feces	none
Analysis	GC/MS method for selegiline and N-desmethyl-selegiline in plasma GLC method for methamphetamine and amphetamine in plasma GLC/MS method for selegiline, N-desmethyl-selegiline, methamphetamine and amphetamine and PEA in urine

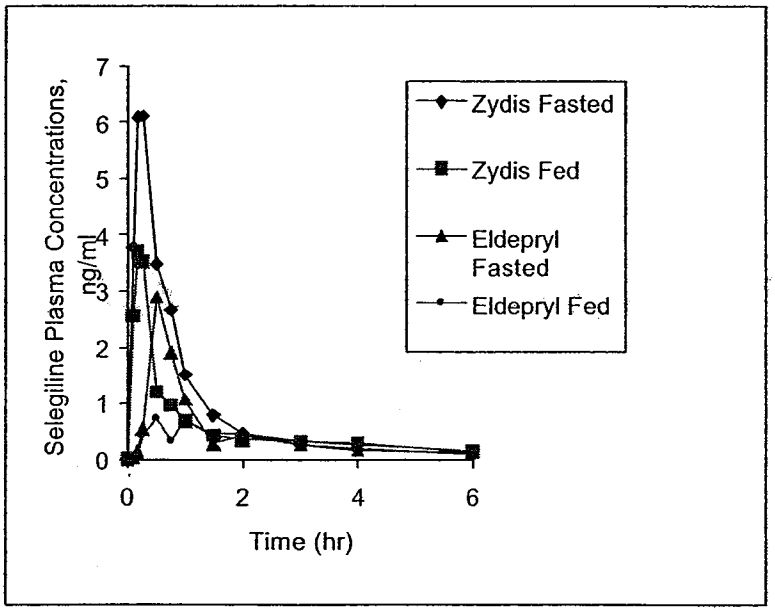
	Lower Limits of Quantitation Plasma / Urine Selegiline 0.01 ng/mL / 1.0 ng/mL N-desmethyl-selegiline 0.04 ng/mL / 1.0 ng/mL L-Amphetamine 0.1 ng/mL / 1.0 ng/mL L-Methamphetamine 0.1ng/mL / 1.0 ng/mL Phenylethylamine / 1.4 ng/mL 5-HIAA / 1 ng/mL Assay validation complete and acceptable
PK Assessment	AUC0-t, AUC0-∞, Cmax, Tmax, t1/2 of selegiline and three metabolites, and total urinary excretion of PEA
PD Assessment	Excretion of PEA was used as a marker for the inhibition of MAO-B. Amount of PEA excreted in each period was determined from the measured concentration and the appropriate urine volume; 24 hour urine excretions of PEA were calculated

Pharmacokinetic Results:

SELEGILINE (SEL):

The mean (%CV) parameters are shown in the following Table:

	Treatment Mean (% CV)				90% CI on Dose Normalized parameters	
Single Dose Plasma PK Parameter	Zydis 5 mg Fasted **A**	Zydis 5 mg Fed **B**	Eldepryl 10 mg Fasted **C**	Eldepryl 10 mg Fed **D**	90% Confidence Interval (%) for **A/B Ratio**	90% Confidence Interval (%) for **C/D Ratio**
AUC_{0-t} (hr*ng/mL)	5.612 (41)	3.533 (91)	3.375 (188)	2.223 (156)	144-399	44-122
AUC_{0-inf} (hr*ng/mL)	5.829 (43)	3.710 (87)	3.584 (189)	2.382 (152)	136-377	43-119
C_{max} (ng/mL)	7.804 (54)	4.490 (62)	3.093 (160)	1.416 (95)	132-446	77-259
T_{max} (hr)	0.208 (27)	0.202 (28)	0.688 (27)	1.604 (82)	-	
$T_{1/2}$ (hr)	3.779 (47)	2.727 (36)	2.814 (79)	2.080 (75)	-	

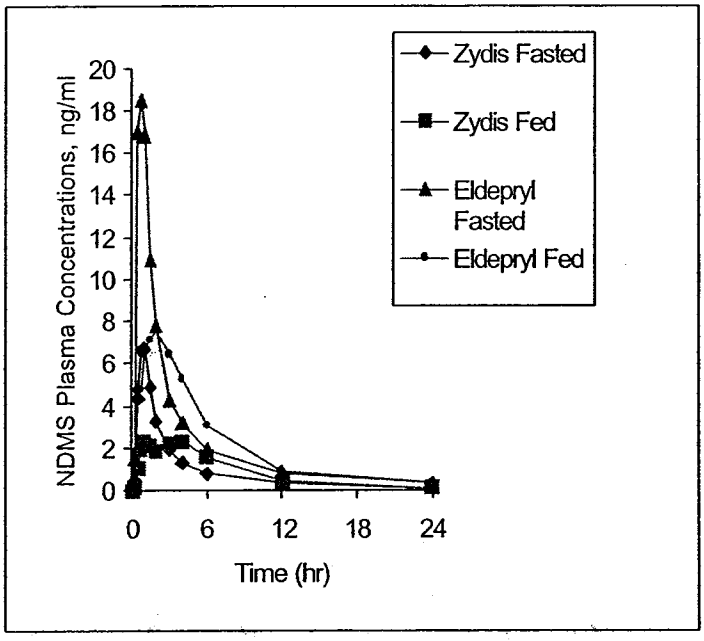


- Food decreased the plasma concentrations of selegiline both with Zydis® and Eldepryl® formulations. Peak exposure of selegiline is greater if Zydis® formulation was administered under fasting conditions by about 1.4-3.8 times. The 90% CI of Eldepryl® fell at either side of unity (0.4-1.2), this is contrary to that reported in the Eldepryl® label, where food increased absorption of selegiline.
- In accordance to the plasma data, the urinary recovery of selegiline is also higher under fasted conditions.

Metabolites:

NDMS

	Treatment Mean (% CV)				90% CI on dose normalized parameters	
Single Dose Plasma PK Parameter	Zydis 5 mg Fasted **A**	Zydis 5 mg Fed **B**	Eldepryl 10 mg Fasted **C**	Eldepryl 10 mg Fed **D**	90% Confidence Interval (%) for **A/B Ratio**	90% Confidence Interval (%) for **C/D Ratio**
AUC_{0-t} (hr*ng/mL)	19.589 (42)	19.2 (35)	51.135 (42)	49.422 (40)	92-111	90-109
AUC_{0-inf} (hr*ng/mL)	20.768 (42)	20.24 (35)	54.27 (43)	52.07 (42)	94-111	92-109
C_{max} (ng/mL)	7.889 (50)	3.451 (32)	22.158 (54)	10.99 (41)	180-279	154-240
T_{max} (hr)	1.063 (38)	2.646 (58)	0.792 (35)	2.042 (61)	-	-
$T_{1/2}$ (hr)	6.007 (31)	5.221 (24)	6.513 (24)	5.520 (33)	-	-



- The NDMS AUC of both Zydis® and Eldepryl® formulations did not change with food, however, Cmax for both formulations was decreased by 2-fold in the presence of food.

L-MA

	Treatment Mean (% CV)				90% CI on dose normalized parameters	
Single Dose Plasma PK Parameter	Zydis 5 mg Fasted **A**	Zydis 5 mg Fed **B**	Eldepryl 10 mg Fasted **C**	Eldepryl 10 mg Fed **D**	90% Confidence Interval (%) for **A/B Ratio**	90% Confidence Interval (%) for **C/D Ratio**
AUC_{0-t} (hr*ng/mL)	77.139 (23)	73.25 (18)	196.17 (16)	188.62 (16)	100-115	96-110
C_{max} (ng/mL)	5.134 (27)	4.810 (18)	12.7 (19)	11.93 (16)	100-116	97-113
T_{max} (hr)	2.771 (55)	5.792 (42)	2.458 (62)	5.583 (18)	-	-
$T_{1/2}$ (hr)	16.922 (31)	17.29 (53)	17.025 (27)	14.82 (26)	-	-

L-AMP

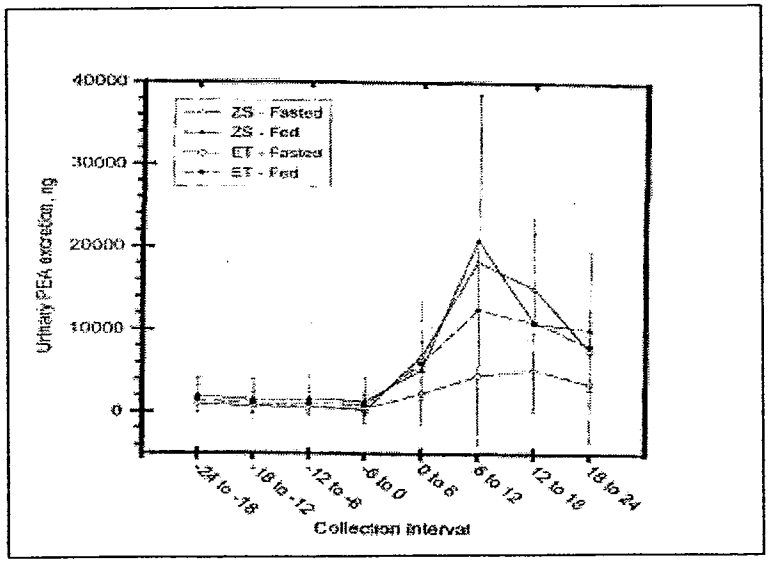
	Treatment Mean (% CV)				90% CI on dose normalized parameters	
Single Dose Plasma PK Parameter	Zydis 5 mg Fasted **A**	Zydis 5 mg Fed **B**	Eldepryl 10 mg Fasted **C**	Eldepryl 10 mg Fed **D**	90% Confidence Interval (%) for **A/B Ratio**	90% Confidence Interval (%) for **C/D Ratio**
AUC_{0-t} (hr*ng/mL)	28.354 (28)	27.296 (25)	69.06 (23)	67.11 (27)	97-115	95-113
C_{max} (ng/mL)	1.577 (28)	1.563 (24)	3.733 (23)	3.748 (27)	92-110	91-109
T_{max} (hr)	4.083 (76)	6.833 (36)	5.542 (64)	6.833 (36)		
$T_{1/2}$ (hr)	29.02 (31)	27.25 (64)	41.21 (123)	24.28 (37)		

- Food did not change either Cmax or AUC of L-MA and L-AMP for both formulations.

Cumulative Urinary Excretion in µg (0-24 hours):

	Treatment Mean (SD)			
	Zydis 5 mg Fasted **A**	Zydis 5 mg Fed **B**	Eldepryl 10 mg Fasted **C**	Eldepryl 10 mg Fed **D**
SEL	0.873 (0.660)	0.508 (0.409)	0.287 (635)	0.671 (1.05)
NDMS	20.084 (7.705)	23.156 (9.57)	45.723 (18.02)	48.803 (17.42)
L-MA	502.944 (148.61)	645.14 (126.12)	1228.01 (397.92)	1337.06 (334.06)
L-AMP	178.67 (44.6)	232.52 (57.48)	432.94 (152.39)	477.05 (114.67)
PEA				

The urinary PEA excretion before and after dosing are shown in the following figure:



- Urinary excretion of PEA is greater after the Zydis® formulation as compared to the Eldepryl® formulation.
- The effect of food on the urinary excretion of PEA was more pronounced with Eldepryl® (3-fold increase) as compared to the Zydis® formulation.

Conclusions:

- There is a significant food associated reduction in absorption of selegiline with the Zydis® formulation. Exposure of selegiline is greater if Zydis® formulation was administered under fasting conditions by about 1.4-3.8 times. The 90% CI of Eldepryl® fell at either side of unity (0.4-1.2). This is contradictory to that provided in the label for Eldepryl® that food increases the absorption of selegiline by 3 fold. The only difference in the design of the current study and that previously conducted with Eldepryl® was that in the previous study the two tablets of Eldepryl® were given 4 hours apart.
- The effect of food was greater on the Zydis® formulation than on the Epedryl® formulation
- The inter-subject variability in the pharmacokinetic parameters of selegiline and NDMS is very high, it is greater for Eldepryl® than for Zydis® formulation.
- Based on dose-normalized AUC, Zydis® 5 mg formulation has 1.9-21.1 times higher exposure than Eldepryl® formulation.

MULTIPLE DOSE PHARMACOKINETICS IN HEALTHY SUBJECTS

Study AN17933-101: Comparison of pressor effect of Tyramine following repeat dose administration of Zydis® selegiline 1.25, 2.5 and 5.0 mg QD and Eldepryl® (conventional selegiline) 5 mg BID in healthy volunteers

This study was conducted to assess the relative selectivity of Zydis® selegiline 1.25, 2.5 and 5 mg QD and Eldepryl® 5 mg BID for MAO-A and MAO-B by pressor responses to orally administered tyramine.

MAOs are intracellular enzymes widely distributed throughout the body. In humans, intestinal MAO is predominantly Type A, while that in the brain is Type B.

Markers for MAO-A inhibition:

- The clinical model for testing MAO-A inhibition is oral tyramine threshold test that detects the pressor response to tyramine. Increase in sensitivity to tyramine to meet threshold systolic blood pressure increment of > 30 mm Hg would indicate non specific inhibition of MAO-A ("Cheese reaction"). Tyramine is present in cheese and is responsible for lowering the threshold for cardiovascular responses to ingested tyramine when ingested with MAO inhibitors. This test is conducted for presenting the 'worst case scenario' for cheese reactions.
- MAO-A primarily degrades serotonin (5-HT) to 5-hydroxyindole acetic acid (5-HIAA), which is excreted in the urine. Significant inhibition of MAO-A leads to marked decrease in urinary excretion of 5-HIAA.
- MAO-A also degrades norepinephrine to 3-methoxy-4hydroxyphenyl glycol (MHPG) and is measured in plasma. Significant inhibition of MAO-A leads to marked decrease in plasma concentration of MHPG.

Markers for MAO-A inhibition:

- MAO-B primarily degrades dopamine and phenylethylamine (PEA). Significant inhibition of MAO-B leads to increased urinary PEA.

The details of the study design and methodology for PD assessment are as follows:

Study Design	Open label, randomized, multiple dose, parallel group study for 12-14 days
Study Population	N= 63 enrolled, 60 completed healthy subjects Gender: 60 M Ages: 18-44 yrs (mean 27.6 yrs), mean age in each group was similar Weight: 57-93 kg (mean 72.4 kg), Race: 51 White, 7 Afro Caribbean and 4 Asian, 1 other
Treatment Group	A: Zydis® seligiline 1.25 mg QD (N=15 enrolled, 14 completed) B: Zydis® seligiline 2.5 mg QD (N=16 enrolled, 15 completed) C: Zydis® seligiline 5 mg QD (N=15 enrolled, 14 completed) D: Eldepryl ® selegiline Capsules 5 mg BID (US-Elan Pharm) (N=17) **Subject 39, 35 and 40 withdrawn: protocol violation

Dosage and Administration	A: Zydis 1.25 mg QD before breakfast without water for 14 days, batch 01C0Z2P B: Zydis® 2.5 mg (2 x 1.25) QD before breakfast without water for 14 days C: Zydis® seligiline 5 mg (4 x 1.25) QD before breakfast without water for 14 days Refrained from swallowing after Zydis tablet had dissolved. Subjects remained upright while dosing. D: 5 mg BID , with second 5 mg given 4 hours apart from the first, ie. after breakfast and lunch, swallowed with 150 ml water for 14 days, batch 3H0382 Diet: A, B and C: Administered after overnight fast, and on tyramine testing Days 12-14 fasted till completion of tyramine testing for that Day. All other days overnight fast and 30 minutes post-dose. No food or drink 5 minutes before and after Zydis tablets administration**. (**_Comment: This appears contrary to the previous sentence-unclear in the protocol_) D: Administered after a light breakfast and lunch, except fasted till tyramine testing on Days 12-14 On each test Day, tyramine dose was given 2 hours apart, starting 30 minutes after dosing with selegiline. Tyramine dose was given with 150 ml water. On the tyramine challenge day subjects were prohibited to take alcohol, caffeine and nicotine on all study days
Sampling: Blood	For selegiline, N-desmethyl-selegiline, L-methamphetamine and L-amphetamine: • At predose and 5, 10, 15, 30, 45, 60 minutes and at 1.5, 2, 2.5, 3, 4, 6, 12 and 24 hours post-dose on Days 1 and 10 for Treatments A, B and C. • At predose and 15, 30, 60 minutes and at 1.5, 2, 4, 4.25, 4.4, 5, 6, 8, 12 and 24 hours post-dose on Days 1 and 10 for Treatment D • Predose on Days 8 and 9 for all Treatments • One hour post dose on Day 12-14 for all Treatments For MHPG on Day –1 and pre dose on Days 1, 9 and 10
Urine	For PEA and 5-HIAA: from 0-6, 6-12 and 12-24 hours on Days –1, 1, 9 and 10
Feces	none
Analysis	GC/MS method for selegiline, N-desmethyl-selegiline, methamphetamine and amphetamine in plasma HPLC for MHPG

	LC/MS/MS for PEA in urine HPLC with electrochemical detection for 5-HIAA Lower Limits of Quantitation Selegiline: Plasma 0.01 ng/mL; Urine 1.0 ng/mL N-desmethyl-selegiline: Plasma 0.04 ng/mL; Urine 1.0 ng/mL L-Amphetamine: Plasma 0.1 ng/mL; Urine 1.0 ng/mL L-Methamphetamine: Plasma 0.1 ng/mL; Urine 1.0 ng/mL Phenylethylamine (PEA): Plasma 0.01 ng/ml; Urine 1.13 ng/mL 5-HIAA: Urine 1.0 ng/mL MHPG: Plasma 1.0 ng/ml Assay validation complete and acceptable
PK Assessment	AUC0-t, Cmax, Tmax on Day 1 Css,min, Css,max, tss,max, tss,min, t1/2, AUC_τ, λ_z, CL/F, PTF on Day 10
PD Assessment	• Oral tyramine pressor threshold measurement, pre-treatment doses were determined over a period of Day –7 to Day –5, during treatment over a period of Day 12-14. Methodology: Baseline threshold test (Day –7 to -5): Tyramine threshold testing started on Day –7. Up to 7 doses of oral tyramine (available as 25, 100 and 300 mg capsules) were administered on 3 successive days in ascending single doses, with a maximum of 3 doses in any given day. For the baseline threshold test, tyramine doses of 100, 200, 300, 400, 500, 600 and 700 mg were scheduled for administration. No further doses of tyramine were administered once the threshold cardiovascular response had been observed (rise in systolic blood pressure in excess of 30 mmHg). Subjects were then admitted in the Unit (Day –1) During treatment threshold test (Days 12-14): Tyramine doses of 25, 50, 100, 200, 300, 400, 500, 600 and 700 mg were scheduled for administration On each test Day, tyramine dose was given 2 hours apart, starting 30 minutes after dosing with selegiline. A repeat tyramine dose was given only if blood pressure returned to < 10 mmHg above the predose reference value for that Day. Analysis: Heart rate and supine blood pressure were measured at 5 minute intervals from 15 minutes before each dose of tyramine until 120 minutes after (or longer if blood pressure remained >10 mmHg above predose reference value for that Day). Reference blood pressure would be an average of 3 values for each Day Pre-treatment tyramine threshold dose was compared with the corresponding threshold dose obtained during treatment using

	Wilcoxan Matched Pairs Signed Rank Sum Test to test for effect of treatment on tyramine threshold dose. Tyramine pressor ratios were calculated using the following equation and compared between treatments Tyramine pressor endpoint ratio = Pre-treatment tyramine threshold dose/ tyramine threshold dose during selegiline treatment • Excretion of PEA was used as a marker for the inhibition of MAO-B on pre-treatment (Days –1 and 1) and during treatment (9 and 10). • MHPG in plasma and 5-HIAA in urine was used as a marker for the inhibition of MAO-A on pre-treatment (Days –1 and 1) and during treatment (9 and 10)

Pharmacokinetic Results:

SEL:

The mean (SD) Day 1 and Day 10 Pharmacokinetic parameters are shown in the following Table:

Treatment	Day1			Day 10				
	Cmax (ng/ml)	Tmax* (h)	AUC (ng.h/ml)	Css, max (ng/ml)	Css, min (ng/ml)	Tss,max* (h)	AUCτ (ng.h/ml)	PTF (%)
Zydis 1.25 mg QD	3.34 (1.68)	0.17 (0.17-0.27)	1.49 (0.77)	3.96 (1.90)	0.03 (0.03)	0.25 (0.17-0.50)	4.77 (2.29)	2051 (625)
Zydis 2.5 mg QD	4.47 (2.56)	0.18 (0.08-0.50)	2.44 (1.64)	4.37 (1.83)	0.05 (0.04)	0.25 (0.17-0.50)	6.52 (2.09)	1643 (533)
Zydis 5 mg QD	5.45 (3.24)	0.18 (0.10-0.50)	3.78 (2.03)	5.54 (3.01)	0.06 (0.04)	0.25 (0.17-0.78)	8.51 (2.74)	1485 (592)
Eldepryl 5 mg BID	1.12 (1.48)	4.55 (0.50-6.03)	1.93 (1.67)	1.73 (1.08)	0.09 (0.07)	1.00 (0.25-6.00)	8.32 (5.06)	604 (484)

*median (range)

NDMS:

Treatment	Day1			Day 10				
	Cmax (ng/ml)	Tmax (h)	AUCτ (ng.h/ml)	Css, max (ng/ml)	Css, min (ng/ml)	Tss,max (h)	AUCτ (ng.h/ml)	PTF (%)
Zydis 1.25 mg QD	1.22 (0.48)	1.00 (0.75-1.50)	2.07 (0.71)	2.06 (0.69)	0.04 (0.05)	1.00 (0.75-2.00)	8.66 (4.39)	677 (338)
Zydis 2.5 mg QD	4.02 (2.05)	1.00 (0.75-3.00)	8.03 (3.64)	6.07 (3.39)	0.16 (0.09)	1.0 (0.5-1.52)	22.13 (10.09)	665 (246)
Zydis 5 mg QD	7.36 (3.16)	1.00 (0.50-2.00)	17.14 (5.16)	10.10 (4.24)	0.19 (0.12)	1.00 (0.50-3.00)	32.29 (10.28)	759 (230)
Eldepryl 5 mg BID	10.65 (5.09)	1.50 (0.50-8.0)	64.03 (38.56)	14.56 (6.44)	1.00 (0.85)	1.50 (0.25-6.17)	100.96 (56.22)	363 (158)

*median (range)

L-AMP

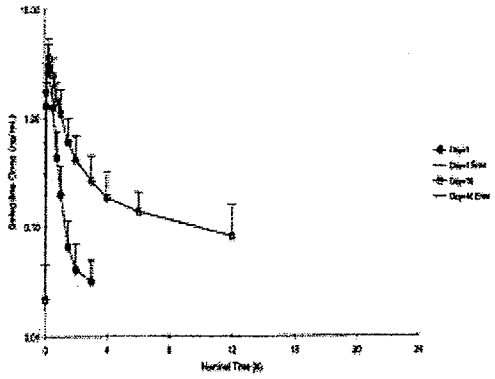
Treatment	Day1			Day 10				
	Cmax (ng/ml)	Tmax (h)	AUC (ng.h/ml)	Css, max (ng/ml)	Css, min (ng/ml)	Tss,max (h)	AUCτ (ng.h/ml)	PTF (%)
Zydis 1.25 mg QD	0.20 (0.09)	1.80 (1.00-6.02)	1.49 (1.54)	1.19 (1.68)	0.28 (0.09)	3.0 (1.0-12.13)	11.92 (5.13)	156 (236)
Zydis 2.5 mg QD	0.58 (0.15)	4.00 (0.75-12.0)	8.0 (1.48)	1.78 (0.82	0.60 (0.26)	3.0 (1.0-6.0)	26.92 (7.92)	107 (51)
Zydis 5 mg QD	1.33 (0.28)	3.0 (1.0-6.0)	19.94 (3.78)	3.24 (0.60)	1.14 (0.39)	3.0 (0.926.0)	50.63 (10.42)	112 (38)
Eldepryl 5 mg BID	2.69 (0.65)	8.0 (4.5-23.98)	44.17 (8.28)	5.30 (1.07)	2.62 (0.59)	8.0 (0.50-12.0)	95.25 (16.90)	69 (22)

*median (range)

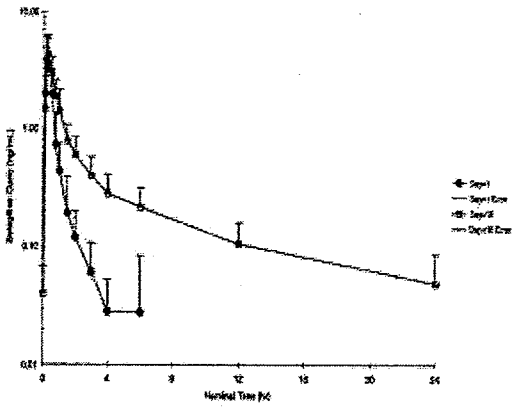
L-MA

Treatment	Day1			Day 10				
	Cmax (ng/ml)	Tmax (h)	AUC (ng.h/ml)	Css, max (ng/ml)	Css, min (ng/ml)	Tss,max (h)	AUCτ (ng.h/ml)	PTF (%)
Zydis 1.25 mg QD	0.62 (0.23)	1.50 (1.0-3.0)	5.68 (2.44)	1.78 (0.84)	0.51 (0.21)	2.00 (1.0-12.13)	24.45 (11.79)	125 (25)
Zydis 2.5 mg QD	1.86 (0.49)	1.50 (0.75-4.0)	20.17 (4.27)	4.29 (1.63)	0.93 (0.50)	2.02 (0.75-6.0)	53.88 (15.56)	151 (45)
Zydis 5 mg QD	5.0 (1.53)	1.50 (1.0-4.02)	57.49 (12.63)	8.76 (1.51)	2.17 (0.85)	1.26 (0.50-6.12)	113.76 (36.91)	150 (46)
Eldepryl 5 mg BID	8.37 (1.28)	8.00 (5.0-12.53)	131.34 (21.83)	16.23 (2.72)	5.12 (1.55)	6.0 (1.5-12.0)	254.98 (66.55)	109 (26)

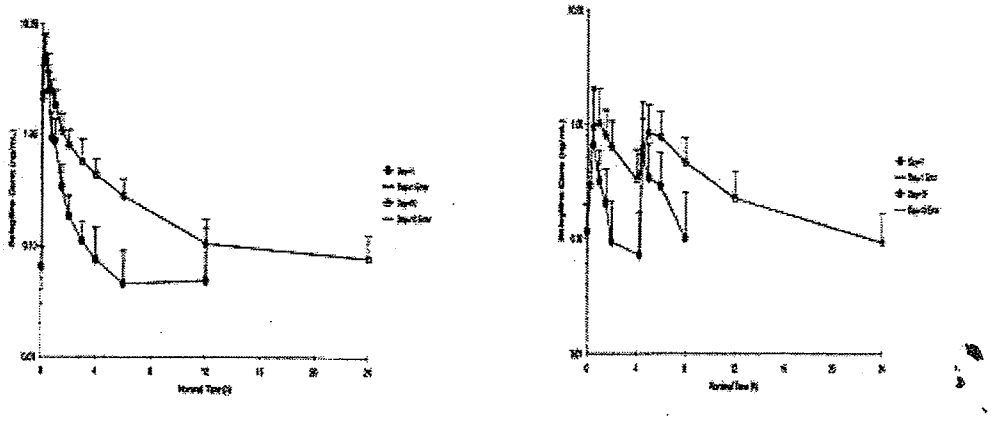
The following are mean (SD) plasma selegiline plasma profiles for Days 1 and 10 with the Zydis® doses and Eldepryl®



Zydis 1.25 mg QD



Zydis 2.5 mg QD



ZYDIS 5 MG QD **ELDEPRYL 5 MG BID**

Similarly, the metabolites concentration at Day 10 was significantly higher than Day 1.

Day 1:
Selegiline

- Eldepryl® 5 mg BID given after breakfast and lunch produced 29% higher exposure of selegiline as compared to 1.25 mg Zydis® QD.
- Mean Cmax of selegiline was ~3-5 fold higher with the different doses of Zydis® as compared to Eldepryl® BID
- Selegiline peak levels were reached at ~10-15 minutes with Zydis® QD and at ~ 4 hours with Eldepryl® given BID.

Metabolites:

- Metabolite concentrations were higher than the parent selegiline with both Zydis® and Eldepryl® formulations
- Metabolite concentrations after Zydis administration were significantly lower than that after Eldepryl® administration

Day 10:
Selegiline:

- On Day 10, selegiline concentrations rose ~2-3 fold higher as compared to Day 1 levels.
- Trough concentrations on Day 8, 9 and 10 indicated that steady state had been reached.
- Similar steady state exposure to selegiline was observed with Zydis® 5 mg QD and Eldepryl® 5 mg BID
- Mean PTF was very high for selegiline, and also higher with the Zydis® formulation, as compared to Eldepryl®.

Metabolites:

- Metabolite concentrations were much lower with Zydis® 5 mg QD as compared to Eldepryl® 5 mg BID. There was an ~70% reduction in NDMS and ~50 reduction in L-AMP and L-MA with the Zydis formulation.
- Mean PTF was lower for metabolites, but was higher with the Zydis formulation, as compared to Eldepryl®.
- The metabolite ratios (AUCτ metabolite/AUCτ selegiline) rose with the increase in dose of the Zydis formulation, but remained lower than those of Eldepryl®.

The mean (SD) metabolic ratios are given in the following Table:

Treatment	Metabolic Ratio		
	NDMS	L-AMP	L-MA
Zydis 1.25 mg QD	2.02 (1.05)	3.50 (3.0)	7.14 (6.44)
Zydis 2.5 mg QD	3.43 (1.29)	4.46 (1.65)	9.34 (4.44)
Zydis 5.0 mg QD	4.34 (2.37)	6.65 (3.05)	14.49 (6.73)
Eldepryl 5.0 mg BID	16.54 (11.24)	18.83 (15.80)	50.32 (45.99)

Dose proportionality:

Although selegiline concentrations rose with the increase in dose with the Zydis formulation, the increase was not statistically dose proportional for selegiline. Although true dose proportionality cannot be assessed from this study as it has a parallel study design.
The following are the dose normalized least square means for the pharmacokinetic parameters after single dose and at steady state:

Parameter	Dose Normalized Least Square Means		
	Zydis 1.25 mg	Zydis 2.5 mg	Zydis 5.0 mg
Day1: Cmax	11.712	7.620	4.654
AUCτ	5.203	4.00	3.294
Day 10: Css,max	13.765	7.995	4.697
AUCτ	16.745	12.318	8.098

Assessment of dose proportionality is shown by the p-values in the following Table:

Parameter	Comparison	p-value
Day1: Cmax	2.5 vs 1.25 mg 5.0 vs 1.25 mg 5.0 vs 2.5 mg	0.0461 <0.0001 0.0231
AUCτ	2.5 vs 1.25 mg 5.0 vs 1.25 mg 5.0 vs 2.5 mg	0.2267 0.0416 0.3689
Day 10: Css,max	2.5 vs 1.25 mg 5.0 vs 1.25 mg 5.0 vs 2.5 mg	0.0107 <0.0001 0.0138
AUCτ	2.5 vs 1.25 mg	0.0606

	5.0 vs 1.25 mg 5.0 vs 2.5 mg	<0.0001 0.0132

For the metabolite dose proportionality the results were inconclusive due to high inter-subject variability

Pharmacodynamic Results:

Tyramine Threshold Testing:

Interaction between MAO inhibitors and tyramine produces cardiovascular effects such as hypertension (also called "Cheese Effect). These interactions are assessed by conducting "Tyramine Challenge Test" (or Tyramine Pressor Test") in healthy subjects in a controlled environment. The test involved monitoring of systolic blood pressure (SBP) and heart rate in response to tyramine administration before and after dosing with MAO inhibitor. The endpoint is the rise in SBP of 30 mmHg. The minimum tyramine dose required to raise the SBP to 30 mm Hg is called the tyramine pressor dose. Increases in SBP greater than 60 mmHg above baseline are terminated by administering alpha-adrenoreceptor blocking agent such as pentolamine or labetalol. The ratio of the pressor dose before and after administration of MAO inhibitor is called as the "Tyramine Sensitivity Factor" which is an index to assess change in cardiovascular sensitivity to tyramine. The dietary intake of tyramine is 10-50 mg. This test presents a 'worst case scenario' of a cheese effect seen with the administration of tyramine containing products along with an MAO inhibitor.

The tyramine pressor doses obtained before and after Zydis® selegiline and Eldepryl® are given in the following Tables:

Tyramine Pressor Ratio: Zydis selegiline, 1.25 mg QD

Subject	Pre-Treatment Tyramine Threshold Dose (mg)	During Treatment Tyramine Threshold Dose (mg)	Tyramine Pressor Ratio
1	[redacted]	[redacted]	8.00
2			8.00
6			8.00
8			5.00
9			3.00
22			2.00
23			1.67
31			1.67
36			1.75
39			NR
41			24.00
50			1.25
55			12.00
57			1.25
61			16.00
N	15	14	14
Arithmetic Mean	460	179	6.69
SD	130	160	6.75
CV%	28	89	101
Median	500	100	4.00
Min	200	25	1.25
Max	700	400	24.00

b(4

NV = No value, as subject withdrawn prior to attainment of threshold dose for a positive ABT.
NR = No result
* = This dose caused an exact increase in systolic blood pressure of 30 mmHg

Tyramine Pressor Ratio: Zydis selegiline, 2.5 mg QD

Subject	Pre-Treatment Tyramine Threshold Dose (mg)	During Treatment Tyramine Threshold Dose (mg)	Tyramine Pressor Ratio
5			8.00
14			1.50
15			1.00
16			1.50
18			2.00
19			1.00
21			4.00
24			1.20
25			1.50
27			2.00
29			1.33
34			1.50
35			NR
44			12.00
54			1.25
60			1.67
N	16	15	15
Arithmetic Mean	356	232	2.76
SD	121	141	3.12
CV%	34	61	113
Median	350	200	1.50
Min	100	25	1.00
Max	600	500	12.00

b(4)

ND = Not done as subject was withdrawn prior to Day 12 for a positive ABT.

NR = No result

* = This dose caused an exact increase in systolic blood pressure of 30 mmHg

Tyramine Pressor Ratio: Zydis selegiline, 5 mg QD

Subject	Pre-Treatment Tyramine Threshold Dose (mg)	During Treatment Tyramine Threshold Dose (mg)	Tyramine Pressor Ratio
4			6.00
10			2.00
11			2.00
17			2.50
26			12.00
28			1.50
30			2.00
38			2.00
40			1.50
43			12.00
46			NR
47			12.00
51			1.50
53			1.67
58			8.00
N	15	14	14
Arithmetic Mean	373	148	4.76
SD	103	92	4.35
CV%	28	62	91
Median	400	200	2.00
Min	200	25	1.50
Max	600	300	12.00

b(4)

ND = Not done as subject was withdrawn prior to Day 12 for a positive ABT.

NR = No result

Tyramine Pressor Ratio: Eldepryl selegiline, 5 mg QD

Subject	Pre-Treatment Tyramine Threshold Dose (mg)	During Treatment Tyramine Threshold Dose (mg)	Tyramine Pressor Ratio
3			2.00
7			8.00
12			8.00
13			8.00
20			12.00
32			5.00
33			8.00
37			10.00
42			6.00
45			10.00
48			3.00
49			2.00
52			1.00
56			1.25
59			8.00
63			20.00
65			3.00
N	17	17	17
Arithmetic Mean	376	104	6.78
SD	148	109	4.82
CV%	39	104	71
Median	400	50	8.00
Min	200	25	1.00
Max	600	400	20.00

b(4)

NA = Not applicable, as subject was withdrawn prior to Day 12.
NR = No result
* = This dose caused an exact increase in systolic blood pressure of 30 mmHg

- With 1.25 mg Zydis®, 6/14 (42%) subjects had tyramine threshold doses ≤50 mg during treatment.
- With 2.5 mg Zydis®, 3/15 (20%) subjects had tyramine threshold doses ≤50 mg during treatment.
- With 5 mg Zydis®, 5/14 (33%) subjects had tyramine threshold doses ≤50 mg during treatment.
- With 5 mg Eldepryl®, 10/17 (59%) subjects had tyramine threshold doses ≤50 mg during treatment.
- About 20-30% of subjects in each treatment group had tyramine threshold dose of 25 mg during treatment.
- With all treatments a significant reduction in threshold doses was observed, indicating evidence for MAO-A inhibition. In 2.5 mg Zydis group there were two subjects that did not show any change in the threshold tyramine dose during treatment with selegiline as compared to pre-treatment.

Survival analysis methods were used to compare tyramine threshold doses from the 4 treatment groups. Results from the survival analysis could not detect any differences in the survival curves of tyramine threshold doses among the 4 treatments groups at pre treatment and post treatment with selegiline ($p>0.05$). See figures below:

Figure: Tyramine threshold doses at pre-treatment:

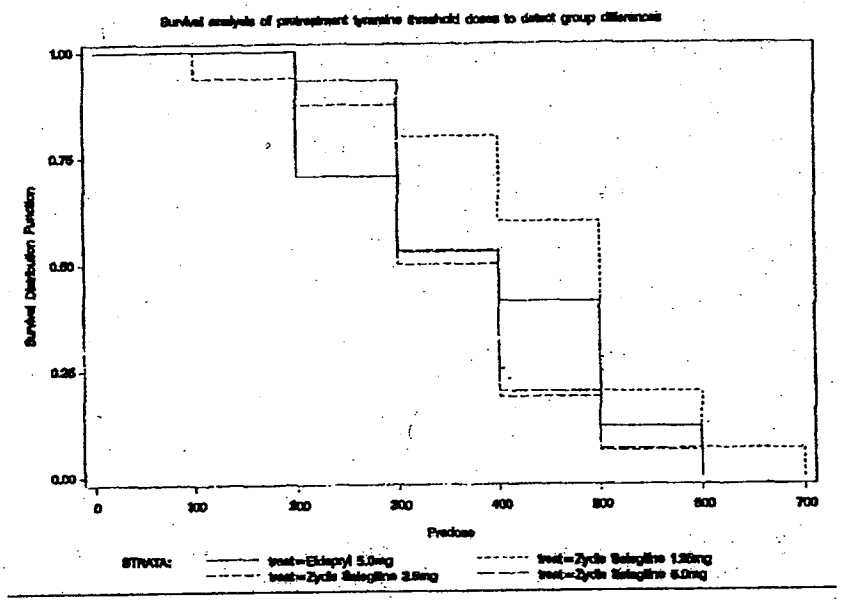
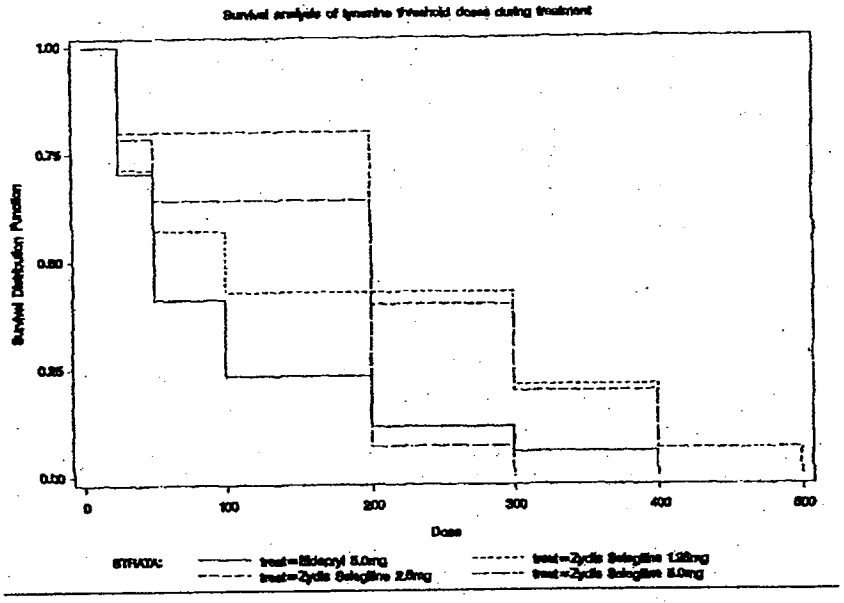


Figure: Tyramine threshold doses during treatment:



The test for equality over treatments prior to selegiline treatment and during selegiline treatment is shown in the following Table:

Test	Pre treatment	During treatment
	p-value	p-value
Log rank	0.1211	0.0538
Wilcoxan	0.1617	0.1182
-2Log (LR)	0.8945	0.1540

All these statistical tests did not show differences in the threshold lowering of the cardiovascular effects of tyramine between the 4 treatments, though Log rank test for during treatment approached significance (p=-0.0538).

The results from the Wilcoxan matched pairs signed rank sum test are shown in the following Table:

Treatment	Median Difference (Point Estimate)	p-value
Zydis 1.25 mg QD	275.0	<0.0001
Zydis 2.5 mg QD	287.5	0.0001
Zydis 5.0 mg QD	100.0	0.0002
Eldepryl 5.0 mg BID	200.0	0.0001

This analysis tested the hypothesis that the median difference between the pre treatment tyramine threshold dose and that during treatment equalled zero. In all the 4 treatment groups tyramine threshold doses during treatment showed a statistically significant reduction compared to pre treatment tyramine doses, indicating all 4 treatments lowered the threshold for cardiovascular effects of tyramine, indicative of MAO-A inhibition.

Statistical comparisons of the tyramine pressor ratios is given in the following Table:

Test		Reference			95 % CI		
Treatment	LS Mean	Treatment	LS Mean	Difference	Lower	Upper	p-value
Zydis Selegiline 1.25 mg OD	6.91	Eldepryl 5.0 mg BID	6.74	0.17	-3.48	3.83	0.2664
Zydis Selegiline 2.5 mg OD	2.65	Eldepryl 5.0 mg BID	6.74	-4.09	-7.60	-0.59	0.0230
Zydis Selegiline 5.0 mg OD	4.71	Eldepryl 5.0 mg BID	6.74	-2.03	-5.60	1.53	0.2578
Zydis Selegiline 1.25 mg OD	6.91	Zydis Selegiline 2.5 mg OD	2.65	4.27	0.45	8.09	0.0292
Zydis Selegiline 1.25 mg OD	6.91	Zydis Selegiline 5.0 mg OD	4.71	2.21	-1.62	6.04	0.2533
Zydis Selegiline 2.5 mg OD	2.65	Zydis Selegiline 5.0 mg OD	4.71	-2.06	-5.73	1.62	0.9244

Data source: Appendix 16.2.7.10

- Zydis® 2.5 mg differed significantly from Eldepryl® 5 mg BID
- Zydis® 1.25 mg differed significantly from Zydis® 2.5 mg

- The LS means suggest the Zydis® 2.5 mg shows less MAO-A inhibition as compared to the other treatments of Zydis, suggesting increasing doses of Zydis® selegiline do not produce a progressive inhibition of MAO-A.

Plasma MHPG concentrations:

Pre-dose mean (SD) plasma MHPG concentrations (ng/ml) are given in the following Table:

Treatment	Day -1	Day 1	Day 9	Day 10
Zydis 1.25 mg QD	0.95 (0.52)	0.84 (0.40)	0.93 (0.52)	0.75 (0.32)
Zydis 2.5 mg QD	1.34 (0.73)	1.09 (0.47)	1.07 (0.53)	1.06 (0.46)
Zydis 5.0 mg QD	1.03 (0.59)	0.83 (0.45)	0.86 (0.47)	0.71 (0.37)
Eldepryl 5.0 mg BID	1.33 (0.67)	0.99 (0.49)	1.03 (0.38)	0.90 (0.39)

- MHPG concentrations showed a statistically significant decrease from baseline for the high doses of Zydis 5 mg QD ($p=0.0498$, 20%↓) and Eldepryl 5 mg BID treatment on Day 10 ($p=0.0054$, 22%↓). All other baseline and Day 9/10 comparisons in the MHPG levels were not significant.
- These results are suggestive of modest inhibition of MAO-A at higher doses.
- On Day 10, Zydis 2.5 mg was statistically significantly different from Zydis 1.25 mg ($p=0.0356$) and Zydis 5.0 mg ($p=0.0363$) in terms of MHPG levels. These differences in MHPG levels were not seen on Day 9. Hence any meaningful conclusions on MAO-A inhibition cannot be derived from these data.
- No other treatment comparisons were significantly different from each other
- There was high inter-subject variability.

Urinary Excretion PEA and 5-HIAA:

- Amount of PEA increased from Day 1 to Day 9 and 10 for all treatments
- Amount PEA excreted by Eldepryl® was similar to that by Zydis® 2.5 mg
- The highest amount of PEA excreted was with the Zydis® 5 mg treatment group.
- These results are suggestive of MAO-B inhibition.

- There was a trend towards increase in 5-HIAA concentrations with the Zydis treatments and a decrease in concentration with Eldepryl® from baseline to Day 10, although these differences were small. This would suggest that Eldepryl® showed modest MAO-A inhibition, but the Zydis treatments did not.

The amount of PEA and 5-HIAA excreted in the urine is presented in the following Table:

Table 11.2.3.1: Mean (SD) Pre-treatment and During Treatment PEA and 5-HIAA 24 Hour Urinary Cumulative Amounts Excreted

Treatment	Dose	PEA (µg)				5-HIAA (mg)			
		Day –1 to Day 1	Day 1 to Day 2	Day 9 to Day 10	Day 10 to Day 11	Day –1 to Day 1	Day 1 to Day 2	Day 9 to Day 10	Day 10 to Day 11
Zydis Selegiline	1.25 mg OD (N=15)	4.01	9.10[1]	71.20	103.94	5.04	6.11[1]	5.70	6.34
		(1.61)	(2.53)	(34.46)	(44.43)	(1.64)	(3.21)	(4.46)	(3.16)
	2.5 mg OD (N = 16)	5.22	20.80[2]	131.91[3]	155.04[3]	5.39	5.85[2]	5.95[3]	6.00[3]
		(3.04)	(11.50)	(90.43)	(75.55)	(2.44)	(2.65)	(3.16)	(2.66)
	5.0 mg OD (N=15)	9.02	52.20	132.62[4]	183.98[4]	5.94	5.28	5.94[4]	6.19[4]
		(20.07)	(36.87)	(83.01)	(81.62)	(1.77)	(2.18)	(3.93)	(2.92)
Eldepryl®	5.0 mg BID (N=17)	4.15	21.80	130.62[5]	158.17[6]	4.29	4.67	3.85[5]	4.11[6]
		(4.08)	(27.32)	(68.06)	(75.56)	(1.71)	(2.77)	(1.34)	(1.37)

[1] N=14, subject 6 not estimable; [2]N=15, subject 25 not estimable; [3]N=15, subject 35 not dosed; [4]N=14, subject 46 not dosed; [5]N=16, subject 63 not estimable; [6]N=16, subject 65 not estimable.

Data source: Tables 14.3.4.1 to 14.3.4.4

Conclusions:

Pharmacokinetics:

- After single dose of 1.25, 2.5 or 5 mg selegiline, the peak plasma concentrations were ~3-5 fold higher as compared to 5 mg Eldepryl® BID. Selegiline peak levels were reached at ~10-15 minutes with Zydis QD and at ~ 4 hours with Eldepryl® given BID. Eldepryl® 5 mg BID given after breakfast and lunch produced 29% higher exposure as measured by AUC of selegiline as compared to 1.25 mg Zydis QD.
- After multiple doses selegiline concentrations rose ~2-3 fold higher as compared to Day 1 levels.
- Dose proportionality at 1.25, 2.5 and 5 mg selegiline could not be established due to high intersubject variability.
- The metabolite concentrations were higher than the parent selegiline with both Zydis® and Eldepryl® formulations. The metabolite concentrations were much lower with the Zydis formulations as compared to Eldepryl®, suggesting less first pass metabolism.

Pharmacodynamics:

- Although all Zydis® and Eldepryl® formulations showed greater sensitivity to tyramine suggestive of MAO-A inhibition, there was no clear dose dependent relationship with increasing doses of selegiline. The tyramine pressor ratio was the least with Zydis® 2.5 mg QD suggesting least MAO-A inhibition at this dose. The tyramine pressor ratio of Zydis® 1.25 mg QD was similar to that of Eldepryl® 5 mg BID.
- Overall the mean tyramine pressor ratios of all Zydis doses of 1.25, 2.5 and 5 mg (6.69, 2.76, 4.76 respectively) were less than Eldepryl® (6.78). Based on these results it cannot be concluded that MAO-A inhibition with the Zydis formulation is less than that from Eldepryl® because there is no clear dose relationship in MAO-A inhibition.
- The tyramine pressor ratios do not appear to be related to any of the PK parameters. Although dose proportionality could not be concluded from this study, the Cmax and AUC of selegiline increased with increase in Zydis dose. The steady state AUC of Zydis® 5 mg QD was similar to Eldepryl 5® mg BID. Similar trends in the tyramine pressor ratios were not observed. Individual subject PK parameters also did not have specific trend towards a high tyramine pressor ratio. Hence, the relationship between PK parameters and the tyramine pressor ratios is inconclusive. Similar conclusions were made by Dr. Jackson in the pharmacometrics review (see page 95).
- Upon discussions with the reviewing Medical Officer it was determined that these tyramine pressor ratios are much higher than that reported in the literature. At a similar dose of selegiline (5 mg BID) from NDA 21-336 (Somerset Study SP9303), the tyramine pressor ratio or the tyramine sensitivity factor was 1.7. The Medical Officer is evaluating these results in detail.

- MHPG concentrations showed a statistically significant decrease from baseline for the high doses of Zydis® 5 mg QD (p=0.0498, 20%↓) and Eldepryl® 5 mg BID treatment on Day 10 (p=0.0054, 22%↓). All the baseline and Day 9/10 comparisons in the MHPG levels were not significant. These results are suggestive of modest inhibition of MAO-A at higher doses.
- There was a trend towards increase in 5-HIAA concentrations with the Zydis® treatments and a decrease in concentration with Eldepryl® from baseline to Day 10, although these differences were small. This would suggest that Eldepryl® showed modest MAO-A inhibition, but the Zydis treatments did not. Although, the tyramine pressor ratio's were not suggestive of similar conclusions as obtained from the urinary excretion of 5-HIAA.

Study: Z/SEL/96/014: Repeat dose study to assess the tolerability and pharmacokinetics of 1.25 mg Zydis selegiline compared with 10 mg Eldepryl and to assess indirect measures of inhibition of monoamine oxidases A and B

The indirect measures for the inhibition of MAO-A and MAO-B are as follows:

Markers for MAO-A inhibition:

- The clinical model for testing MAO-A inhibition is oral tyramine threshold test that detects the pressor response to tyramine. Increase in sensitivity to tyramine to meet threshold systolic blood pressure increment of > 30 mm Hg would indicate non specific inhibition of MAO-A ("Cheese reaction).
- MAO-A primarily degrades serotonin (5-HT) to 5-hydroxyindole acetic acid (5-HIAA), which is excreted in the urine. Significant inhibition of MAO-A leads to marked decrease in urinary excretion of 5-HIAA.
- MAO-A also degrades norepinephrine to 3-methoxy-4hydroxyphenyl glycol (MHPG) and is measured in plasma. Significant inhibition of MAO-A leads to marked decrease in plasma concentration of MHPG.

Markers for MAO-B inhibition:

- MAO-B primarily degrades dopamine and phenylethylamine (PEA). Significant inhibition of MAO-B leads to increased urinary PEA.

The study design is as follows:

Study Design	Open label, randomized, multiple dose, parallel group study for 28 days
Study Population	N=24 (12+12) healthy male and female subjects Gender: 13M & 11F, Ages: 48-70 yrs (mean 62.6 yrs), Weight: 52.2-101 kg (mean 72.2 kg), Race: 21 White and 3 Asian
Treatment Group	A: Zydis® seligiline 1.25 mg B: Eldepryl ® selegiline Tablets 10 mg (UK)
Dosage and Administration	A: 1.25 mg taken each morning before breakfast without water for 28 days, batch 95K03SA B: 10 mg (2 x 5 mg) swallowed with 150 ml water each morning before breakfast for 28 days, batch XBA05A Administered after overnight fast, and 4 hours fast post dose on Days 1, 13, 27 and 28. All other days overnight fast and 30 minutes post-dose. On the tyramine challenge day subjects were prohibited from cigarette smoking. Alcohol, chocolate and cocoa was prohibited on all days
Sampling: Blood	For selegiline (SEL), N-desmethyl-selegiline (NDMS), L-methamphetamine (L-MA) and L-amphetamine (L-AMP): At predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 12 and 24 hours post-dose on Days 1 and 28.

	For plasma 3-methoxy, 4-hydroxyphenylglycol (MHPG): immediately before dosing on Days 1, 2, 7, 13, 14, 21, 24, 27 and 28 hours post dose on Day 29
Urine	For selegiline, N-desmethyl-selegiline, L-methamphetamine and L-amphetamine, PEA and 5-HIAA: At pre-dose and post-dose from 0-6, 6-12 and 12-18, 18-24 hours on Days –1, 1, 13, 27 and 28
Feces	none
Analysis	GC/MS method for selegiline, N-desmethyl-selegiline, methamphetamine and amphetamine in plasma HPLC for MHPG GLC/MS method for selegiline, N-desmethyl-selegiline, methamphetamine and amphetamine and PEA in urine HPLC with electrochemical detection for 5-HIAA Lower Limits of Quantitation Selegiline: Plasma 0.01 ng/mL; Urine 1.0 ng/mL N-desmethyl-selegiline: Plasma 0.04 ng/mL; Urine 1.0 ng/mL L-Amphetamine: Plasma 0.05 ng/mL; Urine 1.0 ng/mL L-Methamphetamine: Plasma 0.05 ng/mL; Urine 1.0 ng/mL Phenylethylamine: Plasma 0.01 ng/ml; Urine 1.40 ng/mL 5-HIAA: Urine 1 ng/mL MHPG: Plasma 1.55 ng/ml Assay validation complete and acceptable
PK Assessment	AUC0-t, AUC0-∞, Cmax, Tmax, t1/2, cumulative and total urinary excretion of selegiline and three metabolites
PD Assessment	• Excretion of PEA is used as a marker for the inhibition of MAO-B. • MHPG in plasma and 5-HIAA in urine was used as a marker for the inhibition of MAO-A • Oral tyramine pressor threshold measurement as a marker for inhibition of MAO-A, pre-treatment doses were determined over a period of Day –7 to Day –5, during treatment over a period of Day 14-16. Tyramine pressor endpoint ratio = Pre-treatment tyramine threshold dose/ tyramine threshold dose during selegiline treatment

Pharmacokinetic Results:

Selegiline mean (%CV) pharmacokinetic parameters:

Parameter	Zydis 1.25 mg		Eldepryl 10 mg	
	Day 1	Day 28	Day 1	Day 28
AUC0-∞ (ng.h/ml) day 1 AUC0-t (ng.h/ml) day 28	0.70 (52)	6.39 (51)	1.09 (67)	11.41 (75)
Cmax (ng/ml)	1.44 (61)	3.38 (40)	1.29 (67)	4.15 (61)
Tmax (h)	0.20 (20)	0.27 (41)	0.61 (38)	0.81 (51)
MRT (h)	1.24 (70)	5.02 (18)	1.74 (68)	5.71 (24)
T1/2 (h)	2.08 (83)	10.04 (29)	1.87 (106)	10.67 (55)

- After Zydis® selegiline, mean peak plasma concentrations rose more rapidly (~15 minutes) on both Days 1 and 28 as compared to Eldepryl®.
- There was a 2-3 fold increase in Cmax on Day 28 as compared to Day 1 for both Zydis® and Eldepryl® formulations.
- There was a 9-10 fold increase in AUC on Day 28 as compared to Day 1 for both Zydis® and Eldepryl® formulations.
- There was no statistical difference between 1.25 mg Zydis and 10 mg Eldepryl® for Cmax and AUC on both Day 1 and 28, due to high variability.
- After a single dose, the dose normalized AUC from the Zydis® formulation was 4.1-7.9 times that of Eldepryl®.
- After multiple doses, the dose normalized AUC from the Zydis® formulation was 3.7-6.9 times that of Eldepryl® on Day 28.
- T1/2 and MRT on Day 1was much shorter than that on Day 28 for both formulations.

NDMS mean (%CV) pharmacokinetic parameters:

Parameter	Zydis 1.25 mg		Eldepryl 10 mg	
	Day 1	Day 28	Day 1	Day 28
AUC0-∞ (ng.h/ml) day 1 AUC0-t (ng.h/ml) day 28	2.89 (45)	10.08 (67)	67.89 (41)	111.63 (47)
Cmax (ng/ml)	1.55 (61)	2.38 (57)	23.45 (27)	29.79(37)
Tmax (h)	0.88 (39)	0.96 (47)	0.92 (27)	0.90 (52)
MRT (h)	3.52 (0.4)	6.64 (0.2)	6.29 (0.16)	6.22 (0.27)
T1/2 (h)	3.11 (0.54)	10.29 (0.40)	6.80 (0.15)	9.30 (0.46)

- On Day 1, following administration of Zydis formulation, the AUC and Cmax of NDMS were much lower (23 and 15 fold lower, respectively) as compared to the Eldepryl® formulation.
- On Day 28, following administration of Zydis formulation, the AUC and Cmax of NDMS were much lower (11 and 12 fold lower, respectively) as compared to the Eldepryl® formulation.
- There was an increase in Cmax and AUC of NDMS on Day 28 as compared to Day 1 for both Zydis® and Eldepryl® formulations.
- T1/2 and MRT on Day 1 were much shorter than that on Day 28 for both formulations, although were similar between treatment and treatment days.

L-MA mean (%CV) pharmacokinetic parameters:

Parameter	Zydis 1.25 mg		Eldepryl 10 mg	
	Day 1	Day 28	Day 1	Day 28
AUC0-∞ (ng.h/ml) day 1 AUC0-t (ng.h/ml) day 28	17.77 (36)	40.62 (28)	282 (26)	358 (31)
Cmax (ng/ml)	0.82 (32)	2.58 (25)	12.97 (19)	26.25 (29)
Tmax (h)	2.0 (56)	3.13 (54)	2.63 (58)	2.04 (72)

MRT (h)	22.30 (18)	10.10 (14)	20.57 (17)	9.74 (14)
T1/2 (h)	15.12 (19)	19.50 (27)	13.77 (17)	16.08 (19)

- On Day 1, following administration of Zydis formulation, the AUC and Cmax of L-MA were much lower (~16 fold lower) as compared to the Eldepryl® formulation.
- On Day 28, following administration of Zydis formulation, the AUC and Cmax of L-MA were much lower (9 and 10 fold lower, respectively) as compared to the Eldepryl® formulation.
- No significant difference in Tmax, T1/2 between treatments and treatment days.

L-AMP mean (%CV) pharmacokinetic parameters:

Parameter	Zydis 1.25 mg		Eldepryl 10 mg	
	Day 1	Day 28	Day 1	Day 28
AUC0-∞ (ng.h/ml) day 1 AUC0-t (ng.h/ml) day 28	9.27 (49)	18.45 (22)	130.92 (35)	152.59 (37)
Cmax (ng/ml)	0.25 (32)	1.0 (27)	3.53 (19)	8.60 (30)
Tmax (h)	3.88 (82)	4.67 (59)	4.75 (55)	3.04 (58)
MRT (h)	41.70 (0.82)	11.13 (0.03)	34.55 (0.27)	10.58 (0.15)
T1/2 (h)	28.70 (0.84)	32.14 (0.43)	23.35 (0.27)	28.25 (0.46)

- On Day 1, following administration of Zydis formulation, the AUC and Cmax of L-AMP were much lower (~14 fold lower) as compared to the Eldepryl® formulation.
- On Day 28, following administration of Zydis formulation, the AUC and Cmax of L-AMP were much lower (~8 fold lower, respectively) as compared to the Eldepryl® formulation.
- No significant difference in Tmax, T1/2 between treatments and treatment days.

Urinary excretion of parent and metabolites combined:

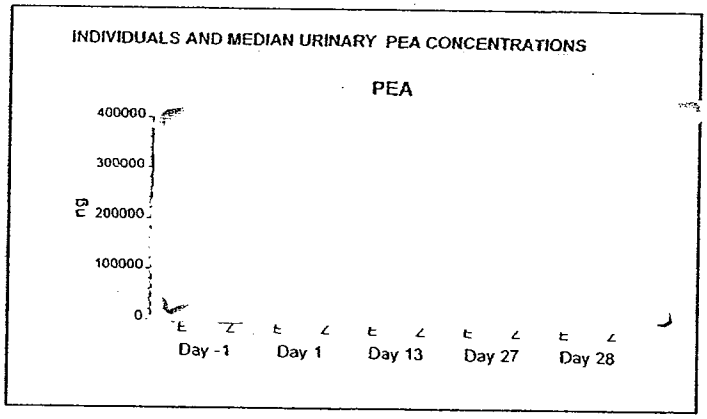
Mean (SD) percent of selegiline dose excreted in the urine is as follows:

Treatment Days	Zydis 1.25 mg	Eldepryl 10 mg
	% of selegiline daily dose	
Day 1	14.48 (4.36)	28.38 (8.89)
Day 27	37.63 (7.19)	43.20 (11.87)
Day 28	50.32 (12.52)	42.71 (12.25)

- On Day 1, less of the selegiline dose was excreted in the urine as parent and/or metabolites compared to Days 27 and 28.
- On Day 27 and 28, the percent of the selegiline dose excreted in the urine was similar for the two formulations.

Pharmacodynamic Results:

Urinary excretion of PEA:

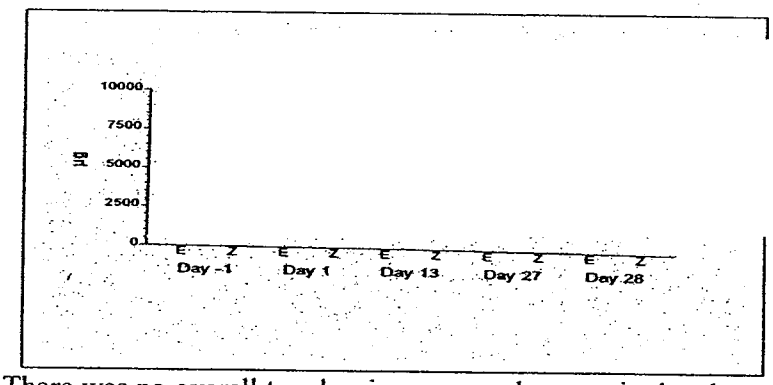


b(4)

- The urinary excretion of PEA increased post dosing on Days 1, 13, 27 and 28 compared to predosing Day –1.
- The increase in 24 hour urinary excretion of PEA was greater for Eldepryl as compared to the Zydis formulation. The plasma AUC of selegiline was also higher after the Eldepryl formulation.

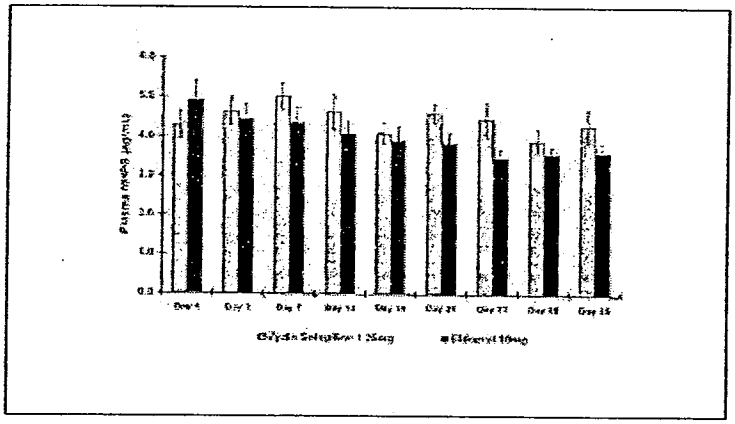
Urinary excretion of MHPG and 5-HIAA:

- Urinary excretion 5-HIAA was unchanged from pre to post dosing (see figure below)



b(4)

- There was no overall trend as increase or decrease in the plasma MHPG concentrations although changes in post dose concentrations were observed (see figure below)
- The largest difference between pre and post dose concentrations of MHPG was on Day 27



Tyramine Pressor Response:

Tyramine pressor ratio threshold data for individual subjects is shown in the following Table:

Subject No.	Treatment group	Tyramine threshold dose (mg) Pre-treatment	Tyramine threshold dose (mg) Day 14/15/16	Tyramine Pressor Ratio
96/014/001	Eldepryl 10mg			2.5
96/014/003				1
96/014/006				1.3
96/014/008				6
96/014/009				1.7
96/014/011				1.3
96/014/014				1.7
96/014/017				4
96/014/018				16
96/014/019				2
96/014/023				1.4
96/014/024				1.5
Mean		408.33 (436.36)	14.58 (225.00)	3.37 (3.58)
SD		144.34 (112.01)	135.03 (136.47)	4.23 (4.36)
Median		400 (400)	200 (200)	1.7 (1.7)
Minimum		100 (300)	25 (25)	1 (1.3)
Maximum		700 (700)	500 (500)	16 (16)
95/014/002	Zydis 1.25mg			1
96/014/004				4
96/014/005				4
96/014/007				1
96/014/010				2
96/014/012				1.5
96/014/013				0.6
96/014/015				1
96/014/016				1.8
96/014/020				1.4
96/014/021				14
96/014/022				1.7
Mean		491.67 (500.00)	312.50 (331.82)	2.83 (2.73)
SD		144.34 (148.32)	159.72 (152.11)	3.68 (3.85)
Median		400 (400)	400 (400)	1.6 (1.5)
Minimum		300 (300)	50 (50)	0.6 (0.6)
Maximum		700 (700)	500 (500)	14 (14)

b(4)

b(4)

Figures in parentheses exclude subjects 96/014/003 and 96/014/004 who showed atypical tyramine pressor responses.

- The tyramine dose that caused threshold increase in systolic blood pressure (>30 mm Hg) was generally decreased during treatment with selegiline in both Zydis and Eldepryl® treatment groups. The pressor threshold for 4 subjects was unaffected by selegiline treatment (subjects 003, 002, 007 and 015). Subject 013 required higher tyramine dose during Zydis selegiline treatment.
- The sponsor excluded subjects 003 and 004 from the analysis because it was felt that their response was atypical. The reason for calling them atypical is unclear.
- Three subjects in the Zydis group had the tyramine pressor ratio of >3 (4, 4 and 14) and three subjects in the Eldepryl® group had ratio's greater than 3 (6, 4 and 16). These subjects did not have PK parameters that were any different from the rest of the population.
- Overall, the tyramine pressor ratio from Zydis 1.25 mg was similar to Eldepryl® 10 mg in subjects between the ages 48-70 years (mean ± SD ratio 2.83 ± 3.68 and 3.37 ± 4.23 respectively for Zydis and Eldepryl)

Conclusions:

Pharmacokinetics:

- Zydis 1.25 mg is absorbed with peak concentrations reaching at ~15 minutes post dose as compared to 1-1.5 hours for Eldepryl® 10 mg.
- All previous studies showed that the Zydis formulation always had higher concentrations than Eldepryl®. On the contrary, this study showed that 10 mg Eldepryl® had higher mean concentration than 1.25 mg Zydis. The sponsor's explanation is that the Eldepryl® group of subjects included slow metabolizers of selegiline. However, this appears to be mere speculation, as the sponsor did not attempt to characterize the slow/fast metabolizers for the individual subjects.
- On a dose normalized basis the Zydis formulation would produce a 3.7-6.9 times higher exposure than Eldepryl®.
- The concentrations of parent drug after Zydis selegiline 1.25 mg were on a dose related basis, higher than Eldepryl®, while the metabolite concentrations were either similar or lower, suggesting the Zydis formulation undergoes less first pass metabolism.

Pharmacodynamics:

- Both Zydis® 1.25 mg and Eldepryl® 10 mg had higher excreted of PEA with treatment, suggestive of MAO-B inhibition by selegiline. The amount of PEA excreted in the urine with Zydis was greater with Eldepryl®.
- The tyramine dose that caused threshold increase in systolic blood pressure (>30 mm Hg) was generally decreased during treatment with selegiline in both Zydis and Eldepryl® treatment groups. Both Zydis 1.25 mg and Eldepryl 10 mg had similar tyramine pressor ratios. Three subjects in each group had the tyramine pressor ratio of

>3, suggesting similar risk for a cheese reaction with both Zydis 1.25 mg and Eldepryl® 10 mg. This study showed a tyramine pressor ratio of 2.83 with 1.25 mg Zydis, however, study 101 showed a tyramine pressor ratio of 6.69 with the same dose. This difference in the two studies cannot be explained. The risk of such reaction should be assessed by the reviewing Medical Officer.

- Plasma MHPG and urinary 5-HIAA did not show any definite effect on MAO-A inhibition.

Study: Z/SEL/95/007: Repeat dose study to assess the tolerability and pharmacokinetics of Zydis selegiline compared with selegiline administered as a standard tablet and to assess indirect measures of inhibition of monoamine oxidases A and B

This study has not been reviewed as the sponsor uses a 10 mg (2x5) Zydis selegiline dose compared to 10 mg (2x5) Deprenyl tablets (France) in this study. Another study has been conducted using 1.25 mg Zydis selegiline compared to 10 mg (2 x 5) Eldepryl Tablets, which are the relevant doses for this application.

DISSOLUTION/DISINTEGRATION

The dissolution method used by the sponsor is given below:

Apparatus:	USP method II
Media:	0.1 M HCl
Volume:	500 mL
Speed of rotation:	100 RPM
Temperature:	37°C ± 5°C
Analysis:	HPLC with UV detection

The sponsor conducted dissolution tests with Zydis 1.25 mg tablets in all three media, as shown in the Tables below. The dissolution was rapid in all media [redacted] b(4)
[redacted] The sponsor proposes to include disintegration specifications in lieu of dissolution specifications.

Zydis 1.25 mg in 0.1M HCl

Time Point (mins)	% Release						
	1	2	3	4	5	6	Mean
2	103	102	104	102	103	107	103.5
6	103	102	104	103	103	107	103.7
10	102	101	104	104	104	108	103.8
15	103	102	106	104	103	107	104.2
20[1]	102	102	103	103	104	108	103.7

[1] After the 15 minute time point, the stirrer speed was increased to [redacted] rpm for [redacted] b(4)

pH 4.5 Buffer

Time Point (mins)	% Release						
	1	2	3	4	5	6	Mean
2	104	105	102	102	102	104	103.2
6	104	105	102	101	101	103	102.7
10	105	106	102	101	101	104	103.2
15	105	106	102	101	101	103	103.0
20[1]	104	105	101	102	102	105	103.2

[1] After the 15 minute time point, the stirrer speed was increased to [redacted] rpm for [redacted] b(4)

pH 6.8 Buffer

Time Point (mins)	% Release						
	1	2	3	4	5	6	Mean
2	100	102	100	102	100	102	101.0
6	100	102	99	103	100	102	101.0
10	100	103	100	103	101	102	101.5
15	101	102	100	103	100	102	101.3
20[1]	100	102	100	103	101	99	100.8

[1] After the 15 minute time point, the stirrer speed was increased to [redacted] rpm for [redacted] b(4)

These Tables show that dissolution of Zydis selegiline 1.25 mg is independent of pH and that complete and rapid release of the active is achieved in [redacted] The following batches were also tested. b(4)

Table 10 Dissolution of Commercial Batch 01D02IC stored for 3 months at 25°C/60%RH

Time Point (mins)	% Release[1]						
	1	2	3	4	5	6	Mean
2	103	102	103	102	104	103	102.8
6	103	102	102	103	104	103	102.8
10	104	102	102	103	103	103	102.8
15	104	102	103	103	104	102	103.0
20[2]	104	103	102	102	104	102	102.8

[1] 0.1M Hydrochloric Acid
[2] After the 15 minute time point, the stirrer speed was increased to [redacted] rpm for [redacted] b(4)

Table 11 Dissolution of Commercial Batch 01D02IC stored for 3 months at 40°C/75%RH

Time Point (mins)	% Release[1]						
	1	2	3	4	5	6	Mean
2	101	102	99	99	99	99	99.8
6	101	101	99	100	99	99	99.8
10	102	102	99	100	98	99	100.0
15	101	102	99	100	99	99	100.0
20[2]	101	102	98	101	99	99	100.0

[1] 0.1M Hydrochloric Acid
[2] After the 15 minute time point, the stirrer speed was increased to [redacted] rpm for [redacted] b(4)

Table 12 Dissolution of Clinical Batch 01C07ZP

Time Point (mins)	% Release[1]						
	1	2	3	4	5	6	Mean
2	102	103	103	104	104	103	103.2
6	102	103	102	104	104	103	103.0
10	103	103	103	105	105	104	103.8
15	104	103	104	106	104	104	104.2
20[2]	103	102	103	105	104	104	103.5

[1] 0.1M Hydrochloric Acid
[2] After the 15 minute time point, the stirrer speed was increased to [redacted] rpm for [redacted] b(4)

These data demonstrate that time, elevated temperature and pH have no impact on the dissolution profile of Zydis selegiline.

Disintegration method:

To ensure that rapid dispersion characteristics are consistent from batch to batch, the sponsor proposes disintegration of the product as part of the release specification.

Two apparatuses were used with the same disintegrating mechanism. b(4)
Apparatus A was used for units less than in diameter. This apparatus include Zydis tablets were randomly selected to be tested. Disintegration time was recorded when the last tablet has disintegrated. Apparatus B was used for tablets . in diameter b(4)

Acceptance Criteria: not more than b(4)

This is acceptable as all the pivotal bio batches and the batches used in pivotal Phase 3 studies meet the acceptance criteria. The sponsor did not provide any data related to the discriminatory ability of the disintegration method, however, since both dissolution b(4) and disintegration are so rapid, the need for justification would not be necessary in this case.

The disintegration of the tablets from the batches used in biostudies and the phase 3 studies in shown in the following Table.

Disintegration Time	Study AN17933-101	Study Z/SEL/96/014	Study Z/SEL/97/025	Study Z/SEL/97/025
	2 seconds	1.5 seconds	1.4 seconds	1.6 seconds

ANALYTICAL VALIDATION

Selegiline in Plasma

Method: Gas Liquid Chromatography/mass spectrometry
Limit of Quantitation: 0.01 ng/mL in plasma.
Linearity: Range 0.01-5.0 ng/mL
Accuracy: % Error less than 6%, Inter-assay % CV less than 7.9%. Intra-assay % CV less than 13.7%.
Precision: Low control % CV less than 5.6%, medium control % CV less than 4.1%, high control % CV less than 6.5%.
Recovery: 55.6-66.7%
Freeze-thaw cycles: 3 cycles, % CV less than 5.8%
Benchtop Stability: 48 hours
Long term stability: 12 months

Selegiline in Urine

Method: Gas Liquid Chromatography/mass spectrometry
Limit of Quantitation: 1 ng/mL in plasma.
Linearity: Range 1-5 ng/mL
Accuracy: Inter-assay % CV less than 6.2%. Intra-assay % CV less than 11.6%
Precision: Low control % CV less than 3.7%, medium control % CV less than 2.7%, high control % CV less than 4.2%.
Recovery: 88.7-90%
Benchtop Stability: 96 hours
Long term stability: 12 months

APPENDIX C

PHARMACOMETRICS REVIEW

Pharmacometrics Review

NDA:	**21479-Vol(1.105; 1.025-1.030)**
Compound:	**Selegiline**
Submission Date:	**3/29/02**
Sponsor:	**Elan Pharmaceuticals**
Pharmacometrics Reviewer:	**Andre Jackson**
Pharmacometrics Team Leader:	**Jogarao Gobburu**

Background:

Selegiline is a selective inhibitor of cerebral monoamine oxidase type B (MAO-B), an enzyme responsible for dopamine metabolism in the brain. It is marketed in the United States and Europe as an adjunct therapy for the treatment of Parkinson's Disease (PD) in patients being treated with levodopa, who exhibit deterioration in the quality of their response to therapy. Zydis is a rapidly dissolving oral dosage form consisting of an open matrix of [redacted] This formulation dissolves quickly in the saliva on the tongue and does not require added water to aid disintegration, dissolution or absorption. b(4)

The firm conducted the following studies:

1. Z/SEL/97/026 - A primary efficacy trial
2. Z/SEL/97/025- Supportive trial
3. Z/SEL/96/014-Study to determine pharmacokinetic parameters
4. AN17933-Comparison of pressor effect of tyramine following Zydis selegiline and Eldepryl

The interaction between MAO (monamine oxidase) inhibitors (Zydis metabolites L-amphetamine and L-methamphetamine following Zydis doses of 1.25 , 2.5 mg and 5.0 mg was also studied in healthy subjects. These interactions were assessed by conducting "Tyramine Challenge Test" (or Tyramine Pressor Test) in healthy subjects in a controlled environment. The test involved monitoring of systolic blood pressure (SBP) and heart rate in response to tyramine administration before and after dosing with MAO inhibitor. The endpoint is the rise in SBP of 30 mmHg. The minimum tyramine dose required to raise the SBP to 30 mm Hg is called the tyramine pressor dose.

Sponsor's Methods:

Design/Data

Study Z/SEL/97/026 and Z/SEL/97/025

Identically designed studies conducted in 292 Parkinsonian patients who were receiving levodopa therapy. Patients were evaluated prior to taking their daily dose and again after taking the daily dose. A total of 201 subjects with concentration-time data were retained in the final data set.

Random plasma samples of selegiline were obtained at visit 6 (1 month after the start of therapy) and visit 10 (3 months after the start of active treatment or 6 weeks after the increase in dose to 2.5 mg). This resulted in a total of 310 samples. Study subjects ranged in age from 39-93 yrs. Subject demographics are presented in Table 1.

Table 1. Demographics of patients in the final data set employed for the PPK model estimation (n=201).

Variable	Mean	SD	Median	95% CI	Range
Weight	77.0	17.9	76.8	74.5, 79.6	43.1, 158.9
Age	67.5	9.5	68.0	66.2, 68.8	39.0, 93.0
SGPT	22.5	16.3	20.0	20.2, 24.8	8, 208
Bilirubin	12.4	4.8	11.0	11.7, 13.1	5, 31
SCr	84.6	18.7	83.0	81.9, 87.2	38.0, 144.0

The firm proposed doing a population analysis (PPK) to understand the influence of covariates on PPK parameters. The initial dosing was 1.25 mg daily and after 6 weeks of treatment patient doses were increased to 2.5 mg daily. Samples were taken prior to dosing. Few plasma samples were obtained from the two studies. Also sampling was limited to Cmin and based upon the firm's assessment rendered the subsequent population pharmacokinetic analyses as unreliable.

Study Z/SEL/96/014
This study was a repeat dose study to assess the PK of 1.25 mg Zydis selegiline compared to 10 mg Eldepryl (N=24). This study was done with frequent sampling. The study population ages ranged between 48-70 years.

Study AN17933-101

An open label study design was used in 60 male subjects. The primary objective was not tolerability, but to assess the relative selectivity of two formulations for MAO-A and MAO-B inhibition. Parallel groups were considered appropriate, as this was a multiple dose study and a crossover design was impractical. In addition, with parallel groups, the tyramine testing was only performed twice in each subject. The clinical model for testing inhibition of MAO-A is the oral tyramine threshold
test that detects the pressor response to tyramine. Tyramine is known to be present in cheese and suggested to be the substance responsible for the "cheese reaction" that lowers the threshold of cardiovascular response to ingested tyramine when ingested with MAO inhibitors.

Each subject received one of the following four treatment regimens, administered for a minimum of 12 days and a maximum of 14 days:
.Treatment A: Zydis Selegiline 1.25 mg OD
.Treatment B: Zydis Selegiline 2.5 mg OD
.Treatment C: Zydis Selegiline 5.0 mg OD
.Treatment D: Eldepryl® 5.0 mg BID orally(Reference selegiline product)

Subjects were screened for eligibility up to 14 days prior to the tyramine threshold test (up to 22 days prior to administration of the first dose of study drug). Tyramine threshold testing was started on Day 7, 8 days prior to study drug administration. Up to 7 doses of oral tyramine were administered on 3
successive days, with a maximum of 3 doses in any given day. No further doses of tyramine were administered once the threshold cardiovascular response had been observed (rise in systolic blood pressure in excess of 30 mmHg). Subjects were then admitted into the Clinical Unit on Day -1, when subject eligibility was reviewed and safety assessments made. Subjects were then enrolled onto the
study and given a randomization number. The subjects received the first dose of the assigned treatment in the morning of Day 1, and for those subjects receiving Treatment D, received the second dose four hours later. Subjects remained in the Clinical Unit overnight. Subjects randomized to Treatments A to C received their second dose of study drug in the morning of Day 2 and were discharged.
Subjects randomized to Treatment D received their third and fourth doses of study drug on Day 2 and were discharged. All subjects returned to the Unit each morning from Day 3 to 9 for dosing. On Day 9 the subjects remained resident in the Unit where they continued to receive the randomized treatment until
completion of the second tyramine threshold test, which was started on Day 12.

Pharmacokinetics

Initial Model

Data for this study were not sufficient to estimate the rate constant for absorption so data from study Study Z/SEL/96/014 done in 24 subjects with dense sampling was used to estimate the ka.

Structural Models

Data from studies Z/SEL/97/026 and Z/SEL/97/025 were use to build the Base model. The data were fit to a one and two-compartment body models. Objective function values were:

1-compartment model (-540.066)
2-compartment model (-581-179)

which indicated that the two-compartment model was best.

Covariate Models

The intersubject differences were estimated as DCL=CL-TVCL and DVV2= V2 – TVV2.
Where DCL was the difference in clearance, CL was the Bayesian estimate of clearance and TVCL was the typical estimate of CL from the population model. Similarly DVV2 was the difference in central compartment volume. These values were plotted against covariates of weight, SGPT, Serum creatinine, Bilirubin and gender that were considered

for inclusion in the model. Visit was also included in the model. Covariates were added to the model based upon an iterative process with parameter addition at the $p<0.05$ level which was reflected by a decrease in the objective function of 3.84 for a single degree of freedom. An irreducible model was constructed by removing covariates from the model one at a time. Covariates were only retained if their removal did not cause an increase in the objective function of greater than 10 points.

Random Effects Model

Random effects were investigated by the firm. Exponential random effects were used to describe the intersubject variation on the model fixed parameters (i.e., clearance-CL; volume of the central compartment-V2; intercompartmental clearance-Q and peripheral volume-V3).

A proportional error model containing terms for drug in the central compartment and for values below the level of quantitation (BQL) were used to explain residual variability.

Plasma concentrations that were below the LOQ were retained in the data set and were assigned a value of 0.005 ug/ml (1/2 LOQ of 0.01 ug/ml). These BLQ values were assigned a fixed inflated residual error (CV=50% based upon the LOQ) to give them less weight . Sigma was set at 0.000025.

Analysis was done using first-order conditional estimates with no interaction. Interoccassion variability was explored to allow for random variation on visit days 1 and 2.

Sponsor's Results

The results from the compartmental analysis from a 23 subject study with frequent samples collected at:
Predose, 0.25,0.5,0.75,1,1.5,2,2.5,3,4,6,12 and 24 hrs gave a value of $18hr^{-1}$(2.31min) however successful termination was not achieved. The firm then used $12hr^{-1}$ (3.4 min) which resulted in successful convergence. Details of this study were:

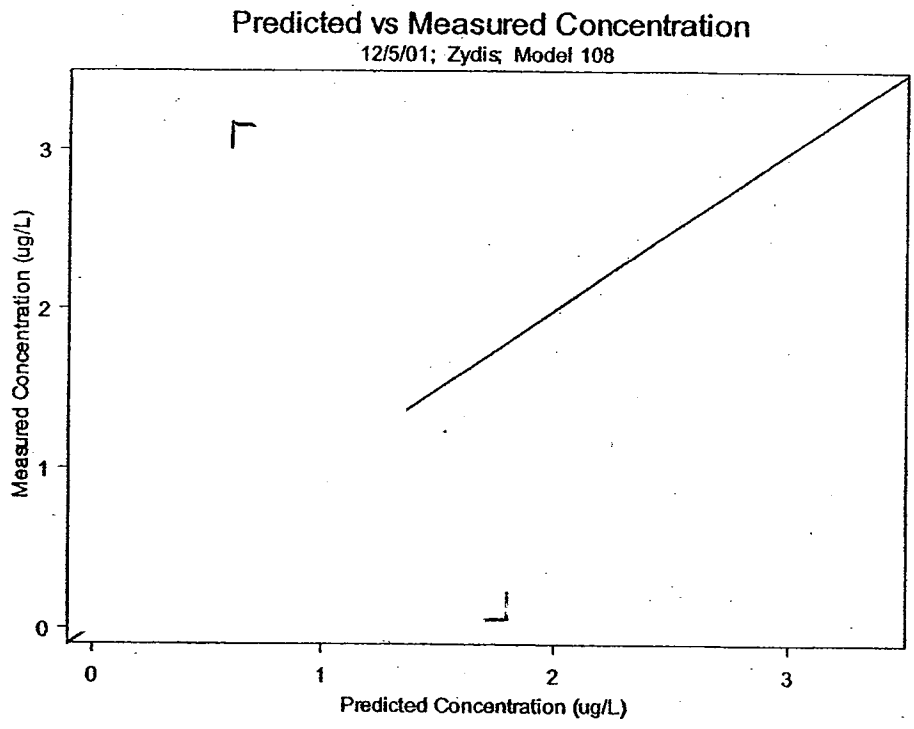
The final PK model (based upon sponsor report Z/SEL/97/PIV) was a 2compartment model with first order absorption. The population mean value of CL was estimated to be 866 L/h with a between-subject %CV of 55%. The intercompartmental CL was 299 L/h. The final PK parameters are presented in Table 2.

Table 2. Final parameter estimates for the irreducible model.

Parameter	Estimate	Std Error	95% CI
Theta1-Cl l/hr	866	137	592,1140
Theta5-Age, yrs	-7.02	1.81	-10.64, -3.62
V1-Central compartment volume, l	2190	380	1430,2950

V2-Peripheral compartment Volume, l	2200	575	1050,3350
Q-Intercompartmental clearance l/hr	299	77	145,453
ΩCL	0.302	0.0782	0.1456,0.4584
ΩV1	0.444	0.255	-0.066,0.054
CVCL	55%		38%,68%
CVV1	66%		Intractable solution
CVRESIDUAL VARIABILITY	53%	0.019	43%, 62%

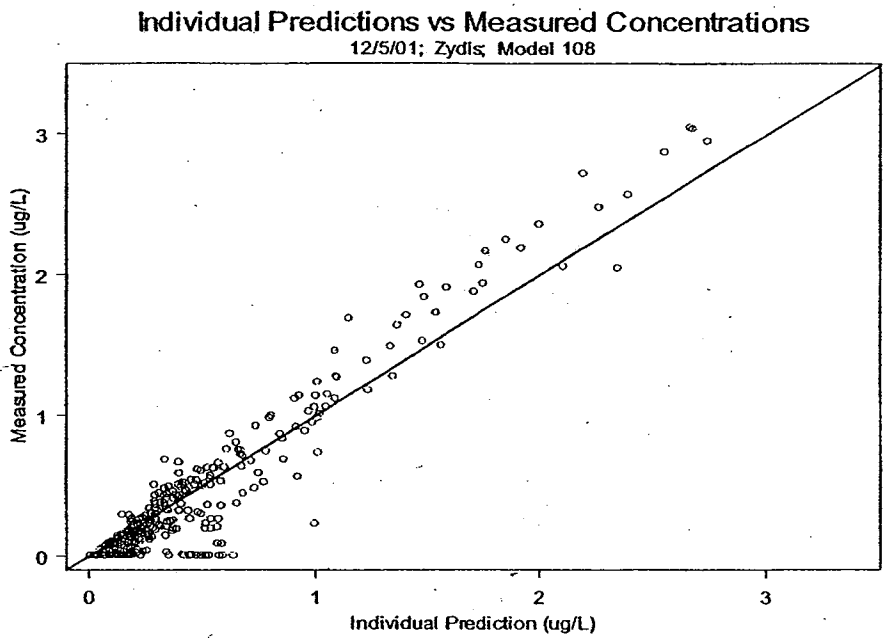
Figure 1. Predicted versus measured concentrations for the base PPK model.



b(4)

Figure 2. Plot of the individual predicted concentrations versus measured concentrations for the base PPK

model.



COVARIATE ANALYSIS

The covariates for age and weight seemed to be influenced by the differences in clearance. The data is presented in Figures 3 and 4.

Figure 3. Plot of the difference between the individual clearance and the population clearance versus weight. DCL (L/hr) is the difference between the Bayesian estimate of clearance and the subject's typical value for clearance.

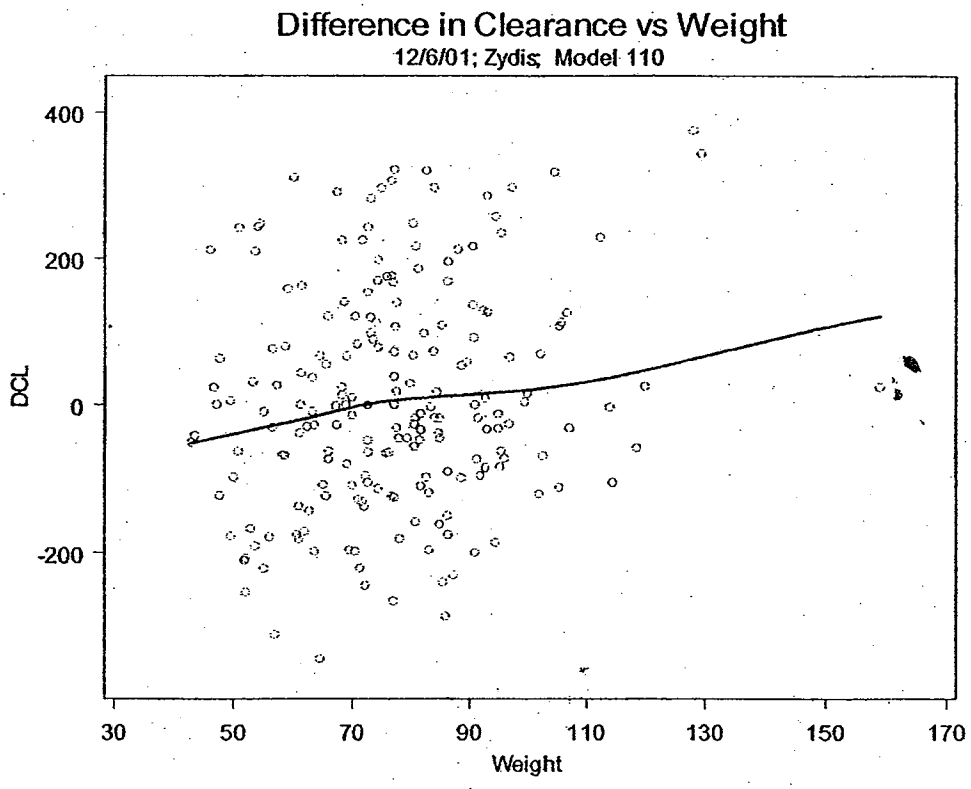
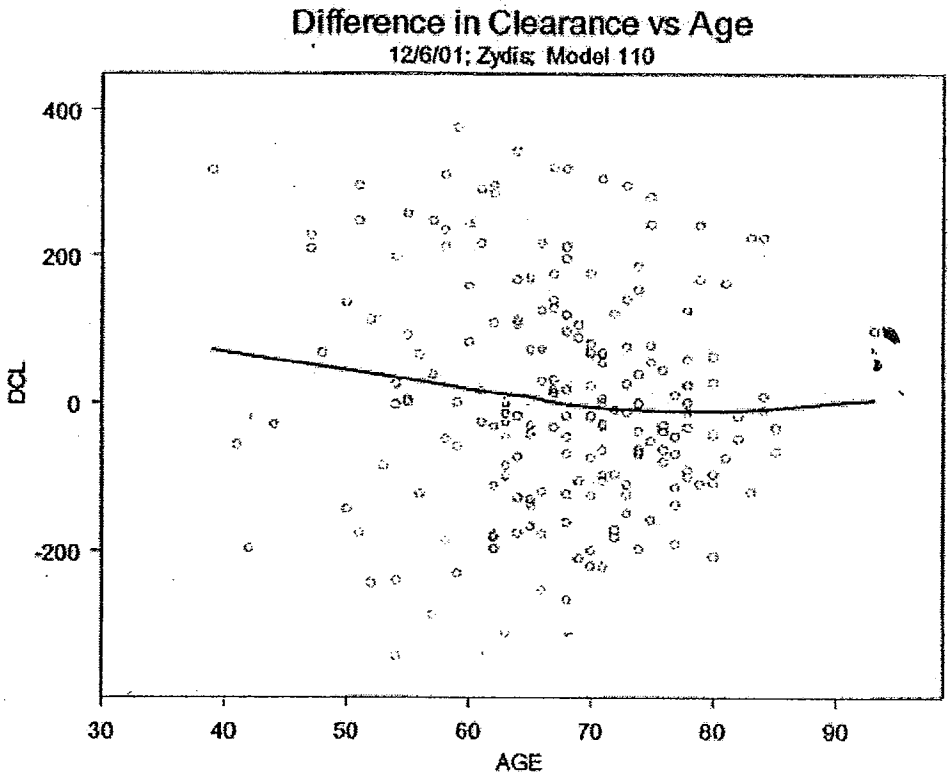


Figure 4. Plot of the difference between the individual clearance and the population clearance versus age. DCL (L/hr) is the difference between the Bayesian estimate of clearance and the subject's typical value for clearance.



Meta Analysis Effect of Age:

No formal age effect studies have been conducted for this application by the sponsor. All pharmacokinetic studies were conducted in healthy subjects between the ages 40- 75 years, except Study 101 which was conducted in young healthy subjects between the ages 18-44 years. Selegiline mean (SD) pharmacokinetic parameters from a cross study comparison after administration of single and multiple doses of 1.25 mg and 2.5 mg Zydis selegiline in the elderly and the young subjects is shown in the following Table 3:

Table 3. Comparison of pharmacokinetic parameters across studies with respect to age.

Treatment	Study No.	Mean Age	N	Day 1		Steady State	
				Cmax	AUC0-∞	Cmax	AUC0-24
Zydis 1.25 mg	023	54.1 years	24	1.12 (0.768)	0.525 (0.252)	NA	NA
	003	50.9 years	23	2.36 (1.14)	1.31 (0.66)	NA	NA
	014	62.6 years	24	1.44 (0.88)	0.70 (0.37)	3.36 (1.36)	6.39 (3.26)
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Zydis 2.5 mg	003	50.9 years	23	3.38 (2.44)	2.29 (1.16)	NA	NA
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

*AUC0-t

The data shows a slightly higher Cmax and AUC(0-inf) on day 1 for the younger subjects but not at steady-state. Due to the large variability in the data the results are difficult to interpret.

PHARMACODYNAMICS

The pharmacodynamic data was obtained from a multiple dose pharmacokinetic study in healthy subjects (ANI 7933-101). This study was conducted to assess the relative selectivity of Zydis® selegiline 1.25, 2.5 and 5 mg and Eldepryl® 5 mg BID for MAO-A and MAO-B based upon the subject's pressor response to orally administered tyramine. MAOs are intracellular enzymes widely distributed throughout the body. In humans, intestinal MAO is predominantly Type A, while that in the brain is Type B.

Markers for MAO-A inhibition:

The clinical model for testing MAO-A inhibition is the oral tyramine threshold test that detects the pressor response to tyramine. The enzyme metabolizes tyramine therefore, any increase in the pressor effect of tyramine (i.e., sensitivity to tyramine to meet the threshold systolic blood pressure increment of> 30 mm Hg) would indicate non-specific inhibition of MAO-A ("Cheese reaction") . In the presence of an MAO inhibitor, the tyramine in cheeses is responsible for lowering the threshold for cardiovascular responses to ingested tyramine. This test forms the basis of the tyramine challenge.

Design/Data

The details of the study design and methodology for PD assessment are as follows:
Study Design Open label, randomized, multiple dose, parallel group study for 12-14 days.

Study Population :	N= 63 enrolled, 60 completed healthy subjects
Gender:	60 M
Ages:	18-44 yr. (mean 27.6 yr.), mean age in each group was similar
Weight:	57-93 kg (mean 72.4 kg)
Race:	51 White, 7 Afro Caribbean and 4 Asian, 1 other

Treatment Groups:
A: Zydis® seligiline 1.25 mg QD before breakfast without water for 14 days (N=15 enrolled, 14 completed)

B: Zydis® seligiline 2.5 mg (2 x 1.25) QD before breakfast without water for 14 days (N=16 enrolled, 15 completed)

C: Zydis® seligiline 5 mg QD (4 x 1.25) before breakfast without water for 14 days subjects refrained from swallowing after Zydis tablet had dissolved. (N=15 enrolled, 14 completed)

D: Eldepryl® selegiline Capsules 5 mg BID with second 5 mg given 4 hours apart from the first,

i.e. after breakfast and lunch, swallowed with 150 ml water for 14 days (US-Elan Pharm) N =17

Sampling:

Blood for selegiline, N-desmethyl-selegiline, L-methamphetamine and L-amphetamine were taken at pre-dose and 5, 10, 15, 30, 45, 60 minutes and at 1.5, 2, 2.5, 3, 4, 6, 12 and 24 hours post-dose on Days 1 and 10 for Treatments A, B and C.

At pre-dose and 15, 30, 60 minutes and at 1.5, 2, 4, 4.25, 4.4, 5, 6, 8,12 and 24 hours post-dose on Days 1 and 10 for Treatment D

Predose on Days 8 and 9 for all Treatments

One hour post dose on Day 12-14 for all Treatments

PK Assessment

AUC(0-t), Cmax, Tmax on Day 1 with Css,min, Css,max, Tss,max, Tss,min, tl/2, AUCT, λz, CL/F , PTF [Cmax-Cmin/Cavg] on day 10, i.e., peak trough fluctuation measured at steady-state.

PD Assessment.

Oral tyramine pressor threshold measurement, pre-treatment doses were determined over a period of Day -7 to Day -5, during treatment over a period of Day 12-14.

Methodology:
Baseline threshold test (Day –7 and -5):

Tyramine threshold testing started on Day -7. Up to 7 doses of oral tyramine (available as 25, 100 and 300 mg capsules) were administered on 3 successive days in ascending single doses, with a maximum of 3 doses on any given day. For the baseline threshold test, tyramine doses of 10, 20, 300, 400, 500, 600 and 700 mg were scheduled for administration. No further doses of tyramine were administered once the threshold cardiovascular response had been observed (rise in systolic blood pressure in excess of 30 mmHg). Subjects were then admitted in the Unit (Day -1)

During treatment threshold test (Days 12-14):

Tyramine doses of 25, 50, 100, 200, 300, 400, 500, 600 and 700 mg were scheduled for administration.
On each test Day, tyramine dose was given 2 hours apart, starting 30 min after dosing with selegiline

A repeat tyramine dose was given only if blood pressure returned to 10 mmHg above the pre-dose reference value for that Day.

Analysis:

Heart rate and supine blood pressure were measured at 5 minute intervals from 15 minutes before each dose of tyramine until 120 minutes after (or longer if blood pressure remained >10 mmHg above pre-dose reference value for that Day). Reference blood pressure would be an average of 3 values for each Day.

Systolic blood pressure greater than 60 mmHg above baseline are terminated by administering alpha-
adrenoreceptor blocking agent such as pentolamine or labetalol.

Tyramine pressor ratios were calculated using the following equation and compared between treatments:

Tyramine pressor endpoint ratio = Pre-treatment tyramine threshold dose/ tyramine threshold dose during selegiline treatment

Pharmacokinetic Results:

Table 4. Mean(±sd) Day 1 and Day 10 pharmacokinetic parameters for Selegiline and NDMS.

Treatment	Day1			Day 10				
	Cmax (ng/ml)	Tmax* (h)	AUC (ng.h/ml)	Css, max (ng/ml)	Css, min (ng/ml)	Tss,max* (h)	AUCτ (ng.h/ml)	PTF (%)
Zydis 1.25 mg QD	3.34 (1.68)	0.17 (0.17-0.27)	1.49 (0.77)	3.96 (1.90)	0.03 (0.03)	0.25 (0.17-0.50)	4.77 (2.29)	2051 (625)
Zydis 2.5 mg QD	4.47 (2.56)	0.18 (0.08-0.50)	2.44 (1.64)	4.37 (1.83)	0.05 (0.04)	0.25 (0.17-0.50)	6.52 (2.09)	1643 (533)
Zydis 5 mg QD	5.45 (3.24)	0.18 (0.10-0.50)	3.78 (2.03)	5.54 (3.01)	0.06 (0.04)	0.25 (0.17-0.78)	8.51 (2.74)	1485 (592)
Eldepryl 5 mg BID	1.12 (1.48)	4.55 (0.50-6.03)	1.93 (1.67)	1.73 (1.08)	0.09 (0.07)	1.00 (0.25-6.00)	8.32 (5.06)	604 (484)

*median (range)

NDMS:

Treatment	Day1			Day 10				
	Cmax (ng/ml)	Tmax (h)	AUCτ (ng.h/ml)	Css, max (ng/ml)	Css, min (ng/ml)	Tss,max (h)	AUCτ (ng.h/ml)	PTF (%)
Zydis 1.25 mg QD	1.22 (0.48)	1.00 (0.75-1.50)	2.07 (0.71)	2.06 (0.69)	0.04 (0.05)	1.00 (0.75-2.00)	8.66 (4.39)	677 (338)
Zydis 2.5 mg QD	4.02 (2.05)	1.00 (0.75-3.00)	8.03 (3.64)	6.07 (3.39)	0.16 (0.09)	1.0 (0.5-1.52)	22.13 (10.09)	665 (246)
Zydis 5 mg QD	7.36 (3.16)	1.00 (0.50-2.00)	17.14 (5.16)	10.10 (4.24)	0.19 (0.12)	1.00 (0.50-3.00)	32.29 (10.28)	759 (230)
Eldepryl 5 mg BID	10.65 (5.09)	1.50 (0.50-8.0)	64.03 (38.56)	14.56 (6.44)	1.00 (0.85)	1.50 (0.25-6.17)	100.96 (56.22)	363 (158)

*median (range)

Table 5. Mean(± sd) Day 1 and Day 10 pharmacokinetic parameters for L-amphetamine and L-methamphetamine.

L-AMP

Treatment	Day1			Day 10				
	Cmax (ng/ml)	Tmax (h)	AUC (ng.h/ml)	Css, max (ng/ml)	Css, min (ng/ml)	Tss,max (h)	AUCτ (ng.h/ml)	PTF (%)
Zydis 1.25 mg QD	0.20 (0.09)	1.80 (1.00-6.02)	1.49 (1.54)	1.19 (1.68)	0.28 (0.09)	3.0 (1.0-12.13)	11.92 (5.13)	156 (236)
Zydis 2.5 mg QD	0.58 (0.15)	4.00 (0.75-12.0)	8.0 (1.48)	1.78 (0.82	0.60 (0.26)	3.0 (1.0-6.0)	26.92 (7.92)	107 (51)
Zydis 5 mg QD	1.33 (0.28)	3.0 (1.0-6.0)	19.94 (3.78)	3.24 (0.60)	1.14 (0.39)	3.0 (0.926.0)	50.63 (10.42)	112 (38)
Eldepryl 5 mg BID	2.69 (0.65)	8.0 (4.5-23.98)	44.17 (8.28)	5.30 (1.07)	2.62 (0.59)	8.0 (0.50-12.0)	95.25 (16.90)	69 (22)

*median (range)

L-MA

Treatment	Day1			Day 10				
	Cmax (ng/ml)	Tmax (h)	AUC (ng.h/ml)	Css, max (ng/ml)	Css, min (ng/ml)	Tss,max (h)	AUCτ (ng.h/ml)	PTF (%)
Zydis 1.25 mg QD	0.62 (0.23)	1.50 (1.0-3.0)	5.68 (2.44)	1.78 (0.84)	0.51 (0.21)	2.00 (1.0-12.13)	24.45 (11.79)	125 (25)
Zydis 2.5 mg QD	1.86 (0.49)	1.50 (0.75-4.0)	20.17 (4.27)	4.29 (1.63)	0.93 (0.50)	2.02 (0.75-6.0)	53.88 (15.56)	151 (45)
Zydis 5 mg QD	5.0 (1.53)	1.50 (1.0-4.02)	57.49 (12.63)	8.76 (1.51)	2.17 (0.85)	1.26 (0.50-6.12)	113.76 (36.91)	150 (46)
Eldepryl 5 mg BID	8.37 (1.28)	8.00 (5.0-12.53)	131.34 (21.83)	16.23 (2.72)	5.12 (1.55)	6.0 (1.5-12.0)	254.98 (66.55)	109 (26)

Results

The tyramine challenge test which monitored the systolic blood pressure (SBP) and heart rate in response to tyramine administration before and after dosing with an MAO inhibitor. The endpoint was the rise in SBP of 30 mmHg. The minimum increase in tyramine dose required to raise the SBP to 30 mm Hg is called the tyramine pressor dose. The ratio of the pressor dose before and after administration of the MAO inhibitor is called the "Tyramine Sensitivity Factor" which is an index to assess change in cardiovascular sensitivity to tyramine.

The tyramine pressor doses obtained before and after Zydis® selegiline and Eldepryl® are presented in the following Tables 6-9.

Table 6. Tyramine pressor ratio: Zydis selegiline, 1.25 mg QD.

Subject	Pre-Treatment Tyramine Threshold Dose (mg)	During Treatment Tyramine Threshold Dose (mg) *	Tyramine Pressor Ratio
1			8.00
2			8.00
6			8.00
8			5.00
9			3.00
22			2.00
23			1.67
31			1.67
36			1.75
39			NR
41			24.00
50			1.25
55			12.00
57			1.25
61			16.00
N	15	14	14
Arithmetic Mean	460	179	6.69
SD	130	160	6.75
CV%	28	89	101
Median	500	100	4.00
Min	200	25	1.25
Max	700	400	24.00

b(4)

Table 7. Tyramine pressor ratio: Zydis selegiline, 2.5 mg.

Subject	Pre-Treatment Tyramine Threshold Dose (mg)	During Treatment Tyramine Threshold Dose (mg)	Tyramine Pressor Ratio
5			8.00
14			1.50
15			1.00
16			1.50
18			2.00
19			1.00
21			4.00
24			1.20
25			1.50
27			2.00
29			1.33
34			1.50
35			NR
44			12.00
54			1.25
60			1.67
N	16	16	16
Arithmetic Mean	358	232	2.78
SD	121	141	3.12
CV%	34	61	113
Median	350	200	1.50
Min	100	25	1.00
Max	600	500	12.00

b(4)

ND = Not done as subject was withdrawn prior to Day 12 for a positive ABT.
NR = No result
* = This dose caused an exact increase in systolic blood pressure of 30 mmHg

Table 8. Tyramine pressor ratio: Zydis selegiline, 5.0 mg

Subject	Pre-Treatment Tyramine Threshold Dose (mg)	During Treatment Tyramine Threshold Dose (mg)	Tyramine Pressor Ratio
4	[redacted]		6.00
10			2.00
11			2.00
17			2.50
28			12.00
28			1.50
30			2.00
38			2.00
40			1.50
43			12.00
46			NR
47			12.00
51			1.50
53			1.67
58			8.00
N	15	14	14
Arithmetic Mean	373	148	4.76
SD	105	92	4.35
CV%	28	62	91
Median	400	200	2.00
Min	200	25	1.50
Max	600	300	12.00

b(4)

ND = Not done as subject was withdrawn prior to Day 12 for a positive ABT.
NR = No result

Table 8. Tyramine pressor ratio: Eldepryl, 5.0 mg.

Subject	Pre-Treatment Tyramine Threshold Dose (mg)	During Treatment Tyramine Threshold Dose (mg)	Tyramine Pressor Ratio
3	[redacted]		2.00
7			8.00
12			8.00
13			8.00
20			12.00
32			5.00
33			8.00
37			10.00
42			6.00
45			10.00
48			3.00
49			2.00
52			1.00
56			1.25
59			8.00
63			20.00
65			3.00
N	17	17	17
Arithmetic Mean	376	104	6.78
SD	148	109	4.82
CV%	39	104	71
Median	400	50	8.00
Min	200	25	1.00
Max	600	400	20.00

b(4)

NA = Not applicable, as subject was withdrawn prior to Day 12.
NR = No result
* = This dose caused an exact increase in systolic blood pressure of 30 mmHg

SPONSOR'S STATISTICAL ANALYSIS

Survival analysis methods were used to compare pre-treatment and Days 12, 13, and 14 tyramine threshold between treatments, with dose required to achieve the tyramine threshold replacing time. The level of statistical significance was set at α=0.05 (two tailed test).

Survival analysis methods were used to compare tyramine threshold doses from the four treatments.
The tyramine threshold dose was the dose of oral tyramine required to achieve the tyramine threshold (i.e. threshold cardiovascular response defined as a rise in systolic blood pressure in excess of 30 mmHg). There were no censored observations.

Initially a survival analysis was performed using PROC LIFE TEST by the Kaplan Meier method comparing pre-treatment Tyramine threshold doses alone to determine whether the four treatment groups differed in their response to tyramine.

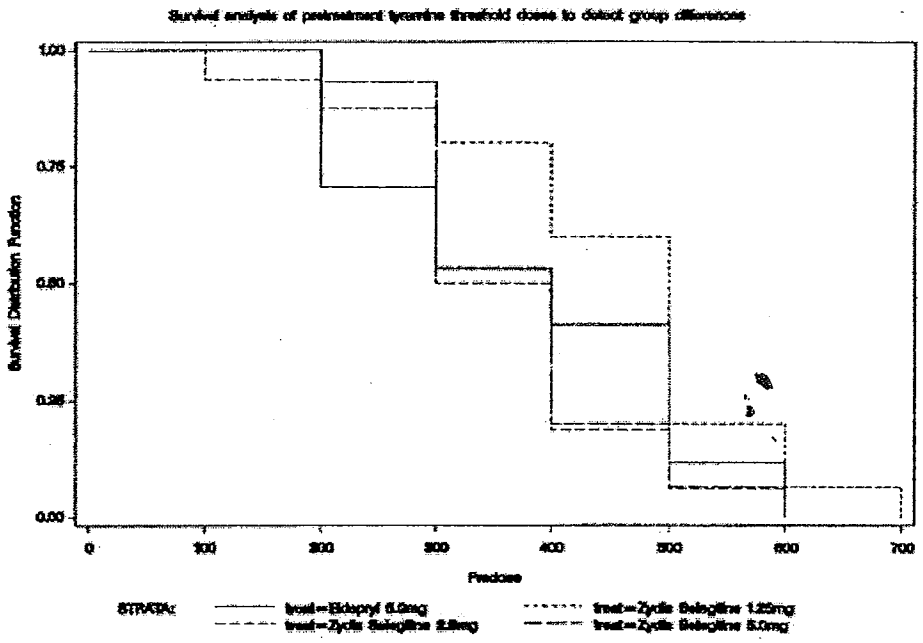
A second analysis was carried out on the tyramine threshold doses obtained during treatment (Days 12, 13, and 14) to compare the effect of the 4 treatments. Pre-treatment tyramine threshold doses were compared with the corresponding tyramine threshold doses reached during treatment, using a Wilcoxon Matched Pairs Signed Rank Sum Test. The analysis was performed stratified by dose group and also unstratified.

Additionally tyramine pressor ratios were compared between treatments by means of a one way ANOVA using PROC GLM in SAS. 95% confidence intervals were calculated for the difference in least squares means. The tyramine pressor ratio is defined as the ratio of the pretreatment tyramine threshold dose
to the tyramine threshold dose reached during treatment.

SPONSOR'S RESULTS

The results from the survival analysis could not detect any differences in the survival curves of the tyramine threshold doses between the 4 treatment groups prior to treatment administration.
The results are presented in Figure 1.

Figure 1. Survival analysis of pre-treatment tyramine threshold doses to detect group differences.



The mean tyramine threshold doses and corresponding standard errors of the individual treatment groups prior to treatment administration estimated by survival analysis are presented in Table 10.

Table 10. Mean tyramine threshold dose(mg) standard error(SE) , median , 25th, and 75th percentiles prior to treatment.

Treatment Group	Mean (SE) (mg Tyramine)	Median (mg Tyramine)	25th Percentile (mg Tyramine)	75th Percentile (mg Tyramine)
Eldepryl 5.0 mg BID	104.41 (26.45)	50	25	100
Zydis Selegiline 1.25 mg OD	178.57 (42.65)	100	25	300
Zydis Selegiline 2.5 mg OD	231.67 (36.31)	200	200	300
Zydis Selegiline 5.0 mg OD	148.21 (24.51)	200	50	200

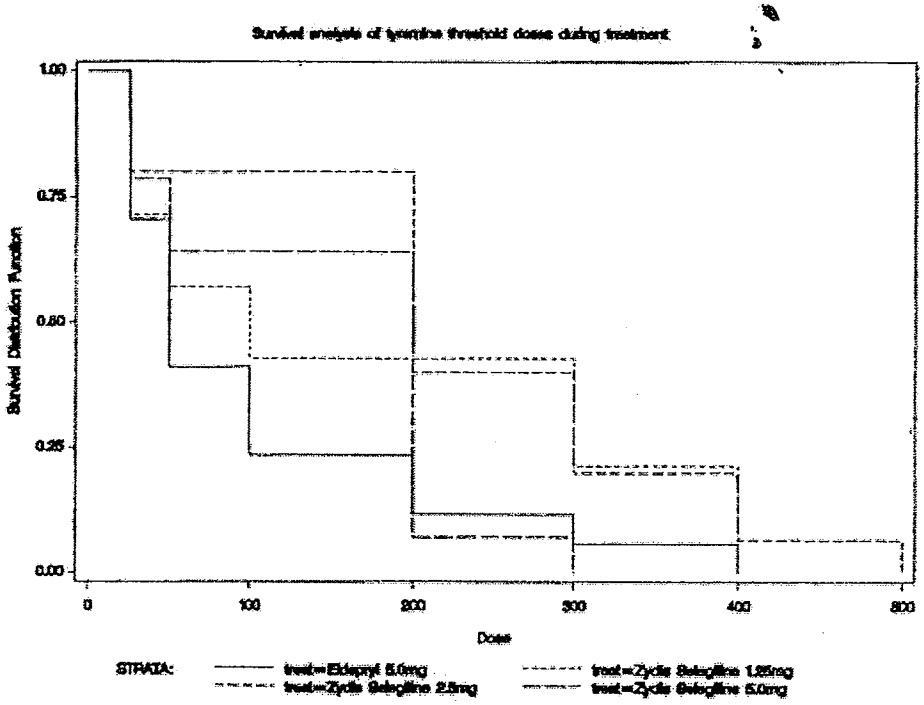
The results from the statistical comparison of the survival curves prior to treatment administration are summarized in Table 11.

Table 11. Tests for equality over Strata(Treatments) prior to treatment.

Test	Chi-square	p-value
Log rank	7.6502	0.0538
Wilcoxon	5.8685	0.1182
-2Log (LR)	5.2561	0.1540

Data source: Appendix 16.2.7.10

The tests for equality over strata (treatments) indicated no significant differences between treatment
groups. The mean tyramine threshold doses and corresponding standard errors of the individual treatment groups during treatment estimated by survival analysis are presented in Figure 2.



Zydis Selegiline 1.25 mg OD and Zydis Selegiline 2.5 mg OD showed the greatest right shift in survival curves suggesting a requirement for higher tyramine threshold doses compared with Eldepryl 5.0 mg BID or Zydis Selegiline 5.0 mg OD.

The results from the statistical comparison of pre-treatment tyramine threshold doses with tyramine threshold doses obtained during treatment are shown in Table 12.

Table 12. Results from Wilcoxin Matched pairs signed rank sum test.

Treatment	Median Difference (Point Estimate)	p-value
Eldepryl 5.0 mg BID	275.0	<0.0001
Zydis Selegiline 1.25 mg OD	287.5	0.0001
Zydis Selegiline 2.5 mg OD	100.0	0.0002
Zydis Selegiline 5.0 mg OD	200.0	0.0001

Data source: Appendix 16.2.7.10

This analysis tested the null hypothesis that the median difference between the pretreatment tyramine threshold dose and that during treatment equalled zero. In all four treatment groups tyramine threshold doses during treatment showed a statistically significantly reduction compared with pre-treatment tyramine threshold doses, indicating that all 4 treatments lowered the threshold of the cardiovascular effects of tyramine.

The lowest mean tyramine pressor ratio was observed on administration of 2.5 mg Zydis Selegiline ratio (arithmetic mean ratio = 2.76), whereas administration of Eldepryl resulted in the highest mean tyramine pressor ratio (arithmetic mean ratio = 6.78).

A statistical comparison of tyramine pressor ratios between treatments using ANOVA indicated that administration of 2.5 mg of Zydis Selegiline OD resulted in a statistically significantly lower ratio (LS mean ratio = 2.65, arithmetic mean ratio = 2.76) compared with administration of 5.0 mg Eldepryl® BID (LS mean ratio = 6.74 arithmetic mean ratio = 6.78). The 1.25 mg and 5.0 mg dose levels of Zydis Selegiline did not differ significantly from the control treatment (5.0 mg Eldepryl® BID). A statistically significant difference was also noted between 1.25 mg Zydis Selegiline OD (LS mean ratio = 6.91, arithmetic mean ratio = 6.69) and 2.5 mg Zydis Selegiline OD.

Table 13. Summary of the statistical comparisons of the tyramine pressor ratios.

Test		Reference			95 % CI		
Treatment	LS Mean	Treatment	LS Mean	Difference	Lower	Upper	p-value
Zydis Selegiline 1.25 mg OD	6.91	Eldepryl 5.0 mg BID	6.74	0.17	-3.48	3.83	0.2664
Zydis Selegiline 2.5 mg OD	2.65	Eldepryl 5.0 mg BID	6.74	-4.09	-7.60	-0.59	0.0230
Zydis Selegiline 5.0 mg OD	4.71	Eldepryl 5.0 mg BID	6.74	-2.03	-5.60	1.53	0.2578
Zydis Selegiline 1.25 mg OD	6.91	Zydis Selegiline 2.5 mg OD	2.65	4.27	0.45	8.09	0.0292
Zydis Selegiline 1.25 mg OD	6.91	Zydis Selegiline 5.0 mg OD	4.71	2.21	-1.62	6.04	0.2533
Zydis Selegiline 2.5 mg OD	2.65	Zydis Selegiline 5.0 mg OD	4.71	-2.06	-5.73	1.62	0.9244

REVIEWER'S ANALYSIS

The objective of the analysis done by the reviewer was to determine the relationship (if any) of the single and multiple dose pharmacokinetic parameters on the tyramine pressor ratios for predictive purposes.

Method:

Multiple linear regression was used to analyze the data. The following model was used:

PR_RATIO=css_max css_min tss_max tss_min lambda_z t_half auc_tau ptf (peak-to-trough fluctuation) dose cmax tmax auct

Regression was done using using pr_ratio and ln(pr_ratio) with backward selection of model variables.

Results:

The best fit final regression equations based upon backwards elimination was:

PR_RATIO= css_max tss_max tss_min lambda_z auc_tau ptf dose cmax t_max

However, none of the factors were significant at the p=0.01 level.

Reviewer Comments

1.Preliminary Analysis

A preliminary analysis of the PPK analysis was done by comparing the firms reported PPK results for clearance with results from study Z/SEL/96/014 to determine the consistency of the two analyses.

The final model presented by the firm was:

Cl = Theta1 + Theta5*age

The firm's estimated values were:
Theta1 = 866 l/h
Theta5 = -7.02 l/h

Therefore at the boundaries of the age range for their subjects 39-93 yr. The regression equations would be:
CL = 866 + (-7.02*39) = 592 l/h
CL = 866 + (-7.02*93) = 213 l/h

The mean data provided by the firm at steady-state for AUC0-tau was 6.39 ng.hr/ml at a dose of 1.25 mg. Calculation of CL=D/ AUC0-inf a value of 195 L/HR was obtained which is below the firm's lowest estimate based upon their PPK analysis (i.e., 213 L/HR). The mean Cl in a population with a mean age of 77 years is outside the range of clearance predicted by the population model.

2. The firm concluded in vol. 60 page 53 under heading 7 " the model indicates that as age increases clearance decreases and that selegiline clearance and apparent volume are high." However in volume 1 pg. 161 the firm states under the section PK data from patients with Parkinson's disease that" since the plasma samples for selegiline were taken prior to the patients daily dose of study medication, this limited the opportunity to obtain samples to a small window around 24 hrs and rendered attempts to generate PPK analyses unreliable." Therefore one would surmise that the data and analysis are not sufficiently reliable to make meaningful conclusions related to covariates.

3. The reviewer was able to duplicate the firm's analyses. However, the quality of the analysis was dependent upon the data which did not provide meaningful pharmacokinetic information. Therefore since the population analysis is inconclusive the results should have no impact on the label content.

4 Age meta analysis from other studies indicated that the data shows a slightly higher Cmax and AUC(0-inf) on day 1 for the younger subjects but not at steady-state. Due to the large variability in the data the results are difficult to interpret. The sponsor has stated in the label [redacted] b(4)
which would seem to indicate that the primary excretion route is metabolism which is consistent with age not being related to clearance.

5.The pharmacodynamic analysis of the data did not indicate any significant effect of any of the pharmacokinetic parameters on the tyramine challenge ratio. This result would indicate that in those instances that the sponsor found a statistically significant effect with the pooled data that it would not be possible to relate this difference to the observed pharmacokinetic parameters for Zydis or Eldepryl. A safety issue was raised by the Medical Officer related to the very high tyramine pressor ratios for Zydis and Eldepryl. His concerns raised questions about study conduct and possible validity of the ratios. These issues are addressed by the Medical Officer in his review.

Overall Conclusions

The results from the population pharmacokinetic modeling of Zydis in Parkinsonian patients did not indicate any effect of age and or weight in this subject group.

There was no clear relationship of the tyramine pressor ratios to any pharmacokinetic parameter for Eldepryl or Zydis.

Recommendation:

There should be no change in the current label for the use of Zydis in elderly Parkinsonian patients based upon the pharmacokinetic results of the study.

APPENDIX D

FILING AND REVIEW FORM

Appears This Way
On Original

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

NDA Number	NDA 21-479	Brand Name	Zydis® selegiline
OCPB Division I	HFD-860	Generic Name	Selegiline HCl
Medical Division	HFD-120	Drug Class	MAO-B inhibitor
OCPB Reviewer	Maria Sunzel, Ph.D.	Indication(s)	Parkinson's Disease, adjunctive therapy
OCPB Team Leader	Ramana Uppoor, Ph.D.	Dosage Form	Orally disintegrating tablet 1.25 mg strength
Date of Submission	March 29, 2002	Dosing Regimen	QD (a.m. before breakfast) 1.25 mg/day or 2.5 mg/ day
Estimated Due Date of OCPB Review	End Nov. 2002	Route of Administration	Oral
PDUFA Due Date	February 8, 2003	Sponsor	Elan Pharmaceuticals Inc
Division Due Date	Mid- Dec 2002	Priority Classification	3S (new formulation)

BACKGROUND:

The Agency has approved oral 5 mg immediate release tablets and capsules of selegiline. Currently, 11 companies have approved products, where Eldepryl® (5 mg tabl & capsules, oral solution, 5 mg/10 mL) is the reference listed drug (RLD) product (the Orange Book).

This new NDA concerns orally disintegrating selegiline tablets (1.25 mg strength) intended for [redacted] This formulation was developed to improve patient compliance, and to make it easier to swallow for patients who experience pain or difficulty in swallowing (dysphagia). Zydis selegiline tablets (open matrix of [redacted] should be taken in the fasting state, without water, [redacted] the tablet disintegrates within seconds in the mouth, and the drug is partially absorbed from the buccal mucosa. According to the sponsor, the pharmacokinetic (PK) studies have shown that this dosage form has a higher systemic bioavailability, since the 1st pass effect is less for this formulation compared to the currently marketed products (F=10%), as a result of mucosal absorption from the oral cavity. Therefore, the current standard daily dosing regimen of 10 mg (2x5 mg) selegiline, can be reduced to 1.25 to 2.5 mg with this new oral formulation (Zydis selegiline).

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The sponsor has performed 9 (6 single dose & 3 repeated dose) Phase I studies in approx. 150 healthy volunteers (exploratory PPK analysis from C_{ss} samples available in patients from combined data sets from 2 Phase III studies). Zydis selegiline tablets were studied in the dose range 1.25 - 5 mg. The sponsor also investigated taste & ease of swallowing in 1 additional study (patients, no PK sampling). The sponsor performed 2 clinical efficacy studies (placebo controlled 3-month trials, one study showed statistically significant improvement vs. placebo; the other one showed no improved response after active drug treatment compared to placebo treatment).

PK information from the submitted trials covers the following items:

- Bioequivalence/relative bioavailability (2x5 mg Zydis vs. 2x5 mg selegiline tabl; 1.25 mg Zydis vs. 2x5 mg RLD product; 5 mg Zydis vs. 5 mg oral solution, Eldepryl Syrup 5 mg/10 mL)
- Absorption - oral mucosa vs. GI tract (swallowed tablet vs. tablet kept in oral cavity)
- Food effects (5 mg Zydis vs. 2x5 mg RLD tabl, indirect MAO inhibition)
- PK single dose (1.25, 2.5, 5 mg Zydis tabl vs. 2x5 mg RLD tabl, indirect MAO inhibition)
- PK repeated doses (2x5 mg Zydis tabl/ 1.25 mg Zydis tabl/ 1.25, 2.5, 5 mg Zydis tabl vs. 2x5 mg selegiline, oral tyramine pressor tests & indirect MAO inhibition)

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	No. studies submitted	No. studies reviewed	Comments
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 & 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	6		
multiple dose:	X	3		
Patients-				
single dose:	-			
multiple dose:	-			
Dose proportionality -				
fasting single dose:	(X)			1 study: 1.25, 2.5, & 5 mg Zydis tabl. Incomplete block design
fasting multiple dose:	(X)			1 study: 1.25, 2.5, & 5 mg Zydis tabl. Parallel group study
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-			
In-vivo effects of primary drug:	-			
In-vitro:	-			
Subpopulation studies -				
ethnicity:	-			
gender:	-			See 'comments to the firm'
pediatrics:	-			Waiver request
geriatrics:	- (?)			See 'comments to the firm'
renal impairment:	-			
hepatic impairment:	-			
PD:				
Phase 2:	-			
Phase 3:	-			
PK/PD:				
Phase 1 and/or 2, proof of concept:	X			3 multiple dose studies: indirect MAO response, & pressor response to tyramine challenge
Phase 3 clinical trial:	-			
Population Analyses -				
Data rich:	-			
Data sparse:	X			PPK in patients (C_{min} only)
II. Biopharmaceutics				
Absolute bioavailability:	-			

Relative bioavailability -				
solution as reference:	X			5 mg Zydis vs. 10 mg/5 mL Eldepryl syrup
alternate formulation as reference:	X			2x5 mg or 1.25 mg Zydis vs conventional selegiline or RLD tablets as reference
Bioequivalence studies -				
traditional design; single dose:	-			
replicate design; single / multi dose:	-			
Food-drug interaction studies:	X			
Dissolution:	X			3 pH media
(IVIVC):	-			
Bio-waiver request based on BCS	-			
BCS class	-			
III. Other CPB Studies				
Genotype/phenotype studies:	-			
Chronopharmacokinetics	-			
Pediatric development plan	-			Pediatric waiver requested
Literature References	X			28 references
Total Number of Studies		9		

Filability and QBR comments		
	"X" if yes	Comments
Application filable?	X	
Comments sent to firm?	X	• Please provide the study-specific analytical reports for the 8 PK studies (all except Study AN17933-101) • Please provide a correct reference for the cross-study PK comparison with regard to old age that is included in the annotated label (lt. 6/vol 15/p 1 does not contain this comparison). • Please provide a cross-study PK comparison with regard to gender (Phase I studies in healthy subjects) • Please update the annotated label for all references to Item 6, to reflect the volume/page numbers according to the overall NDA volume numbers given in volume 1, p 2-14. • Please provide an extra desk copy of the combined report of Studies Z/SEL/97/025-026 including Appendix A-4 (PPK report). Please provide the data sets that were used for the NONMEM analysis electronically as SAS transport files. Please also include the control files used in the NONMEM analysis. • Please provide data sets (as SAS transport files) for the pharmacokinetic parameters (individual values) with the corresponding subject demographics from the studies that the pharmacokinetic information in the label is based on. • Please provide data sets (as SAS transport files) for the pharmacokinetic/ pharmacodynamic data (individual values: plasma selegiline concentrations, and the pharmacodynamic variables vs. time) for Study AN17933-101 • If the sponsor would like to schedule a telecon to discuss the formats of the requested data sets with the OCPB reviewers, please contact Ms. Wheelous. • Please submit the requested reports/data sets within 6 weeks, and the requested additional analyses within 12 weeks.
QBR questions (key issues to be considered)		• Are the analytical methods appropriately validated and documented? • Does the submitted data support the proposed label text? • Are the proposed dosing recommendations appropriate from a PK point of view (8-fold decrease in oral dose)? Is the study data adequate to support the dosing instructions to enhance buccal absorption [redacted] Were special dosing instructions given in the Phase III studies (do not swallow within 2 min after tablet disintegration)? • Is the exploratory PPK analysis adequately conducted? • Is the proposed *in vitro* disintegration method acceptable? (The sponsor proposes that no dissolution specifications are set due to the very rapid disintegration/dissolution of the proposed tablets - dissolution [redacted] in 3 pH media).
Other comments or information not included above		The food study was conducted with a 5 mg Zydis tablet (only 1.25 mg tabl intended to be marketed). The study is considered acceptable, since the 5 mg tablet only differ from the 1.25 mg with respect to amount of active drug. The sponsor has performed analyses of selegiline and metabolites (plasma, urine, saliva) as well as bio marker analyses (e.g. 5-HIAA) in various biological fluids. The sponsor has performed most PK studies on Zydis tablets from a batch size of [redacted]. The to-be-marketed (TBM) batch size seems to be [redacted] batch was partially used in one clinical efficacy trial (Study Z/SEL/97/027) and one PK/PD Phase I trial (Study AN17933-101). The primary stability validation batches have not been used in any clinical trials (in part, the same drug substance lots were used in the clinical trials & these stability batches of the TBM formulation). The sponsor has provided published references (28 articles) on the pharmacokinetics and pharmacodynamics of selegiline. At the filing meeting (5/15/02) it was made clear that the PK/PD analysis will not be used as supportive information for efficacy (will be based on empirical Phase III results). However, the PK/PD analysis will be interesting for the clinical safety evaluation.
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

b(4

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cc: NDA 21-479, HFD-850 (Electronic Entry /Lee), HFD-120 (Wheelous), HFD-860 (Mehta, Uppoor, Marroum, Sunzel)

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/s/

Veneeta Tandon
1/17/03 01:51:26 PM
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Andre Jackson
1/17/03 01:55:36 PM
BIOPHARMACEUTICS

Jogarao Gobburu
1/17/03 01:56:46 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
1/17/03 02:12:53 PM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 860/870/880)** **Tracking/Action Sheet for Formal/Informal Consults**

From: **Ronald E. Kavanagh, BS Pharm, PharmD, PhD**			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: 8/27/02	IND No.: Serial No.:	NDA No. **21-479**	DATE OF THIS DOCUMENT	18 December 2002
NAME OF DRUG Zydis® Selegiline	PRIORITY CONSIDERATION **S or P**		Date of informal/Formal Consult:	8/27/02

NAME OF THE SPONSOR: Elan

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS ASSIGNMENT

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☒ OTHER *(SPECIFY BELOW)*: [Pharmacodynamic Analysis]
☐ PHASE IV RELATED		

REVIEW ACTION

☐ **NAI (No action indicated)**

☐ E-mail comments to: ☐Medical ☐Chemist ☐Pharm-Tox ☐Micro ☐Pharmacometrics ☐Others (Check as appropriate and attach e-mail)	☒ Oral communication with Name: Len Kapcala, M.D. ☐ Comments communicated in meeting/Telecon. see meeting minutes dated:	☐ Formal Review/Memo (attached) ☐ See comments below ☐ See submission cover letter ☐ OTHER *(SPECIFY BELOW)*:

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:
30 minute PD consult regarding tyramine pressor tests with MAO inhibitors.

SIGNATURE OF REVIEWER: _____	Date _____
SIGNATURE OF TEAM LEADER: _____	Date _____
CC.: HFD # [120]; TL: [Baweja]; DD: [ ] CDR;	**Project Manager:** _____ **Date** _____

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/s/

Ron Kavanagh
12/18/02 04:16:28 PM
BIOPHARMACEUTICS

Raman Baweja
12/18/02 05:13:24 PM
BIOPHARMACEUTICS

Memo to file

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

NDA Number	NDA 21-479	**Brand Name**	Zydis® selegiline
OCPB Division I	HFD-860	**Generic Name**	Selegiline HCl
Medical Division	HFD-120	**Drug Class**	MAO-B inhibitor
OCPB Reviewer	Maria Sunzel, Ph.D.	**Indication(s)**	Parkinson's Disease, adjunctive therapy
OCPB Team Leader	Ramana Uppoor, Ph.D.	**Dosage Form**	Orally disintegrating tablet 1.25 mg strength
Date of Submission	March 29, 2002	**Dosing Regimen**	QD (a.m. before breakfast) 1.25 mg/day or 2.5 mg/ day
Estimated Due Date of OCPB Review	End Nov. 2002	**Route of Administration**	Oral
PDUFA Due Date	February 8, 2003	**Sponsor**	Elan Pharmaceuticals Inc
Division Due Date	Mid- Dec 2002	**Priority Classification**	3S (new formulation)

BACKGROUND:

The Agency has approved oral 5 mg immediate release tablets and capsules of selegiline. Currently, 11 companies have approved products, where Eldepryl® (5 mg tabl & capsules, oral solution, 5 mg/10 mL) is the reference listed drug (RLD) product (the Orange Book).

This new NDA concerns orally disintegrating selegiline tablets (1.25 mg strength) intended for [redacted] **This formulation was developed to improve patient compliance, and to make it easier to swallow for patients who experience pain, or difficulty in swallowing (dysphagia). Zydis selegiline tablets (open matrix of** [redacted] **should be taken in the fasting state, without water,** [redacted] **The tablet disintegrates within seconds in the mouth, and the drug is partially absorbed from the buccal mucosa. According to the sponsor, the pharmacokinetic (PK) studies have shown that this dosage form has a higher systemic bioavailability, since the 1st pass effect is less for this formulation compared to the currently marketed products (F=10%), as a result of mucosal absorption from the oral cavity. Therefore, the current standard daily dosing regimen of 10 mg (2x5 mg) selegiline, can be reduced to 1.25 to 2.5 mg with this new oral formulation (Zydis selegiline).**

b(4)

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The sponsor has performed 9 (6 single dose & 3 repeated dose) Phase I studies in approx. 150 healthy volunteers (exploratory PPK analysis from C_{min} samples available in patients from combined data sets from 2 Phase III studies). Zydis selegiline tablets were studied in the dose range 1.25 - 5 mg. The sponsor also investigated taste & ease of swallowing in 1 additional study (patients, no PK sampling). The sponsor performed 2 clinical efficacy studies (placebo controlled 3-month trials, one study showed statistically significant improvement vs. placebo; the other one showed no improved response after active drug treatment compared to placebo treatment).

PK information from the submitted trials covers the following items:

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- **Absorption - oral mucosa vs. GI tract (swallowed tablet vs. tablet kept in oral cavity)**
- **Food effects (5 mg Zydis vs. 2x5 mg RLD tabl, indirect MAO inhibition)**
- **PK single dose (1.25, 2.5, 5 mg Zydis tabl vs. 2x5 mg RLD tabl, indirect MAO inhibition)**
- **PK repeated doses (2x5 mg Zydis tabl/ 1.25 mg Zydis tabl/ 1.25, 2.5, 5 mg Zydis tabl vs. 2x5 mg selegiline, oral tyramine pressor tests & indirect MAO inhibition)**

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	No. studies submitted	No. studies reviewed	Comments
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 & 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	6		
multiple dose:	X	3		
Patients-				
single dose:	-			
multiple dose:	-			
Dose proportionality -				
fasting single dose:	(X)			1 study: 1.25, 2.5, & 5 mg Zydis tabl. Incomplete block design
fasting multiple dose:	(X)			1 study: 1.25, 2.5, & 5 mg Zydis tabl. Parallel group study
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-			
In-vivo effects of primary drug:	-			
In-vitro:	-			
Subpopulation studies -				
ethnicity:	-			
gender:	-			See 'comments to the firm'
pediatrics:	-			Waiver request
geriatrics:	- (?)			See 'comments to the firm'
renal impairment:	-			
hepatic impairment:	-			
PD:				
Phase 2:	-			
Phase 3:	-			
PK/PD:				
Phase 1 and/or 2, proof of concept:	X			3 multiple dose studies: indirect MAO response, & pressor response to tyramine challenge
Phase 3 clinical trial:	-			
Population Analyses -				
Data rich:	-			
Data sparse:	X			PPK in patients (C_{min} only)
II. Biopharmaceutics				
Absolute bioavailability:	-			

Relative bioavailability -				
solution as reference:	X			5 mg Zydis vs. 10 mg/5 mL Eldepryl syrup
alternate formulation as reference:	X			2x5 mg or 1.25 mg Zydis vs conventional selegiline or RLD tablets as reference
Bioequivalence studies -				
traditional design; single dose:	-			
replicate design; single / multi dose:	-			
Food-drug interaction studies:	X			
Dissolution:	X			3 pH media
(IVIVC):	-			
Bio-waiver request based on BCS	-			
BCS class	-			
III. Other CPB Studies				
Genotype/phenotype studies:	-			
Chronopharmacokinetics	-			
Pediatric development plan	-			Pediatric waiver requested
Literature References	X			28 references
Total Number of Studies		9		

Filability and QBR comments		
	"X" if yes	Comments
Application filable?	X	
Comments sent to firm?	X	• Please provide the study-specific analytical reports for the 8 PK studies (all except Study AN17933-101) • Please provide a correct reference for the cross-study PK comparison with regard to old age that is included in the annotated label (lt. 6/vol 15/p 1 does not contain this comparison). • Please provide a cross-study PK comparison with regard to gender (Phase I studies in healthy subjects) • Please update the annotated label for all references to Item 6, to reflect the volume/page numbers according to the overall NDA volume numbers given in volume 1, p 2-14. • Please provide an extra desk copy of the combined report of Studies Z/SEL/97/025-026 including Appendix A-4 (PPK report). Please provide the data sets that were used for the NONMEM analysis electronically as SAS transport files. Please also include the control files used in the NONMEM analysis. • Please provide data sets (as SAS transport files) for the pharmacokinetic parameters (individual values) with the corresponding subject demographics from the studies that the pharmacokinetic information in the label is based on. • Please provide data sets (as SAS transport files) for the pharmacokinetic/ pharmacodynamic data (individual values: plasma selegiline concentrations, and the pharmacodynamic variables vs. time) for Study AN17933-101 • If the sponsor would like to schedule a telecon to discuss the formats of the requested data sets with the OCPB reviewers, please contact Ms. Wheelous. • Please submit the requested reports/data sets within 6 weeks, and the requested additional analyses within 12 weeks.
QBR questions (key issues to be considered)		• Are the analytical methods appropriately validated and documented? • Does the submitted data support the proposed label text? • Are the proposed dosing recommendations appropriate from a PK point of view (8-fold decrease in oral dose)? Is the study data adequate to support the dosing instructions to enhance buccal absorption [redacted] Were special dosing instructions given in the Phase III studies (do not swallow within 2 min after tablet disintegration)? • Is the exploratory PPK analysis adequately conducted? • Is the proposed *in vitro* disintegration method acceptable? (The sponsor proposes that no dissolution specifications are set due to the very rapid disintegration/dissolution of the proposed tablets - dissolution at [redacted] in 3 pH media).
Other comments or information not included above		The food study was conducted with a 5 mg Zydis tablet (only 1.25 mg tabl intended to be marketed). The study is considered acceptable, since the 5 mg tablet only differ from the 1.25 mg with respect to amount of active drug. The sponsor has performed analyses of selegiline and metabolites (plasma, urine, saliva) as well as bio marker analyses (e.g. 5-HIAA) in various biological fluids. The sponsor has performed most PK studies on Zydis tablets from a batch size of [redacted] The to-be-marketed (TBM) batch size seems to be [redacted] batch was partially used in one clinical efficacy trial (Study Z/SEL/97/027) and one PK/PD Phase I trial (Study AN17933-101). The primary stability validation batches have not been used in any clinical trials (in part, the same drug substance lots were used in the clinical trials & these stability batches of the TBM formulation). The sponsor has provided published references (28 articles) on the pharmacokinetics and pharmacodynamics of selegiline. At the filing meeting (5/15/02) it was made clear that the PK/PD analysis will not be used as supportive information for efficacy (will be based on empirical Phase III results). However, the PK/PD analysis will be interesting for the clinical safety evaluation.
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

b(4)

b(4)

b(4)

cc: NDA 21-479, HFD-850 (Electronic Entry /Lee), HFD-120 (Wheelous), HFD-860 (Mehta, Uppoor, Marroum, Sunzel)

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/s/

Maria Sunzel
5/20/02 10:02:18 AM
BIOPHARMACEUTICS

Ramana S. Uppoor
5/20/02 01:14:34 PM
BIOPHARMACEUTICS