

From these figures it appears that subjects on 10 mg ZELAPAR dose do appear to be at steady state, however, subjects on 5 mg ZELAPAR have not quite approached steady state.

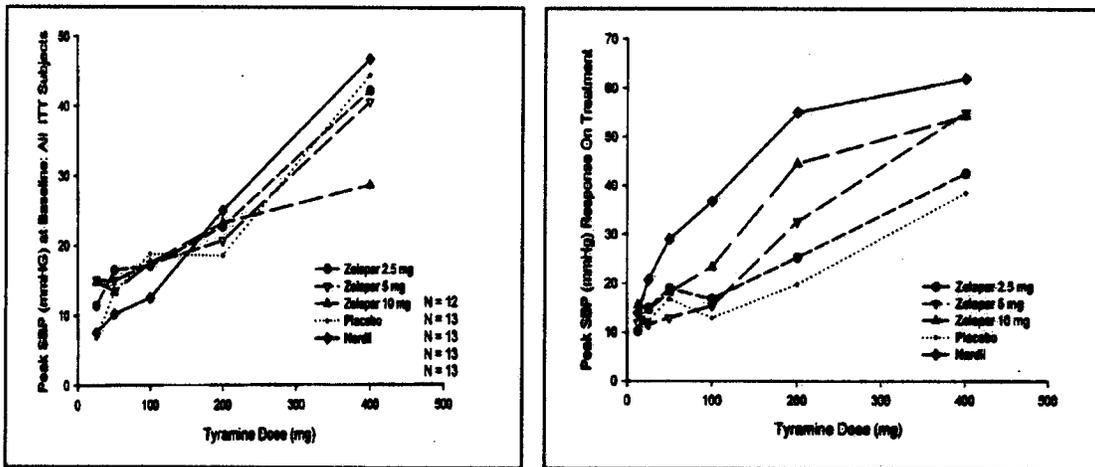
**A response to this reviewer question was received by OCPB and is appended to this review.**

Pharmacodynamic Results:

Primary PD variables:

1) Baseline and treatment tyramine response: The magnitude of the mean peak SBP (Emax) was associated with the dose of tyramine.

The peak SBP at baseline and treatment are shown in the following figures:



The number of subjects at each dose of tyramine is shown in the following Table:

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Tyramine Dose (mg)	ZELAPAR 2.5 mg N = 12	ZELAPAR 5 mg N = 13	ZELAPAR 10 mg N = 13	Placebo N = 13	NARDIL 30 mg N = 13
Randomized (N)	12	13	13	13	13
12.5	12	13	13	13	13
25	12	13	13	13	12
50	11	13	13	12	13
100	10	13	12	12	8
200	10	13	12	12	5
400	8	7	3	9	2

The drop off rate in the ZELAPAR 2.5 and 5 mg group were similar to placebo, but ZELAPAR 10 mg group drop off rate was similar to NARDIL.

The effect of ZELAPAR on the peak SBP response to the highest dose of tyramine administered (Emax) is summarized in the following Table. In the first primary effect analysis, the change from baseline represents the difference between the peak SBP response at the highest dose of tyramine administered while on randomized treatment (Days 11-16) and the peak SBP response at the corresponding tyramine dose at baseline (Days -5 to -1).

Period	ZELAPAR 2.5 mg N = 12 Mean (SD)	ZELAPAR 5 mg N = 13 Mean (SD)	ZELAPAR 10 mg N = 13 Mean (SD)	Placebo N = 13 Mean (SD)	NARDIL 30 mg N = 13 Mean (SD)
Baseline (mmHg)	32.3 (25.21)	29.9 (12.14)	19.3 (11.03)	37.0 (23.63)	17.2 (13.77)
On Treatment (mmHg)	42.5 (23.33)	55.0 (21.81)	54.3 (24.79)	38.5 (20.14)	61.9 (30.86)
Change (mmHg)	10.2 (18.85)	25.1 (23.11)	35.0 (30.68)	1.5 (16.28)	44.7 (23.16)
p - value <sup>a</sup>	0.3484	0.0113	<0.001		<0.001
p - value <sup>b</sup>	<0.001	0.0338	0.2872		

SD = Standard Deviation

<sup>a</sup> p-value for ANOVA comparing active treatments to placebo

<sup>b</sup> p-value for ANOVA comparing ZELAPAR to NARDIL (positive control)

The NARDIL positive control group demonstrated a mean increase in SBP pressor response to tyramine of approximately 45 mmHg over baseline, which represented a statistically significant difference from placebo (p <0.001). Administration of ZELAPAR resulted in an increase in the SPB response to tyramine of 10 mmHg, 25 mmHg, and 35 mmHg for the ZELAPAR 2.5, 5 and 10 mg dose, respectively.

10 mg dose of ZELAPAR was not significantly different from NARDIL.

2) Tyramine Threshold Dose:

*Primary Definition:*

- The tyramine threshold dose was defined as the lowest dose of tyramine observed to elicit a  $\geq 30$  mmHg increase in SBP.

Tyramine Threshold Dose Producing an Increase in SBP (Emax)  $\geq 30$  mmHg during Randomized Treatment

Treatment Comparison: T vs R	Geometric LS Mean		Ratio	(90% CI)
	T	R	T/R	
ZELAPAR 2.5 mg vs NARDIL 30 mg	141.421	66.724	2.1189	(1.0709, 4.1927)
ZELAPAR 5 mg vs NARDIL 30 mg	200.000	66.742	2.9966	(1.6276, 5.5172)
ZELAPAR 10 mg vs NARDIL 30 mg	168.179	66.742	2.5198	(1.3686, 4.6394)
ZELAPAR 2.5 mg vs Placebo	141.421	272.158	0.5196	(0.2513, 1.0745)
ZELAPAR 5 mg vs Placebo	200.000	272.158	0.7349	(0.3801, 1.4208)
ZELAPAR 10 mg vs Placebo	168.179	272.158	0.6179	(0.3196, 1.1947)
NARDIL 30 mg vs Placebo	66.742	272.158	0.2452	(0.1268, 0.4741)

The tyramine threshold dose for ZELAPAR 2.5 mg was approximately 2-fold higher than that of NARDIL. The tyramine threshold dose for ZELAPAR 5 mg and 10 mg was 3-fold and 2.5-fold higher, respectively, than that of NARDIL.

The 90% CIs constructed for the tyramine threshold dose ratios indicate that the three doses of ZELAPAR could not be distinguished from placebo with regard to their effect on the tyramine threshold dose required to produce a  $\geq 30$  mmHg increase in the SBP response.

Evaluation of the tyramine threshold dose (30 mmHg) was influenced by a number of subjects with isolated and possibly spurious elevations in blood pressure. For example, Subject 074 in the ZELAPAR 2.5 mg group was identified as having an on-treatment tyramine threshold dose ( $\geq 30$  mm Hg) of 50 mg based on a peak SBP response of 36 mmHg after treatment with 50 mg tyramine; however, the subject did not show any increase in SBP in response to 100 mg or 200 mg tyramine. Similarly, Subject 054 in the ZELAPAR 5 mg group was considered to have reached a threshold dose at 12.5 mg tyramine based on SBP response of 35 mm hg, however, the successive doses failed to produce a threshold pressor response  $\geq 30$  mm Hg.

*Secondary Definitions:*

- When the threshold response was defined as the lowest dose of tyramine producing an increase in SBP  $\geq 15$  mmHg at two consecutive time points (10

minutes apart), where one of the two measurements was  $\geq 30$  mmHg ("15-30"), the results of the comparative analysis were essentially the same as for the primary analysis definition of threshold dose, since the redefined threshold dose only changed for one subject (Subject No.029 in the 2.5 mg ZELAPAR group).

- Definition of the threshold dose as a sustained response of an increase in SBP  $\geq 30$  mmHg for two consecutive measurements taken 10 minutes apart ("30-30") revealed a more pronounced difference between the two lower doses of ZELAPAR and NARDIL than was apparent in the primary analysis. The LS mean threshold dose (30-30) for ZELAPAR differed from the NARDIL mean threshold dose by 4.2-, 4-, and 2.7-fold, respectively. The 90% confidence limits around the relative potency estimates all excluded 1.0, indicating that all three doses of ZELAPAR were significantly less potent than NARDIL.

Under the alternate threshold dose definition (30-30), all three doses of ZELAPAR were more similar to placebo than was demonstrated for the less stringent primary analysis definition of threshold dose (30 mmHg).

Tyramine Threshold Dose Producing a Sustained Increase in SBP during Steady State on Study Treatment:

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Treatment Comparison: T vs R	Geometric LS Mean		Ratio T/R	(90% CI)
	T	R		
<b>Threshold Dose = 15-30 mmHg</b>				
ZELAPAR 2.5 mg vs NARDIL 30 mg	154.221	66.742	2.3107	(1.1597, 4.6041)
ZELAPAR 5 mg vs NARDIL 30 mg	200.000	66.742	2.9966	(1.5952, 5.6291)
ZELAPAR 10 mg vs NARDIL 30 mg	168.179	66.742	2.5198	(1.3601, 4.6684)
ZELAPAR 2.5 mg vs Placebo	154.221	272.158	0.5667	(0.2720, 1.1805)
ZELAPAR 5 mg vs Placebo	200.000	272.158	0.7349	(0.3727, 1.4489)
ZELAPAR 10 mg vs Placebo	168.179	272.158	0.6179	(0.3175, 1.2028)
NARDIL 30 mg vs Placebo	66.742	272.158	0.2452	(0.1260, 0.4773)
<b>Threshold Dose = 30-30 mmHg</b>				
ZELAPAR 2.5 mg vs NARDIL 30 mg	336.359	79.370	4.2379	(2.3992, 7.4856)
ZELAPAR 5 mg vs NARDIL 30 mg	317.480	79.370	4.0000	(2.5903, 6.1769)
ZELAPAR 10 mg vs NARDIL 30 mg	213.008	79.370	2.6837	(1.7787, 4.0493)
ZELAPAR 2.5 mg vs Placebo	336.359	303.143	1.1096	(0.5729, 2.1490)
ZELAPAR 5 mg vs Placebo	317.480	303.143	1.0473	(0.6045, 1.8146)
ZELAPAR 10 mg vs Placebo	213.008	303.143	0.7027	(0.4130, 1.1956)
NARDIL 30 mg vs Placebo	79.370	303.143	0.2618	(0.1550, 0.4424)

Secondary Pharmacodynamic Analyses:

Tyramine Threshold Dose Ratios for Sustained Response

The ratio of the baseline tyramine threshold dose to the on-treatment threshold dose was determined for each treatment using the two previously described alternate definitions of sustained threshold response (SBP 15-30 mmHg and 30-30 mmHg). The threshold dose ratios thus obtained for each active treatment were compared to placebo, and the threshold dose ratios for each ZELAPAR dose were compared to NARDIL.

The results of these analyses are presented in the following Table:

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Comparison of Tyramine Threshold Dose Ratios for Sustained SBP Response

Comparison T vs R		Tyramine Dose Ratio (Baseline/On-Treatment)			
Test (N)	Reference (N)	T Mean (SD)	R Mean (SD)	Difference T - R	(90% CI)
<b>Threshold Dose = 15 - 30 mmHg<sup>a</sup></b>					
ZELAPAR 2.5 mg (6)	Placebo (7)	2.33 (2.858)	1.75 (2.773)	0.5833	(-2.965 , 4.1312)
ZELAPAR 5 mg (8)		1.30 (0.813)		-0.4531	(-3.754 , 2.8473)
ZELAPAR 10 mg (7)		0.95 (0.577)		-0.8036	(-4.212 , 2.6051)
NARDIL 30 mg (11)		7.00 (6.245)		5.2500	(2.1668 , 8.3332)
ZELAPAR 2.5 mg (6)	NARDIL 30 mg (11)	2.33 (2.858)	7.00 (6.245)	-4.6667	(-7.903 , -1.430)
ZELAPAR 5 mg (8)		1.30 (0.813)		-5.7031	(-8.666 , -2.740)
ZELAPAR 10 mg (7)		0.95 (0.577)		-6.0536	(-9.137 , -2.970)
<b>Threshold Dose = 30 - 30 mmHg<sup>b</sup></b>					
ZELAPAR 2.5 mg (3)	Placebo (3)	1.33 (0.577)	0.83 (0.289)	0.5000	(-4.169 , 5.1689)
ZELAPAR 5 mg (4)		1.06 (0.718)		0.2292	(-4.138 , 4.5965)
ZELAPAR 10 mg (3)		1.50 (0.866)		0.6667	(-4.002 , 5.3355)
NARDIL 30 mg (7)		5.57 (5.094)		4.7381	(0.7922 , 8.6840)
ZELAPAR 2.5 mg (3)	NARDIL 30 mg (7)	1.33 (0.577)	5.57 (5.094)	-4.2381	(-8.184 , -0.2922)
ZELAPAR 5 mg (4)		1.06 (0.718)		-4.5089	(-8.093 , -0.9249)
ZELAPAR 10 mg (3)		1.50 (0.866)		-4.0714	(-8.017 , -0.1255)

T = Test

R = Reference

*a* Lowest dose of tyramine producing an increase in SBP  $\geq 15$  mmHg at two consecutive time points (taken 10 minutes apart), where one of the measurements was  $\geq 30$  mmHg

*b* Lowest dose of tyramine producing an increase in SBP  $\geq 30$  mmHg at two consecutive time points (taken 10 minutes apart)

Using either definition for sustained SBP response for tyramine threshold dose, the threshold dose ratios for ZELAPAR were less than NARDIL and similar to placebo.

In this analysis, a threshold dose ratio of "1" would indicate that the treatment had no effect on the tyramine pressor response. A threshold dose ratio  $> 1$  indicated that the treatment interacts with tyramine in a positive manner and potentiates the pressor effect.

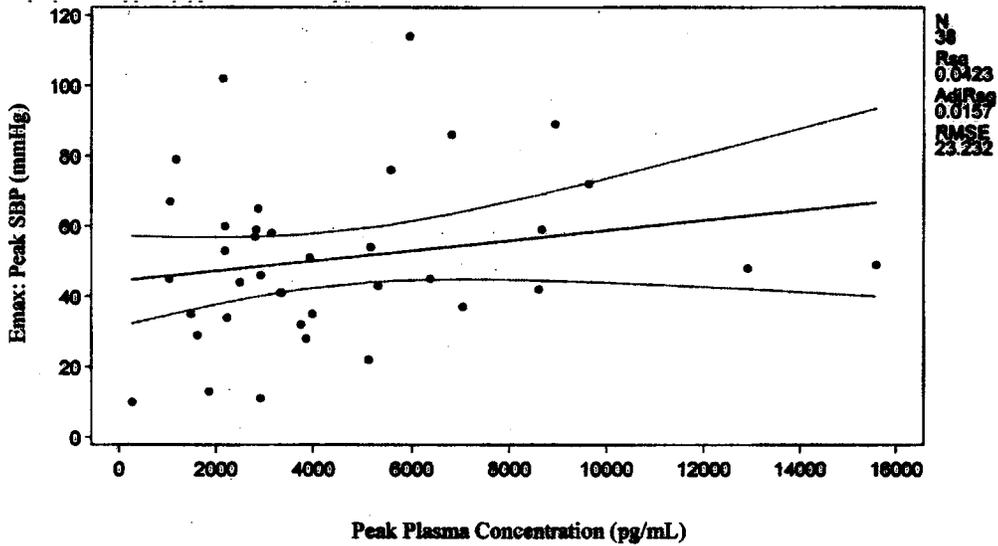
A ratio  $> 1$  was obtained in the placebo group for the "15-30" definition of threshold dose, showing spurious results. A number of subjects in the placebo group and in all three ZELAPAR groups required a higher dose while on treatment than at baseline to elicit the same predefined pressor response. One subject (No. 027) in the placebo group exhibited a 400 mg threshold dose for the 15-30 mm Hg response at baseline and 5 mg during the on-treatment tyramine challenge, representing a 8-fold increase in sensitivity to tyramine.

#### Correlation of Systolic Blood Pressure Response to Peak Plasma Concentrations of Selegiline:

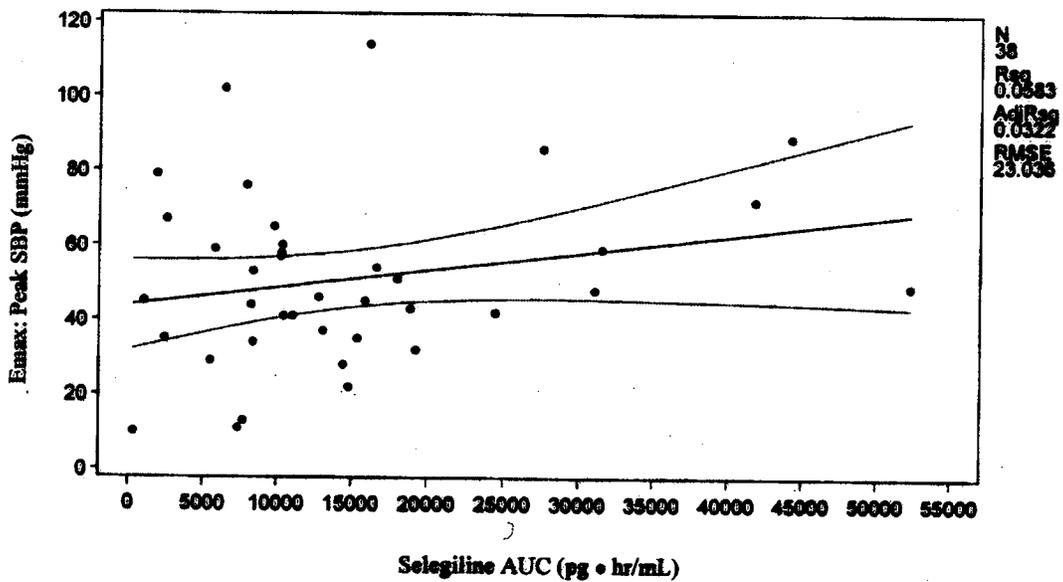
A simple linear regression analysis was performed to correlate the peak SBP response ( $E_{max}$ ) at the highest dose of tyramine on treatment to the observed peak plasma concentrations ( $C_{max}$ ) and

total exposure (AUC) to selegiline at steady-state for the 38 subjects in the ITT population that received ZELAPAR. The correlation statistics are provided to the right of the figure.

Correlation of peak SBP tyramine response on treatment to selegiline Cmax at steady state (95% CI)



The slope of the Emax-Cmax regression line was 0.0014, indicating the lack of any relationship between peak plasma levels of selegiline and the peak on-treatment SBP response to tyramine. The plasma concentration and SBP Emax data were highly variable as evidenced by the low r2 value for the linear regression (0.0423).



The slope of the E<sub>max</sub>-AUC regression line was 0.0005, and the r<sup>2</sup> was low (0.0583), indicating a high degree of variation and the lack of any relationship between total exposure to selegiline and the peak on-treatment SBP response to tyramine. Regression analyses for the combined ZELAPAR dose groups showed no meaningful correlation of E<sub>max</sub> to selegiline C<sub>max</sub> or AUC at steady state was demonstrated for any of the ZELAPAR dose groups when examined individually.

#### Change in Peak and Mean Diastolic Blood Pressure and Heart Rate:

The change in the peak DHP response from baseline (pre-randomization) was 1.3 mmHg, 9.2 mmHg, and 6.3 mmHg for the 2.5 mg, 5 mg, and 10 mg doses of ZELAPAR, respectively. None of the ZELAPAR treatment groups demonstrated a change in peak DHP from baseline that was significantly different from that observed in the placebo group (1.2 mmHg).

In contrast, the NARDIL control group demonstrated an 18.4 mmHg change from baseline DBP at the highest tyramine dose, which was significantly different from placebo (p<0.001). The magnitude of the increase in DBP response over baseline was smaller for all three ZELAPAR doses than for NARDIL, and the relative difference attained statistical significance for the 2.5 mg (p<0.001) and 10 mg (p=0.0136) ZELAPAR groups.

Treatment with ZELAPAR resulted in further peak HR decreases from the baseline response of -4.7 bpm, -6.4 bpm, and -9 bpm for the 2.5 mg, 5 mg, and 10 mg doses of ZELAPAR, respectively. Only the ZELAPAR 10 mg group showed an effect on the HR response that was significantly different (p = 0.0236) from the placebo change from baseline response of -1.4 bpm. The effect of NARDIL on the HR response was -5.5 bpm (p = 0.2098). Comparison of the ZELAPAR on-treatment change from baseline peak HR response to that of NARDIL did not demonstrate any significant differences. Comparison of the treatment effect on the mean DBP response at the maximum on-treatment tyramine dose to the corresponding response at baseline did not reveal any significant differences between the active treatments and placebo nor between the 5 mg and 10 mg ZELAPAR treatments and NARDIL. The 5 mg and 10 mg ZELAPAR groups demonstrated increases from baseline in the maximum DBP response of 3.6 mmHg and 3.1 mmHg, respectively, and the placebo and NARDIL groups demonstrated increases of 2.1 mmHg and 6.6 mmHg, respectively. The 2.5 mg ZELAPAR group actually showed a small decrease in the mean DBP response (-0.3 mmHg) from baseline that was significantly different from placebo (p = 0.0107). No significant differences in the maximum mean HR response from baseline were evident between the active treatment groups and placebo, nor between the ZELAPAR treatment groups and NARDIL.

#### Safety Evaluations:

This section of the study will be reviewed by the Medical Officer.

## **CONCLUSIONS:**

The therapeutic dose of ZELAPAR (2.5 mg) was similar to placebo with regard to any potential effect of tyramine pressor response at steady state. The 5 mg (2x recommended therapeutic dose) and 10 mg (4x recommended therapeutic dose) of ZELAPAR showed higher tyramine response, but were lower than NARDIL. The increase in SBP response to tyramine was 10 mmHg, 25 mm Hg, 35 mm Hg and 45 mm Hg for the 2.5 mg, 5 mg, 10 mg ZELAPAR and 30 mg NARDIL tablets.

Several analyses to show the relative potencies of the three ZELAPAR doses and NARDIL showed that ZELAPAR was 2- to 4-fold less potent than NARDIL. The decision on the best criteria for defining tyramine threshold dose, to show the relative potency should be made by the reviewing Medical Officer. Some subjects showed higher SBP response to tyramine and lower doses of tyramine compared to the subsequent higher doses. These results suggest unreliable elevation in the blood pressures.

There was no correlation between peak SBP tyramine response and Cmax and AUC for selegiline at steady state.

The results for the effect of mean DBP at the maximum on treatment tyramine dose to the corresponding response at baseline also appeared spurious, because the lowest ZELAPAR dose (2.5 mg) showed a small decrease in mean DBP response from baseline that was statistically different from placebo, but the higher doses did not show any difference.

## **Reviewer's Comments (sent via email to Teresa on April 21, 2005):**

1. NARDIL tablets were overencapsulated for blinding purposes. The sponsor has not provided any in vitro dissolution data to show similarity between the NARDIL tablets and overencapsulated NARDIL tablets by F2 comparisons. The sponsor should provide this data for acceptability of the results obtained from Study RNA-ZEL-B-21-102.
2. The maximum study sample storage from the first blood draw to the last sample was 49 days. The sponsor has provided long term stability data for only 8 days so far. Please provide additional long term stability data to support the PK data.
3. Is trough PK data available from all subjects at Day 8 and 9. If yes, please indicate its location in the submission and also provide an assessment of the attainment of steady state in all subjects by evaluating trough data from Days 8, 9 and 10.

## **Firm's Response to OCPB Questions**

FDA Question 1 :

"NARDIL tablets were overencapsulated for blinding purposes. The sponsor has not provided any in vitro dissolution data to show similarity between the NARDIL tablets and overencapsulated NARDIL tablets by F2 comparisons. The sponsor should provide this data for acceptability of the results obtained from Study RNA-ZEL-B21-102."

Valeant Response:

The in vitro dissolution data was not provided as part of the March 29, 2005 Complete Response to the Approvable Letter. Included in this Response to Request for Information, the complete results and requested F2 comparison have been included in Attachment I. Dissolution was performed in USP Method I (Basket) at 100 rpm in 900 mL of simulated gastric fluid. Aliquots were collected at 15, 30 and 45 min and analyzed by HPLC. In summary, the mean percent dissolved for the "blinded" dosage form, over-encapsulated 15 mg Nardil tablets at 15 min compared to the "unblinded" Nardil tablets was 60% vs. 84%, respectively. At both the 30 and 45 min sampling points, the mean percent dissolved for each product was greater than >95%. This initial slightly slower dissolution at 15 min resulted in an F2 calculation of 42.9, less than the allowable value of 50, thus failing to confirm similarity in dissolution between products. Despite the difference in the dissolution profile between products, as characterized by the F2 analysis, it is the opinion and conclusion of Valeant that there is no meaningful difference that impacts the pressor pharmacodynamic effects of the Nardil active ingredient, phenelzine. This is based upon both theoretical and results-driven arguments, which are characterized below:

- 1) The active ingredient of Nardil tablets is phenelzine, a high solubility-high permeability drug product (FDA Biopharmaceutics Classification System-Case 1). For Case 1 products, it is anticipated that gastric emptying will be rate limiting for drug absorption. The in vitro dissolution in simulated gastric fluid of the over-encapsulated tablet demonstrated a difference between the products only at the initial 15 min time point. By thirty minutes that earlier difference in dissolution was no longer evident, with both products being completely dissolved (>95%). Since it is reported in the FDA Guidance "Dissolution Testing of Immediate Release Solid Oral Dosage Forms" (Aug 1997) that "The mean T50% gastric residence (emptying) time is 15-20 minutes under fasting conditions", the difference observed at 15 minutes would not be expected to be clinically relevant.
- 2) For the T max to be impacted, the disintegration and subsequent dissolution differences between the two tablets formulations would need to be apparent at or near the Tmax of the product. In plasma, the Tmax for phenelzine following administration of Nardil Tablets to healthy volunteers is estimated to be 43 min (ref. Nardil tablet package insert). Since the only potential difference in dissolution is evident. at 15 min and is no longer evident by 30 minutes, in vivo T max would not be expected to change; likewise,

no effect would be expected on the peak concentration of phenelzine nor on its pharmacodynamic effects.

3) Even if the reported differences in the rate of dissolution between the products were significant, the effect on absorption would at most be on the rate of absorption alone, thus the total systemic absorption would not be affected. This is based upon the fact that the absorption half-life is at least an order of magnitude shorter than the 11.6 hour elimination half-life and would be solely manifested by a change in the T<sub>max</sub> of the product, not the peak concentration itself. Since the pharmacodynamic effects are more closely associated with the drug concentrations, changes in T<sub>max</sub>, even if realized, would not be expected to be manifest in changes in the pharmacodynamic effects of phenelzine.

4) The use of daily administrations of 30 mg Nardil (15 mg of twice daily), was demonstrated to be a positive control in Study RNA-ZEL-B21-102, with a sustained tyramine-pressor ratio computed to be 5.57 (Table 11, Clinical Study Report [Volume 13, page 83 of 2367 of the March 29, 2005 Complete Response to the Approvable Letter], which is comparable to that reported in the literature. This is the strongest, and most relevant evidence that the over-encapsulation of the Nardil tablets, required for study blinding, did not influence its intended pharmacodynamic pressor response. In conclusion, Valeant believes that over-encapsulating Nardil tablets, despite an apparent difference in the in vitro dissolution F2 analysis, did not adversely influence the in vivo-pressor effects observed following daily administration of 30 mg of Nardil which was comparable to that reported in the literature.

OCPB Reply:

**The firm's explanation is acceptable since as they pointed out any effect is much earlier than the T<sub>max</sub> for Nardil and sampling is for 3 hrs with the extent of absorption not impacted by the overencapsulation.**

FDA Question 2:

"The maximum study sample storage from the first blood draw to the last sample was 49 days. The sponsor has provided long term stability data for only 8 days so far. Please provide additional long term stability data to support the PK data."

Valeant Response:

Although it is true that the initial validation report documented bioanalytical sample stability for 8 days for the analysis of selegiline, additional validation data support continued stability of stored samples for greater than 275 days. The additional validation extending sample stability is included in the Revised Validation Report 45031FXD, as Revision 1 (dated 4 May 2005). The Revised Validation Report and the associated revisions to the Bioanalytical Report, Amendment 1 ( dated 9 May 2005), are included in Attachment 2.

OCPB Reply:

**The firm's response to question 2 is acceptable.**

FDA Question 3:

"Is trough PK data available from all subjects at Day 8 and 9? If yes, please indicate its location in the submission and also provide an assessment of the attainment of steady state in all subjects by evaluating trough data from Days 8, 9 and 10".

Valeant Response:

Since it had been previously requested and acknowledged by the Division that steady-state for Zydis Selegiline was attained by Day 10, the initial protocol RNA-ZEL-B-21-102, submitted to the IND on June 25, 2004, did not include trough PK samples on Days 8 and 9 but only on Days 10 and 11, as part of the sampling to define the pharmacokinetics of selegiline at steady state. As such, the response to the first question is that not all subjects had PK data for Days 8 and 9. Once the request for these samples was received by Valeant via email on August 16, 2004, an amendment to the protocol was prepared and submitted to the Clinical Study Site for submission to the IRB. Following approval of this amendment, the remaining subjects had additional trough sampling for Days 8 and 9. Each of the three Zydis selegiline dose groups, 2.5 mg, 5 mg and 10 mg; had 4-5 subjects with trough samples on Days 8-11; 12-13 subjects in each group had trough samples on Days 10 and 11. The location of the listing of individual selegiline concentrations, including trough values (Listing 4), was Volume 17, pages 1369 of 2357, of Valeant's March 29, 2005 Complete Response to the Approvable Letter. For convenience, we have provided anew listing (Listing 22) which only includes trough concentrations, and it is located as Attachment 3 to this Response to Request for Information. In addition, the firm has provided an analysis of the trough data (Attachment 3), including statistical tables, demonstrating that the trough PK results for selegiline following administration of 2.5 mg, 5 mg and 10 mg of Zydis selegiline, confirmed the earlier findings that steady state was achieved by Day 10.

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Table 25  
Analysis of Trough Concentrations by Day

Treatment Parameter	Day Vs Day Comparison T - R	LS Means			Difference	95 % Confidence Interval		Overall p-value	Day p-value	Subject p-value
		Test	Reference	Reference						
Zelapar 2.5 mg	8 - 9	17.6150	22.1230	-4.5100	(-36.3109 , 27.2989)	0.0016	0.2210	0.0004		
	8 - 10	17.6150	38.4425	-20.8275	(-52.6364 , 10.9814)					
	8 - 11	17.6150	45.6375	-28.0225	(-59.8314 , 3.7864)					
	9 - 10	22.1250	38.4425	-16.3175	(-48.1264 , 15.4914)					
	9 - 11	22.1250	45.6375	-23.5125	(-55.3214 , 8.2964)					
	10 - 11	38.4425	45.6375	-7.1950	(-39.0039 , 24.6139)					
	8 - 9	88.4680	97.8480	-9.3800	(-22.6840 , 3.9240)	<.0001	0.0050	<.0001		
	8 - 10	88.4680	115.1880	-26.7200	(-40.0240 , -13.4160)					
	8 - 11	88.4680	107.4380	-18.9700	(-32.2740 , -5.6660)					
	9 - 10	97.8480	115.1880	-17.3400	(-30.6440 , -4.0360)					
9 - 11	97.8480	107.4380	-9.5900	(-22.8940 , 3.7140)						
10 - 11	115.1880	107.4380	7.7500	(-5.5540 , 21.0540)						
Zelapar 10 mg	8 - 9	209.5617	213.3220	-3.7603	(-33.8288 , 26.3082)	<.0001	0.5554	<.0001		
	8 - 10	209.5617	214.8640	-5.3023	(-35.3708 , 24.7662)					
	8 - 11	209.5617	227.7540	-18.1923	(-48.2608 , 11.8762)					
	9 - 10	213.3220	214.8640	-1.5420	(-29.3800 , 26.2960)					
	9 - 11	213.3220	227.7540	-14.4320	(-42.2700 , 13.4060)					
	10 - 11	214.8640	227.7540	-12.8900	(-40.7280 , 14.9480)					

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OCPB Reply:

**The firm's response to question 3 is acceptable.**

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## **ANALYSIS OF A THOROUGH QT STUDY**

- The primary objective of this study was to determine the electrocardiographic effects of selegiline delivered as a ZYDIS formulation (ZELAPAR) .
- The secondary objectives of the study were to:

Investigate the correlation of any observed effects of selegiline on ECG parameters to plasma concentrations of selegiline, and;

.Evaluate the safety and tolerability of ZELAPAR.

### **METHODS**

#### **INVESTIGATIONAL PLAN**

##### **Overall Study Design and Plan**

This was a randomized double-blind (for ZELAPAR), placebo-controlled, parallel group, multiple-dose study designed to define the ECG effects of ZELAPAR in healthy volunteer subjects at steady-state for selegiline compared to baseline, placebo, and a positive control (moxifloxacin). A total of 160 subjects were planned for randomization to 1 of 4 study treatments, with 40 subjects per treatment group. Each treatment group was balanced with respect to gender and consisted of 20 men and 20 women. Following an initial screening period (Day -21 to -1), qualified subjects were randomized in a 1: 1: 1: 1 ratio to one of the four treatment groups. A more detailed description of the study treatments and method of administration is provided in Table 1.

Table 1. Description of study treatments.

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Dose Group	N		Treatment
	Total	Male/Female	
1	40	20/20	ZELAPAR 2.5 mg Two 1.25 mg ZYDIS selegiline HCl tablets and six ZELAPAR placebo tablets QD po X 10 days
2	40	20/20	ZELAPAR 10.0 mg Eight 1.25 mg ZYDIS selegiline HCl tablets QD po X 10 days
3	40	20/20	Placebo Eight ZELAPAR placebo tablets QD po X 10 days
4	40	20/20	Moxifloxacin 400 mg Eight ZELAPAR placebo tablets QD po X 9 days One 400 mg moxifloxacin tablet po on Day 11 (10 <sup>th</sup> dosing day)

Subjects randomized to Group 1 or Group 2 received a clinical or suprathapeutic dose of ZELAPAR, respectively, once daily for 10 days. Subjects in Group 3 received placebo once daily for 10 days. The active and placebo treatments were blinded using a double-dummy dosing procedure. Subjects randomized to Group 4 served as a positive control group and received 9 daily doses of placebo followed by a single dose of open-label moxifloxacin on the tenth day.

This was a double-blind study with respect to ZELAPAR and placebo tablets. The ZELAPAR study medication was provided in a double-dummy manner so that all subjects in the ZELAPAR or placebo groups received eight tablets daily. Subjects in the moxifloxacin group received eight placebo tablets daily for the first 9 dosing days in a blinded manner. Open-label moxifloxacin was administered as one 400 mg tablet to these subjects on the 10th treatment day (Study Day 11).

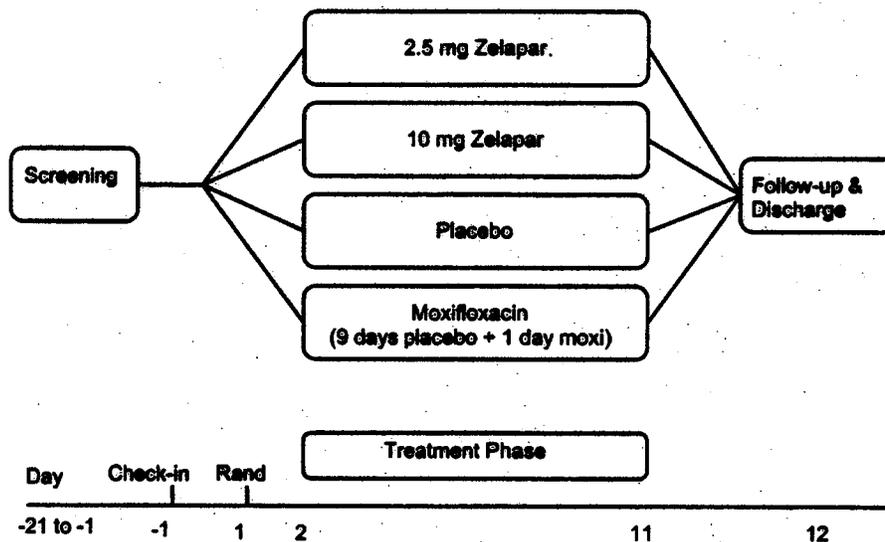
#### Treatments Administered

Each subject received one of the four 10 -day treatment regimens described in Table 1. Study medication was administered in the morning before breakfast. With the exception of the moxifloxacin tablet administered to subjects in Group 4 on Day 11, the study medication was taken without liquid and subjects refrained from ingesting food or liquid for 5 minutes before and after taking the medication. Subjects receiving moxifloxacin were allowed a sufficient amount of water to swallow the tablet.

The following study schematic, Figure 1, describes the entire course of the study:

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Figure 1 Study Schematic



#### Selection of Doses in the Study

The two doses of ZELAPAR chosen for this study were selected on the basis of the pharmacokinetic (PK) profile and safety of the two doses in healthy volunteers. The lower dose of ZELAPAR (2.5 mg/d for 10 days) was anticipated to yield the plasma concentrations of selegiline achieved at steady state with the recommended clinical dose and regimen. The higher dose (10 mg/d for 10 days) was selected in consultation with the FDA (May 25, 2004). This suprathreshold dose was predicted to provide approximately 4-5 times the steady state concentration of selegiline attained after 10 days of dosing with 2.5 mg per day and exhibit an acceptable safety profile as demonstrated in previous healthy volunteer studies. The target PD population is predominately elderly and too heterogeneous in terms of magnitude of disease states, concomitant medication use and co-morbidities. This could confound the conduct and interpretation of a definitive QT study, in light of the marked variability in QTc durations. Therefore, the firm used a homogeneous healthy population to facilitate the conduct and interpretation of a definitive QTc study in order to adequately define the potential of ZELAPAR to affect ECG parameters, in particular, cardiac repolarization.

Moxifloxacin was selected as the positive control to validate the sensitivity of the assay to detect a 5 msec increase in QTc interval duration. The Package Insert for moxifloxacin (AVELOX® tablets; Bayer Pharmaceuticals) states that following oral dosing with 400 mg moxifloxacin, the mean ( $\pm$ SD) change in QTc from the pre-dose value at the time of maximum drug concentration was 6 msec ( $\pm$ 26; n = 787).

The placebo group provided for a concurrent negative control and was used to correct for spontaneous variability in QTc duration. The risks of moxifloxacin and selegiline for causing clinically significant ECG effects as determined in clinical trials to date are remote and therefore, the risk to volunteers exposed for 10 days of therapy with selegiline

or a single dose of moxifloxacin was considered clinically acceptable with a wide margin of safety .

#### Digital 24-Hour ECG Assessment Methodology

Digital 12-lead ECG data were digitally obtained using a Mortara Instrument digital H-12 ECG continuous recorder. The ECG data were collected continuously every 10-15 seconds for all 12 leads simultaneously for a 24-hour period on Day 1 (baseline) and on Day 11, which coincided with the 10th and last dose of study medication. Each 10-15 second recording was separated by an interval of approximately one minute. Subjects assumed a supine or semi-supine position for 10-15 minutes prior to each ECG assessment time point in order to stabilize their resting heart rate. The ECG data for each subject were recorded on a 40 MB compact flash memory cards.

The ECG assessments were performed at 0.25, 0.5, 1,2,3,4,5,6,8, 12, 18, and 23.5 hours post-dose on Day 1 and Day 11 (since no study medication was administered on Day 1, the ECG assessment points corresponded to the Day 11 post-dose time points according to the clock). Both ECG assessment days provided a total of 36 baseline (Day 1 ) and 36 on-treatment (Day 11) measurements per subject. If the ECG data packet recorded at a given time point was of poor quality or showed artifacts, another 4-second data packet suitable for analysis was captured as close as possible to the specified time point.

#### Drug Concentration Measurements

Serial blood samples were obtained for the determination of selegiline plasma concentrations at specified times over an 8-hour period commencing immediately prior to dosing on Day 11. The timing of the blood sample collection was designed to measure the peak plasma concentration profile of selegiline to determine if any effect on the ECG parameters was related to the plasma levels of selegiline. Blood samples were obtained for selegiline analysis from all subjects, including those in the open-label moxifloxacin treatment group. Blood samples were not analyzed for moxifloxacin. The time points for blood sample collection were:

Pre-dose (0),0.25,0.5, 1,2,3,4,6, and 8 hours post dose  
All results were reported as free base (pg/mL).

#### ECG Analyses

The ECG intervals were analyzed to describe central tendency and outlier effects for heart rate and PR, QRS, QT, and QTc {QTc-I (individual correction), QTc-F, QTc-B} intervals. Baseline was defined as the mean of all of the values of ECG measurements taken on Day I.

The primary QT to QTci correction formula was derived for each subject using the 36 baseline ECGs (3 ECGs at each of 12 time points) taken on Day I. The QT-RR relationship was iterated to determine an individual correction exponent for each individual using NONMEM. The resulting exponent provided for a formula to fit a correlation line for all RR and QT points approximating a zero slope. This is considered the most accurate method for the correction of QT to QTc and was the primary endpoint of the trial.

The QTci was calculated by selecting the exponent of the standard QTc formula (i.e.,  $QT_{ci} = QT / (RR)^{**exponent}$ ) which, when plotting RR against QTci gave the slope closest to zero. Only baseline ECGs were used in the calculation of the exponent. This subject-specific exponent was then used for the calculation of all QTci.

QT intervals were also corrected using standard formulae:

Bazett's formula:  $QT_{cB} = QT / (RR)^{**1/2}$

Fridericia's formula:  $QT_{cF} = QT / (RR)^{**1/3}$

QT intervals corrected using Bazett's or Fridericia's formulae were considered secondary endpoints. Central tendency and outlier analyses were performed for each ECG interval.

#### Bioanalytical Method-

The maximum study sample storage period from first blood draw June 5, 2004 to last sample analysis on August 3, 2004 was 59 days.

Assay: HPLC/Plasma Tandem Mass Spectrometry

<b>Parameter</b>	Selegiline
Method	HPLC/Plasma Tandem Mass Spectrometry
Freeze-thaw	3 cycles
Benchtop Stability at RT	24 hrs
Long term at -80° C	283 days

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Recovery	Parent
Low	79%@374 pg/mL
Med	<u>83.1%</u> @6249 pg/mL
High	80%@ 8749pg/mL

Parameter	Selegiline
Method	HPLC/Plasma Tandem Mass Spectrometry
Sensitivity/LOQ	50 pg/ml
Linearity (Standard curve samples)	50-4999 pg/ml
Quality Control (QC) Samples	149, 2499, 3499, 1499 pg/ml
Precision of Standards (%CV)	5.0%@ 50.0pg/ml 2.8%@ 4999pg/ml
Precision of QC Samples (%CV)	4.88%@ 149pg/ml 3.91%@ 1499pg/ml
Accuracy of Standards (%)	99.2%@ 0.25 ng/ml 93%@ 10.2 ng/ml
Accuracy of QC Samples (%)	2.7%@ 1499 pg/ml 3%@ 149 pg/ml

## RESULTS

Table 2. Summary of Demographics and Baseline Characteristics

Demographic Characteristic	Zelapar 2.5 mg (N = 44)	Zelapar 10 mg (N = 45)	Placebo (N = 44)	Moxifloxacin (N = 44)
<b>Age (years)</b>				
Mean [SD]	32.6 [7.64]	31.9 [7.48]	29.1 [7.00]	30.3 [7.84]
Median	34.0	31.0	29.0	29.5
(Min - Max)	(18 - 44)	(19 - 45)	(18 - 44)	(18 - 45)
<b>Gender</b>				
Female (%)	22 (50.0%)	23 (51.1%)	22 (50.0%)	22 (50.0%)
Male (%)	22 (50.0%)	22 (48.9%)	22 (50.0%)	22 (50.0%)
<b>Race</b>				
Hispanic (%)	27 (61.4%)	28 (62.2%)	31 (70.5%)	25 (56.8%)
Black (%)	11 (25.0%)	11 (24.4%)	10 (22.7%)	10 (22.7%)
Caucasian (%)	6 (13.6%)	6 (13.3%)	3 (6.8%)	9 (20.5%)
<b>BMI (Kg/m<sup>2</sup>)</b>				
Mean [SD]	25.3 [2.92]	25.3 [2.84]	24.1 [2.78]	25.6 [3.05]
Median	25.3	24.4	24.0	25.8
(Min - Max)	(20 - 31)	(21 - 31)	(20 - 31)	(20 - 31)
SD = Standard Deviation				
BMI = Body mass index				
Data Source: Table 15.1				

Table 3. Summary of Mean (SD) Plasma Concentration of Selegiline by Treatment and Time at Steady-State on Study Day 11

Time (hours) <sup>a</sup>	2.5 mg ZELAPAR N completed = 40			10 mg ZELAPAR N completed = 44		
	n	Mean pg/mL	(SD)	n	Mean pg/mL	(SD)
0 (pre-dose)	40	6.79	(21.143)	43	185.29	(125.724)
0.25	40	984.44	(523.523)	44	3768.1	(2128.72)
0.5	30	1096.8	(542.309)	35	5440.2	(2671.13)
1	40	899.35	(589.102)	44	5289.3	(2361.07)
2	40	456.20	(350.143)	44	3161.2	(1503.89)
3	40	264.06	(211.444)	44	1880.9	(927.959)
4	30	175.28	(146.511)	34	1272.6	(626.925)
6	40	84.96	(81.145)	44	668.52	(308.887)
8	40	57.35	(63.282)	44	494.70	(239.063)

<sup>a</sup> The 0.5 and 4 hour sampling timepoints were added under Protocol Amendment No.1 after 2 cohorts (32 subjects) had completed the Day 11 procedures.

SD = Standard Deviation

Data Source: Table 15.3

Table 4. Mean Baseline ECG Parameters by Treatment

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Parameter (SD)	2.5 mg Zelapar N=44	10 mg Zelapar N=45	Placebo N=44	Moxifloxacin N=44
Heart Rate (bpm)	68.03 (9.449)	67.31 (7.472)	65.97 (6.521)	66.52 (7.150)
RR (msec)	916.51 (118.545)	922.56 (107.253)	942.61 (98.570)	934.77 (102.604)
PR (msec)	154.08 (17.574)	152.23 (17.383)	150.29 (14.877)	148.79 (17.173)
QRS (msec)	86.12 (6.067)	88.20 (5.738)	86.92 (6.214)	86.44 (4.911)
QT (msec)	387.66 (26.579)	382.05 (24.926)	387.44 (19.334)	390.15 (20.430)
QTcI (msec)	402.23 (21.934)	394.28 (21.397)	397.24 (16.936)	401.20 (16.206)
QTcB (msec)	407.86 (18.572)	400.56 (20.125)	402.09 (17.593)	406.57 (16.814)
QTcF (msec)	400.58 (17.560)	393.93 (19.231)	396.75 (15.692)	400.62 (15.007)

SD = Standard Deviation

Data Source: Table 15.5; Appendix 16.2, Listing 25

Table 5. Mean (SD) QTcI Change from Baseline at each Time Point on Day 11.

Time Point (h)	2.5 mg Zelapar	10 mg Zelapar	Placebo	Moxifloxacin
	Mean QTcI (SD) msec			
0.25	-3.68 (12.738)	-0.86 (13.417)	-1.36 (13.641)	-6.67 (13.847)
0.5	-9.05 (15.888)	-3.95 (16.472)	-4.68 (15.730)	-1.32 (15.509)
1	-11.45 (12.798)	-7.09 (13.743)	-4.20 (16.689)	2.19 (14.754)
2	-5.15 (15.994)	-4.65 (13.355)	-1.71 (12.966)	5.79 (16.114)
3	-3.28 (16.752)	-1.42 (15.684)	-4.63 (15.022)	7.85 (16.103)
4	2.34 (17.339)	-1.35 (17.246)	-0.61 (17.221)	4.85 (16.107)
5	0.64 (12.824)	2.78 (11.042)	1.56 (14.219)	6.41 (10.931)
6	-6.05 (12.674)	-2.72 (12.969)	-0.59 (17.320)	0.39 (20.516)
8	-2.87 (14.343)	-3.67 (12.964)	-1.15 (13.941)	2.61 (14.963)
12	0.18 (14.616)	1.73 (16.785)	-3.13 (10.020)	4.59 (15.209)
18	5.93 (10.751)	3.04 (15.066)	2.83 (12.706)	7.24 (18.185)
23.5	-1.95 (15.070)	-4.38 (12.907)	-4.56 (15.615)	0.01 (17.687)

SD = Standard Deviation

Data Source: Table 15.4.2; Appendix 16.2, Listing 25

Table 6. Comparison of the means  $\pm$  SD of the maximum QTC values based upon Bazett's and Fridericia's corrections for heart rate on the Seligiline 2.5 mg and 10 mg treatment groups compared to the positive control Moxifloxacin.

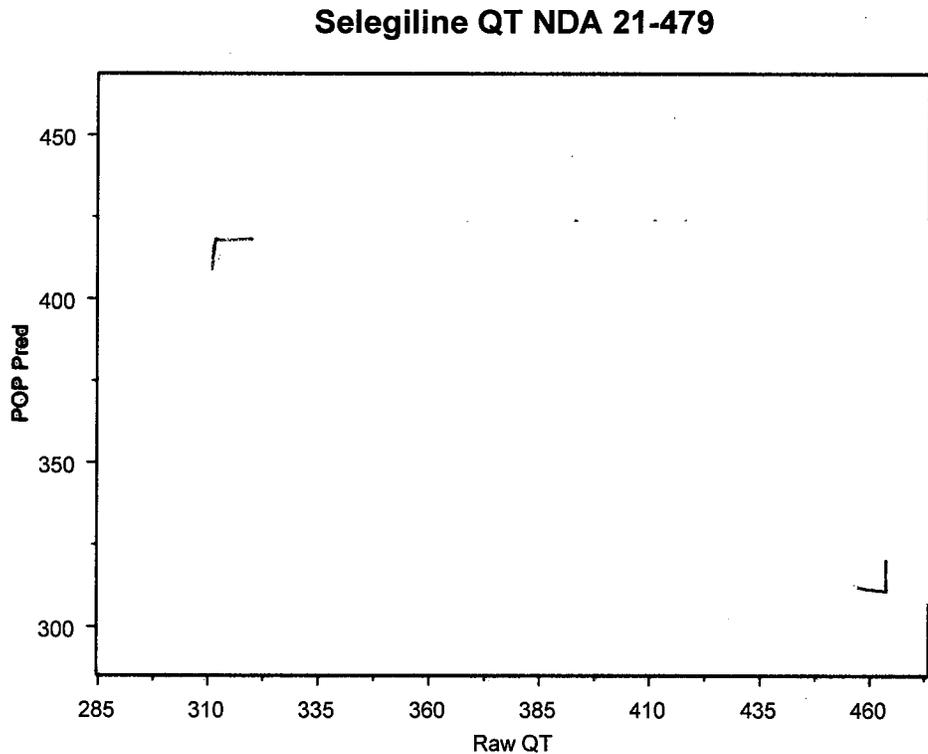
TREATMENT		
2.5 MG Seligiline	Bazetts	429.0+ 22.1 msec
	Fridericia	417.9 + 20.3 msec
10 MG Seligiline	Bazetts	422.9+19.9 msec
	Fridericia	410.5+ 19.6 msec

Moxifloxacin	Bazetts	425.19+ 15.9 msec
	Fridericia	437.3+ 16.2 msec

Table 7. Mean delta QTc  $\pm$  SD(baseline subtracted only) for subjects in the selegiline study.

TREATMENT	
2.5 mg Selegiline	-9.25 + 26.5 msec
10 mg Selegiline	-9.21 + 27.5 msec
Placebo	-10.06+ 28.1 msec
Moxifloxacin	-5.80 + 29.6 msec

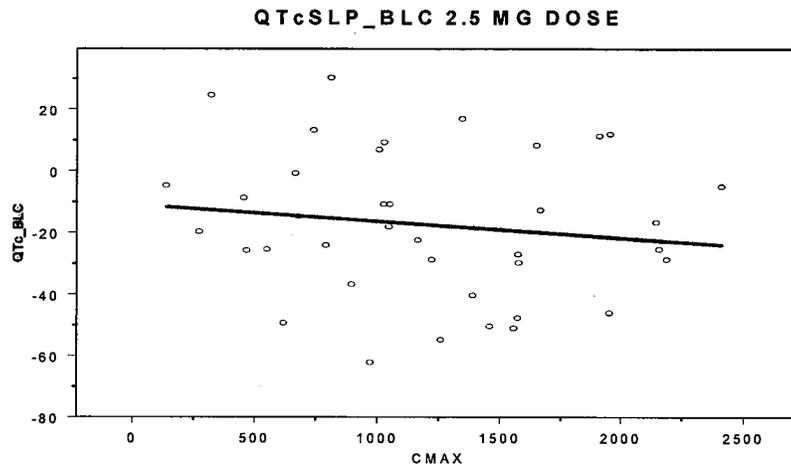
Figure 2. Comparison of the model predicted population QTci values with the observed raw QT values.



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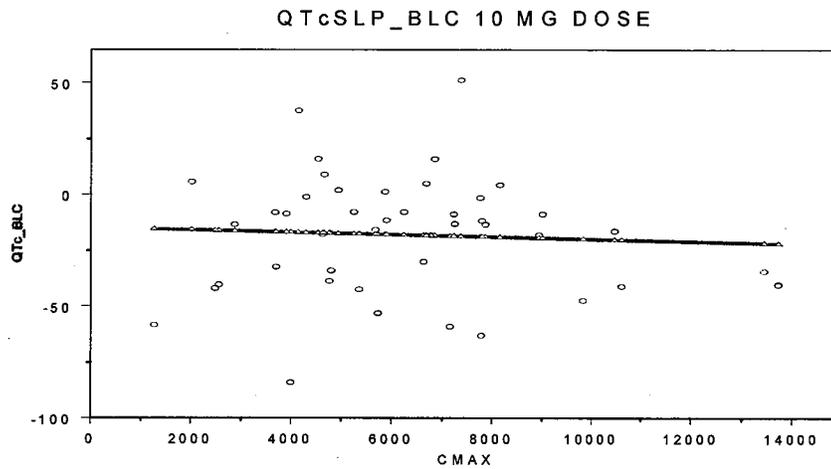
Figure 3. Relationship between the baseline corrected QT values QTc\_BLC and Cmax values for the 2.5 mg dose of selegiline.

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THETA:        1) INT            2) SLOPE  
 THETA        = -10.9            -0.00543

Figure 4. Relationship between the baseline corrected QT values QTc\_BLC and Cmax values for the 10 mg dose of selegiline.



THETA:        1) INT            2) SLOPE  
 THETA        = -14.7            -0.000531

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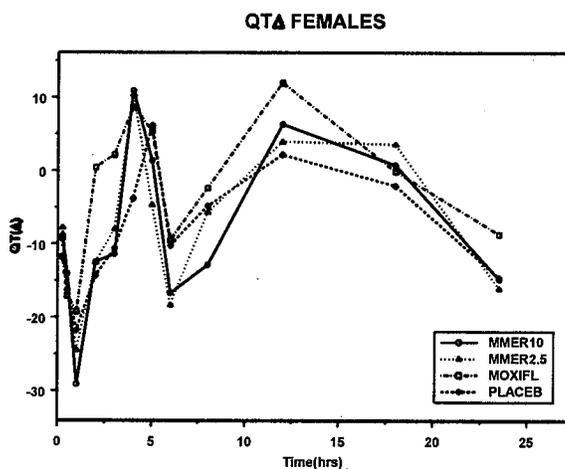


Figure 5. QTΔ values( baseline corrected) as a function of dose in females.

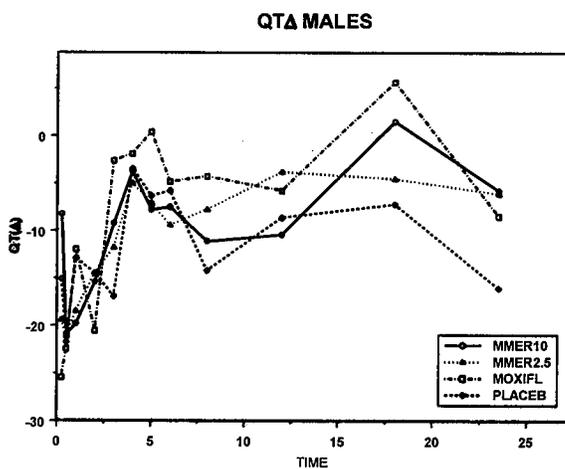


Figure 6. QTΔ values( baseline corrected) as a function of dose in males.

- The results in Table 5 shows a mean high of 7.85 msec increase at 3 hr for the positive control moxifloxacin treatment which is far below the reported 20 msec level which substantially increases the likelihood of the drug being proarrhythmic. All other values are well below 10 msec. For the treated groups no values was larger than 6 msec.

- **Results in Tables 6 and 7 for the Bazett's and Fridericia's corrections for heart rate** indicate mean values far below the 500 msec QTc prolongation which has been a concern in clinical trials.
- The population individual corrected values were well correlated with the raw QT values in Figure 2.
- There appeared to be a weak relationship between the QTc (baseline corrected values) single delta corrected and C<sub>max</sub> as shown by the slope of -0.00543 QTc\_BLC units change per unit of C<sub>max</sub> value. Also the slope was negative further supporting the lack of correlation for the 2.5 mg dose Figure 3. A similar result was observed for the 10 mg dose, Figure 4.
- Figures 5 and 6 show that there is no effect of dose on QTΔ although the QTΔ values for the females were higher than those for males, the active control Moxifloxacin was also higher than any of the treatments in females which makes it difficult to interpret this observation.

## **GENDER EFFECTS**

### **SINGLE DOSE**

#### **OBJECTIVE**

The objective of this analysis was to examine the effects of gender on the pharmacokinetics of selegiline when administered as the Zelapar™ Zydys tablet formulation.

#### **DATA SETS**

Selegiline pharmacokinetic parameters from all Phase I studies in which the Zelapar Zydys tablet was administered as a single dose under fasted conditions were used. Pharmacokinetic parameters were determined using standard, noncompartmental analysis. The studies, doses, and treatments used are summarized in Table I.

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**Table 1: Studies, doses, and treatments used in the analysis of gender effects on Zelapar Zydys pharmacokinetics.**

Study No.	Dose(s) <sup>1</sup>	Treatment Used
AN17933-101	1.25 mg, 2.5 mg, 5 mg	Single dose (Day 1)
Z/SEL/94/030	10 mg (2 × 5 mg)	Single dose
Z/SEL/95/001	10 mg	Single dose (Zydys, not swallowed)
Z/SEL/95/003	1.25 mg, 2.5 mg, 5 mg	Single Dose
Z/SEL/95/007	10 mg	Single dose (Day 1)
Z/SEL/95/023	1.25 mg	Single dose
Z/SEL/96/007	5 mg	Single dose
Z/SEL/96/008	5 mg	Single dose — fasting
Z/SEL/96/014	2.5 mg	Single dose (Day 1)

<sup>1</sup>Unless otherwise indicated, dose represents the strength of a single dosage unit.

The pharmacokinetic parameters examined were those calculated from plasma selegiline concentrations and are dose-normalized maximum concentration (C<sub>max</sub>); time to C<sub>max</sub> (T<sub>max</sub>); dose-normalized area under the curve to infinity (AUC<sub>0-inf</sub>); and elimination half-

life (t<sub>1/2</sub>). Not all parameters were available for all of the studies nor for all subjects within a study.

#### STATISTICAL ANALYSIS

The effect of gender on C<sub>max</sub>, AUC<sub>0-inf</sub>, and t<sub>1/2</sub> was examined using an analysis of variance with gender as the classification variable. Since T<sub>max</sub> is a discrete rather than continuous variable, the effect of gender was evaluated using the Wilcoxon Rank Sum test. For both types of analyses, differences were considered to be significant if the respective p-value was less than or equal to 0.05.

#### DATABASE

The database for the analysis included data from a total of 190 subjects, 72 females and 118 males.

#### RESULTS

As shown in Table 2, mean values for dose-normalized AUC<sub>0-inf</sub> and t<sub>1/2</sub> and median values for T<sub>max</sub> were comparable for males and females and p-values for the respective comparisons were not significant. This is further illustrated by the distributions within each gender, as illustrated in the box-and-whisker plots (Figure 1 - Figure 3, T<sub>max</sub>, AUC<sub>inf</sub>, and t<sub>1/2</sub>, respectively). Dose-normalized C<sub>max</sub>, however, was ~25% lower in female subjects than in male subjects, a difference that was statistically significant (p = 0.0222) (Table 2). This difference is also apparent from examination of the distribution

with gender (Figure 4) which shows a shift to lower values for dose-normalized Cmax in female subjects.

Table 2: Comparison of pharmacokinetic parameters between male and female subjects.			
Parameter <sup>1,2</sup>	Males	Females	p-value <sup>3</sup>
Cmax (ng/mL)	1.78 ± 1.31	1.36 ± 1.06	0.0222
Tmax (h)	0.25	0.25	0.1805
AUC <sub>∞</sub> (h•ng/mL)	1.13 ± 0.81	1.10 ± 0.71	0.8069
t <sub>1/2</sub> (h)	3.84 ± 4.76	3.59 ± 3.26	0.7240

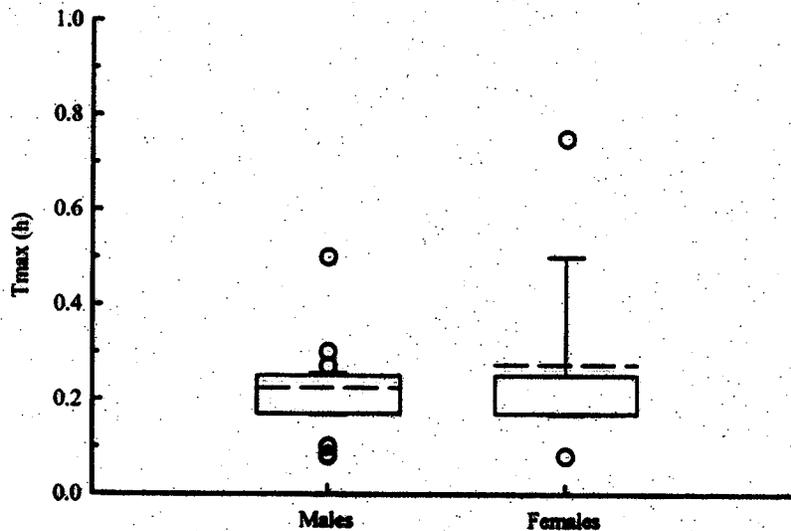
<sup>1</sup>Mean ± standard deviation except for Tmax for which the median is reported.

<sup>2</sup>Cmax and AUC<sub>∞</sub> were normalized to a 1.25 mg dose before analysis.

<sup>3</sup>p-value for the gender effect from an analysis of variance (Cmax, AUC<sub>∞</sub>, t<sub>1/2</sub>) or Wilcoxon Rank Sum Test (Tmax).

References: Appendix II → V.

Figure 1: Box-and-Whisker plot of Tmax by gender.



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Figure 2: Box-and-Whisker plot of dose-normalized  $AUC_{\infty}$  by gender.

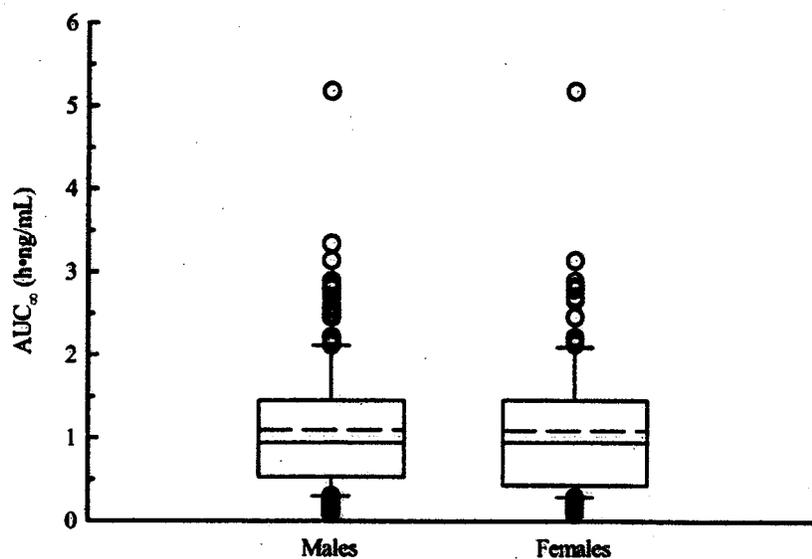
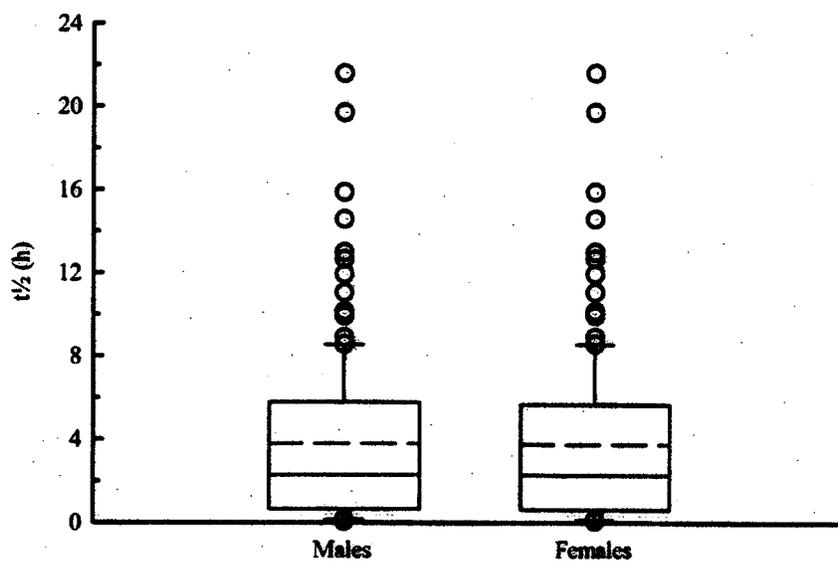
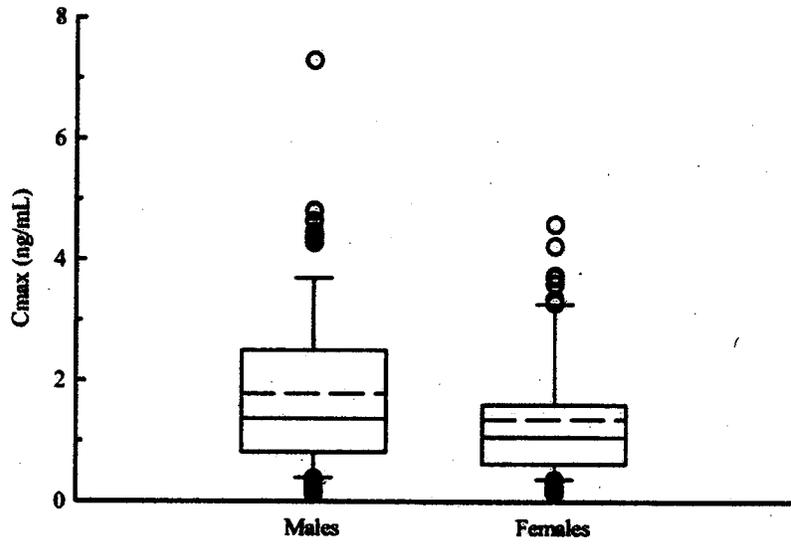


Figure 3: Box-and-Whisker plot of  $t_{1/2}$  by gender.



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Figure 4: Box-and-Whisker plot of dose-normalized C<sub>max</sub> by gender.



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## STEADY-STATE

### OBJECTIVE

The objective of this analysis was to examine the effects of gender on the pharmacokinetics of selegiline when administered as the Zelapar™ Zydys tablet formulation at steady-state.

### METHODS

The firm has conducted a thorough QT study RNA 6003-1-101 and a Tyramine study RNA ZEL-B21-102. The QT study was done in normal while the Tyramine study was done in subjects 40-70 yrs old. Study details are in the respective reviews for these studies. In each study subjects were dosed to steady-state.

The data from these studies were analyzed for gender differences.

### RESULTS

Table 1. Comparison of parameters by gender for normal subjects in the thorough QT study RNA 600301-101 at the 2.5 mg and 10 mg doses. All missing values were set to zero.

DOSE=2.5 MG							
PARAMETER		GENDER			GENDER		% DIFF FEMALE/MALE
		MALE			FEMALE		
	N	MEAN	STD	N	MEAN	STD	
AREA-TAU	19	2440.84	1757.5	21	2033.54	1358.86	16% DEC
C <sub>MAX</sub>	19	1309.33	624.3456	21	1167.79	580.369	11% DEC

DOSE=10 MG							
PARAMETER		GENDER			GENDER		% DIFF FEMALE/MALE
		MALE			FEMALE		
	N	MEAN	STD	N	MEAN	STD	
AREA-TAU	22	13422	5156.74	22	14716.13	7253.69	10% INC
C <sub>MAX</sub>	22	5792.69	1922.57	22	6692.57	3344.73	15% INC

Table 2. Comparison of parameters by gender for subjects in the Tyramine study (RNA-ZEL-B21-102) at the 2.5 mg, 5 mg and 10 mg doses. Subjects were 40-70 yrs old and N=3-7.

DOSE=2.5 MG							
PARAMETER		GENDER			GENDER		% DIFF FEMALE/MALE
		MALE			FEMALE		
	N	MEAN	STD	N	MEAN	STD	
AREA-TAU	6	5371.23	3578.61	5	5156.26	2962.46	4% DEC
CMAX	6	2016.23	847.3866	5	1879.94	677.8304	7% DEC

DOSE=5 MG							
PARAMETER		GENDER			GENDER		% DIFF FEMALE/MALE
		MALE			FEMALE		
	N	MEAN	STD	N	MEAN	STD	
AREA-TAU	7	12419.88	7162.90	5	11895.22	3744.91	4% DEC
CMAX	7	3863.54	1737.74	5	3037.56	630.67	21% DEC

DOSE=10 MG							
PARAMETER		GENDER			GENDER		% DIFF FEMALE/MALE
		MALE			FEMALE		
	N	MEAN	STD	N	MEAN	STD	
AREA-TAU	7	24312.01	8930.93	5	26966.15	16050.11	11% INC
CMAX	7	8076.14	2608.41	5	7740.65	4336.42	4% DEC

Comment:

1. Female Cmax values were 25% lower in single dose studies compared to males. For the multiple dose Tyramine study, females were 7% lower at 2.5 mg, 21% lower at 5 mg and 4% lower at 10 mg. There appears to be a trend for a lower Cmax in females, but it was not consistent in all studies (e.g., in QT study RNA 600301 Cmax increased by 15%). Overall there appears to be no Gender effect for Seligiline.

## COMMENTS ON THE LIVER AND RENAL REFERENCE

### 1. Clin Pharm and Therap 77, 54-62, 2005

Statistically significant changes in serum selegiline concentrations were observed in patients with altered liver function. The peak serum concentrations and AUC values were 7- and 18 fold higher in patients with impaired liver function and 15 and 23-fold lower in patients with drug-induced liver function. Patients with impaired kidney function had peak concentrations and AUC values 4-6 fold higher than normals.

## FIRM'S PROPOSED LABEL PHARMACOKINETICS

ZELAPAR™'s benefit in Parkinson's disease has only been documented as an adjunct to levodopa/carbidopa in patients with significant OFF time.

b(4)

b(5)

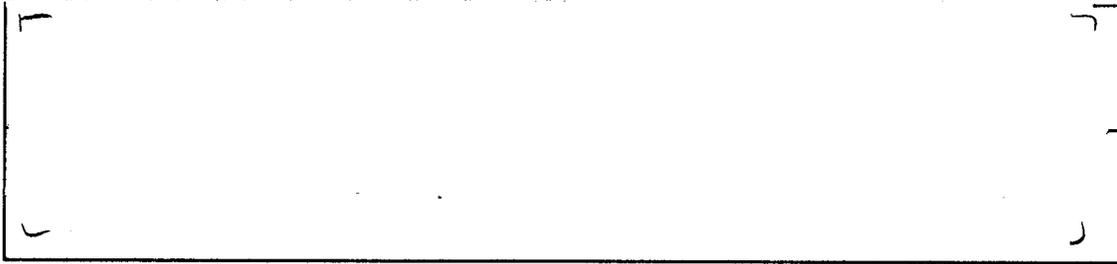
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       Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

✓ Draft Labeling (b5)

       Deliberative Process (b5)



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**SIGNATURES**

Andre Jackson \_\_\_\_\_

RD/FT Initialed by Raman Baweja,  
Ph.D. \_\_\_\_\_

Cc-NDA 21479, HFD-860 (Jackson, Baweja, Rahman, Mehta),  
Central Documents Room (Biopharm-CDR)

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# APPENDIX

## 1. Control Stream for QTc individual correction:

```
$PROB QT INDIVIDUAL CORRECTION
$DATA C:\Data\REVIEWS\SELEGILINE_NDA21479VALEANT\QTPLACraw.csv IGNORE=#
$INPUT ID RACE SEX TIME HT WT DV HR AGE

$PRED

TVAL=THETA(1)
TVB=THETA(2)

ETAL=ETA(1)
ETAB=ETA(2)

RR=60/HR

ALPHA = TVAL*EXP(ETAL)
BETA  = TVB*EXP(ETAB)

Y = ALPHA*(RR**BETA)*(1+ERR(1))

QTC=DV/(RR**BETA)

$THETA
(0,400)      ;ALPHA
(0,0.5)      ;BETA

$OMEGA

0.2          ;ALPHA
0.2          ;BETA

$SIGMA
0.01         ;PROPORTIONAL RESIDUAL ERROR

$EST METH=0 MAKEVAL=9999 PRINT=5 NOABORT POSTHOC
$COVARIANCE

$TABLE ID DV HR BETA Y RR QTC WT RACE SEX AGE
ONEHEADER NOPRINT FILE=qt.fitQT.FIT
```

## 2. Control Streams for model building:

### a. Intercept Model

```

$PROB CONCENTRATION QT ANALYSIS
$INPUT ID CMAX RACE SEX TIME AGE WT DV TMAX DROP
$DATA C:\Data\REVIEWS\SELEGILINE_NDA21479VALEANT\cmaxqt_1\CMXQT_1.csv
IGNORE=#
$PRED
    TVIN=THETA(1)
    ETIN=ETA(1)
    INT=TVIN +ERR(1)

Y=INT +ERR(1)

$THETA  -9

$OMEGA  5

$SIGMA  1

$EST METH=0 MAKEVAL=9999 PRINT=5 NOABORT POSTHOC
$COVARIANCE

$TABLE ID CMAX RACE SEX TIME AGE WT Y
ONEHEADER NOPRINT FILE=INTERCEPT

```

## b. Slope Model

```

$PROB CONCENTRATION QT ANALYSIS
$INPUT ID CMAX RACE SEX TIME AGE WT DV TMAX DROP
$DATA C:\Data\REVIEWS\SELEGILINE_NDA21479VALEANT\cmaxqt_1\CMXQT_1.csv
IGNORE=#
$PRED
    TVIN=THETA(1)
    TVSL=THETA(2)

    ETAIN=ETA(1)
    ETSL=ETA(2)

    INT=TVIN +ERR(1)
    SLP=TVSL+ETSL

Y=INT + (SLP*CMAX) +ERR(1)

$THETA
( -29)                ;1) INT
(0.002)                ;2) SLOPE

$OMEGA
( 5)                  ;1) ETA1
(0.001)                ;2) ETA2

$SIGMA  1              ;SIGMA

```

\$EST METH=0 MAXEVAL=9999 PRINT=5 NOABORT POSTHOC  
\$COVARIANCE

\$TABLE ID CMAX RACE SEX TIME AGE WT Y  
ONEHEADER NOPRINT FILE=SLOPE

### c. Concentration Model

\$PROB CONCENTRATION QT ANALYSIS  
\$INPUT ID CMAX RACE SEX TIME AGE WT DV TMAX DROP  
\$DATA C:\Data\REVIEWS\SELEGILINE\_NDA21479VALEANT\cmaxqt\_1\CMXQT\_1.csv  
IGNORE=#  
\$PRED

TVIN=THETA(1)  
TVSL=THETA(2)  
TVPL=THETA(3)

ETIN=ETA(1)  
ETSL=ETA(2)  
ETPL=ETA(3)

INT=TVIN+ETIN  
SLP=TVSL+ETSL  
PLB=TVPL+ETPL

Q=0  
IF (TIME.GT.0) Q=1

Y=INT+PLB\*Q+(SLP\*CMAX)+ERR(1)

\$THETA  
(-9) ;1) INTERCEPT  
(0.002) ;2) SLOPE  
(-1) ;3) PLACEBO

\$OMEGA  
5 ;1) ETA1  
0.0001 ;2) ETA2  
0.1 ;3) ETA3

\$\$SIGMA  
1

\$EST MAXEVAL=9999 SIGD=3 PRINT=10 METHOD=0 NOABORT POSTHOC

\$COV

\$TABLE ID CMAX RACE SEX TIME AGE WT Y  
ONEHEADER NOPRINT FILE=CONC

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/s/  
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Andre Jackson  
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Raman Baweja  
9/15/2005 02:30:08 PM  
BIOPHARMACEUTICS

Mehul Mehta  
9/15/2005 04:46:28 PM  
BIOPHARMACEUTICS

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## Clinical Pharmacology/Biopharmaceutics Review

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PRODUCT (Generic Name): Selegiline HCl  
PRODUCT (Brand Name): Eldepryl  
DOSAGE FORM: Immediate Release Tablets  
DOSAGE STRENGTHS: 1.25 mg  
NDA: 19-334  
INDICATION: Adjunct treatment for the management of Parkinson's disease in patients who are exhibiting deterioration of response to levodopa/carbidopa therapy  
NDA TYPE: Consult  
SUBMISSION DATE: July 21, 2003  
SPONSOR: Valeant Pharmaceuticals International.  
REVIEWER: Andre Jackson  
TEAM LEADER: Raman Baweja, Ph.D.  
OCPB DIVISION: DPE I, HFD 860  
OND DIVISION: HFD 120

### REPLY TO A CONSULT RELATED TO ORAL CONTRACEPTIVES AND SELEGILINE DRUG DRUG INTERACTIONS

#### **Comments to the MO Contraceptive Study:**

1. A single dose of selegiline was given at doses of 5, 10, 20 and 40 mg. Based upon median values there was a 16-45 fold increase in AUC and an 11-18 fold increase for C<sub>max</sub> selegiline levels. The data is inconsistent and difficult to interpret.
2. OCPB has responded to Dr. Feeney's inquiry as to how a Phase IV study should be designed.
3. OCPB has requested that the firm conduct a Phase IV study to investigate the drug-drug interaction between selegiline and oral contraceptives.

**4. A CAUTION SHOULD BE PLACED IN THE LABEL ABOUT POSSIBLE INCREASED SELEGILINE AUC AND CMAX LEVELS IN THE PRESENCE OF CONTRACEPTIVES.**

## **ORAL CONTRACEPTIVES**

The following Questions were consulted to OCPB on July 21, 2003 related to two publications on contraceptive use and selegiline. The request was forwarded by Theresa Wheelous:

At the request of Dr. Feeney, I am forwarding the following questions for your consideration.

Please review these 2 publications (Laine et al., Brit J. Clin Pharmacol 47:249-254, 1999 and Palovaara et al. Eur. J. Clin Pharmacol) about pharmacokinetic drug-drug interactions between selegiline and sex steroids. (I gave them to Veneeta) These 2 studies involved single dosing of selegiline. We have several questions to answer:

1. Would you recommend that the sponsor conduct studies to investigate the effects of female sex steroids on steady state dosing of selegiline dosed according to the U.S. regimen for selegiline such as 5 mg BID (at breakfast and lunch times, approximately 4 hours apart)?

### **OCPB Response**

The sponsor should conduct a study to investigate the effects of female sex steroids on steady state dosing of selegiline dosed according to the U.S. regimen for selegiline such as 5 mg BID.

2. Would you recommend studying the PK interaction with a commonly used form of oral contraceptive in the U.S. (? which one) and also hormone replacement therapy such as Premarin and medroxyprogesterone acetate (the most commonly used drugs in the U.S.) or would you recommend only studying a PK interaction of these drugs for hormone replacement therapy?

### **OCPB Response:**

There are two recent paper which discuss the effect of ethinylestradiol on CYP2C19 and hormone replacement therapy on CYP2B6 activity.

1. Clin Pharmacol Ther. 2003 Oct;74(4):326-33. Inhibition of cytochrome P450 2B6 activity by hormone replacement therapy and oral contraceptive as measured by bupropion hydroxylation.

2. Br J Clin Pharmacol. 2003 Aug;56(2):232-7. The effect of ethinylloestradiol and levonorgestrel on the CYP2C19-mediated metabolism of omeprazole in healthy female subjects.

OCPB recommends that the studies should be done with a product which contains ethinylloestradiol such as ORTHO TRI-CYCLEN which contains norgestimate and the estrogenic compound, ethinyl estradiol and is one of the top 200 drugs in US sales.

Based upon the first reference Premarin and medroxyprogesterone acetate as replacement therapy should also be studied.

3. If you recommend studying the PK interaction between selegiline and Premarin/medroxyprogesterone acetate, would you use the Prempro combination (Premarin 0.625 mg daily and medroxyprogesterone acetate 2.5 mg or 5 mg daily)?

**OCPB Response**

The highest dose should be studied i.e. Premarin 0.625 mg daily and medroxyprogesterone acetate 5 mg daily.

4. If you recommend conducting any PK studies, please specify your recommendations on how to conduct these investigations.

**OCPB Response**

The study could be designed similar to reference #1 as a three-way cross-over between Premarin 0.625 mg daily and medroxyprogesterone acetate 5 mg, selegiline and ORTHO TRI-CYCLEN. The focus of the study would be to determine the effect of the contraceptive on selegiline pharmacokinetics.

Phase I- subjects would receive only Selegiline for 9-10 days with measurements taken for drug levels on the final day.

Phase II- Subjects would be pre-treated with Prempro for 14 days and then administered selegiline 5 mg BID for 9 days with selegiline plasma samples taken on day 24.

Phase III - Subjects would be pre-treated with ORTHO TRI-CYCLEN for 14 days and then administered selegiline 5 mg BID for 9 days with selegiline plasma samples taken on day 24.

**COMMENTS ON THE ORAL CONTRACEPTIVE REFERENCES:**

**1. Eur J. Clin Pharmacol 58:,259-263, 2002**

12 Subjects received 2 mg estradiol valerate and 250 ug levonorgestrel. On day 10 a single 10 mg dose of selegiline was given. Data was highly variable 74-92% CV. Reported 59% increase in AUC for selegiline but no change for metabolites desmethylselegiline or methamphetamine. Data is inconsistent and can not be interpreted. Authors conclude no effect.

**2.Br. J. Clin Pharmacol 47, 249-254, 1999**

3 subjects received gestodene 75 ug/ethinylestradiol 30 ug and 1 subject levonorgestrel 50-125 ug/ ethinylestradiol 30-40 ug. A single dose of selegiline was given at doses of 5, 10, 20 and 40 mg. Based upon median values there was a 16-45 fold increase in AUC and a 11-18 fold increase for Cmax selegiline levels. Desmethylselegiline AUC values increased about 1-2.3 fold whereas there was no change for Cmax in the presence of the contraceptive. The increase in the desmethylselegiline values would be unexpected and makes the results a bit difficult to interpret.

Andre Jackson \_\_\_\_\_

RD/FT Initialed by Ray Baweja, Ph.D. \_\_\_\_\_

Team Leader

Cc NDA 19334, HFD-120, HFD-860(Jackson, Baweja, Mehta, Rahman), Central Documents Room (Biopharm-CDR)

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/s/

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Andre Jackson  
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9/15/2005 02:11:37 PM  
BIOPHARMACEUTICS

Mehul Mehta  
9/15/2005 04:52:35 PM  
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# Clinical Pharmacology/Biopharmaceutics Review PROTOCOL REVIEW

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PRODUCT (Generic Name): ZYDIS® Selegiline HCl  
PRODUCT (Brand Name): ZELAPAR ODT  
DOSAGE FORM: Orally Disintegrating Tablets (ODT)  
DOSAGE STRENGTHS: 1.25 mg  
NDA: 21-479  
INDICATION: Adjunct treatment for the management of **Parkinson's disease in patients who are exhibiting deterioration of response to levodopa/carbidopa therapy**  
NDA TYPE: Tyramine Test Protocol  
SUBMISSION DATE: 6/25/04  
SPONSOR: Valeant Pharmaceuticals International.  
REVIEWER: Veneeta Tandon, Ph.D.  
TEAM LEADER: Ramana Uppoor, Ph.D.  
OCPB DIVISION: DPE I, HFD 860  
OND DIVISION: HFD 120

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## PROTOCOL SYNOPSIS

**Protocol Number: RNA-ZEL-B102**

A Phase I Study in Healthy Subjects to Evaluate the Effect of Steady-State Doses of Zelapar® (Zydis® Selegiline HCl) on Blood Pressure Responses to Tyramine.

**Phase of Study:** Phase I

**Study Population:** Healthy subjects of both sexes 40 to 70 years of age (inclusive)

### **Study Design:**

This study is a multiple-dose, randomized, double-blind, double-dummy, positive controlled, placebo-controlled, parallel group study. A total of 5 groups of 16 subjects, 8 male and 8 female per group (80 subjects total) will be enrolled in this study, to complete up to 60 subjects for analysis purposes. Subjects will be housed continuously from baseline through the steady-state tyramine assessment. There will be no replacements for discontinuations. The effect of selegiline (Zelapar®) on tyramine-induced blood pressure elevations will be determined by assessing the effects of selegiline (Zelapar®) at steady state (after 10 days of dosing) compared to that at baseline.

Nardil® (Phenelzine sulfate) will be used as a positive control. After completing the baseline tyramine challenge, the Nardil® group will receive 15 mg once daily (morning) plus placebo for 3 days, then beginning on Study Day 4 a dose of 30 mg Nardil® (15 mg BID) daily. The positive control group will then undergo the tyramine challenge again. All other groups will concurrently receive Nardil® placebo to maintain the double-blind, double-dummy study design.

### **Dose and Administration:**

The Zelapar® tablet dissolves in seconds and is absorbed in the tissues of the mouth. There is no need to swallow or use liquid in conjunction with this dosage. Study medication should be taken in the morning and without liquid. Subjects should avoid ingesting food or liquid for 5 minutes before and after taking the study medication.

<u>Dosing Group</u>	<u>Gender (N)</u>	<u>Dosage</u>
1	Males (8) Females(8)	<b>Zelapar® 2.5 mg once a day orally</b>
		Morning
		Two 1.25 mg Zelapar® tablets
		Six Zelapar® placebo tablets
		One placebo Nardil® capsule

2	Males (8) Females(8)	Evening 8:00 PM	One placebo Nardil® capsule
		<b>Zelapar® 5 mg once a day orally</b>	
		Morning	Four 1.25 mg Zelapar® tablets Four Zelapar® placebo tablets One placebo Nardil® capsule
3	Males (8) Females(8)	Evening 8:00 PM	One placebo Nardil® capsule
		<b>Zelapar® 10.0 mg once a day orally</b>	
		Morning	Eight 1.25 mg Zelapar® tablets One placebo Nardil® capsule
4	Males (8) Females(8)	Evening 8:00 PM	One placebo Nardil® capsule
		<b>Placebo Group</b>	
		Morning	Eight Zelapar® placebo tablets One placebo Nardil® capsule
5	Males (8) Females(8)	Evening 8:00 PM	One placebo Nardil® capsule
		<b>Positive Control – Nardil® Group</b>	
		Morning	<b>Days 1- 3:</b> Eight placebo Zelapar® tablets One 15.0 mg Nardil® capsule <b>Days 4 - 16:</b> Eight placebo Zelapar® tablets One 15.0mg Nardil® capsule
		Evening 8:00 PM	<b>Days 1- 3:</b> One placebo Nardil® capsule <b>Days 4 – 16:</b> One 15.0mg Nardil® capsule

**Duration of Treatment:** Up to 16 days of dosing with study medication

**Primary Objectives:**

- To evaluate the effect of Zelapar® on potential blood pressure elevations induced by tyramine.
- To determine if Zelapar® induces orthostatic hypotension. The primary outcome measures will be systolic and diastolic blood pressure both lying and standing for 2 minutes, and the change in systolic and diastolic blood pressure after standing for 2 minutes.

**Secondary Objectives:**

- To assess if effects on tyramine-induced blood pressure elevations are correlated with peak selegiline concentrations or other pharmacokinetic parameters.
- To measure safety and tolerance of Zelapar® tablets via routine monitoring of adverse events (AEs) and other safety assessments, e.g., clinical laboratory testing.

**Subjects:**

80 subjects will be enrolled at two sites to complete up to 60 subjects. Age 40-70 years (inclusive)

**Inclusion Criteria:**

Have a BMI  $\geq 18.5$  and  $\leq 30.0$  kg/m<sup>2</sup> and weigh at least 50 kg;

Be in good general health and have no significant or past diseases

If female, be either of non-childbearing potential or, if of child-bearing potential, be using or agree to use an acceptable method of contraception (which must also include a barrier method if using a hormonal contraceptive).

**Exclusion Criteria:** Known or suspected hypersensitivity to any of the components of Zelapar® (Zydis® selegiline HCl) orally disintegrating tablets, Nardil® (Phenelzine sulfate) tablets or tyramine capsules;

Systolic blood pressure (SBP) < 100 or > 140 mmHg, diastolic blood pressure (DBP) <60 or > 85 mmHg, pulse rate <50 or > 100 bpm at screening or before the first dose of tyramine, unless a repeat test within 15 minutes later shows values within these ranges; History of undiagnosed chest pain or vascular malformation, including intracranial aneurysm (with the exception of minor skin vascular malformations);

Any disease or condition that might affect drug absorption, metabolism or excretion or compromise the cardiovascular, hematological, renal, hepatic, pulmonary, endocrine, central nervous, or gastrointestinal systems (unless deemed not clinically significant by the Investigator and the Sponsor);

History of alcoholism or drug addiction, use of any recreational drugs within 3 months prior to receiving study medication, or positive screen for substances of abuse pre-study;

Positive screen for hepatitis B surface antigen (HbsAg), hepatitis C antibody or HIV antibody;

A female who is pregnant or lactating, or has a positive pregnancy test result (serum human  $\beta$ -chorionic gonadotrophin [ $\beta$ -hCG]) pre-study;

Does not have a systolic blood pressure response of  $\geq 15$  mm Hg for three consecutive measures during the baseline tyramine challenge portion of the study (defined as a non-responder);

Chronic use of systemic medications, use of a drug therapy (including herbal preparations, e.g. **St. John's Wort**) known to induce or inhibit drug metabolism within 30 days prior to dosing; or use of any medications (prescription or over-the-counter, including antacids, multivitamins, nutritional supplements, and herbal preparations), within 14 days prior to dosing, unless approved by the Sponsor;

Subjects who smoke more than 10 cigarettes a day (by history only);

Receipt of an investigational drug or product, or participation in a drug study within a period of 30 days prior to receiving study medication; for investigational drugs with a  $t_{1/2}$  greater than 15 days, this will be extended to 60 days, or five-times the  $t_{1/2}$ , whichever is longer;

An employee or contractor of the facility conducting the study;

#### **Procedures:**

After baseline screening for inclusion/exclusion criteria, subjects will be admitted to the clinic remain at the site for the duration of the study. Subjects will be admitted to the clinic by 5:00 PM **on Study Day -7. Starting on Study Day -6**, subjects will be evaluated for orthostatic hypotension. **On Study Day -5, subjects will begin** a set of tyramine challenge tests to determine their blood pressure response over the course of tyramine dosing at baseline. Tyramine will be given 10 minutes prior to the scheduled morning dose of drug or double blind placebo. Tyramine testing for baseline will be scheduled as follows:

Study Day	Tyramine Dose
-5	25 mg
-4	50 mg
-3	100 mg
-2	200 mg
-1	400 mg

The subjects will take oral tyramine in gelatin capsules. Subjects will become semi-supine and measurements of heart rate and BP will be made at 10 minute intervals for the next 120 minutes. BP measurements will continue to be taken every 15 minutes for the next hour (for a total of 3 hours of BP and heart rate measurements following tyramine challenge). If a subject develops a significant hypertensive response requiring intervention following a dose of tyramine, the subject may not be advanced to a higher dose of tyramine based on the resultant BP levels during the study and the clinical judgment of the investigator.

Subsequently, any subjects that had a baseline systolic blood pressure increase of  $\geq 15$  mm Hg for three consecutive measures during baseline tyramine challenge will be randomized to receive either Zelapar<sup>®</sup> (2.5 mg), Zelapar<sup>®</sup> (5 mg), Zelapar<sup>®</sup> (10 mg), Nardil<sup>®</sup>, (3 days of Nardil<sup>®</sup> 15 mg once a day then Nardil<sup>®</sup> 15 mg BID), or placebo for 10 days to ensure steady-state conditions. Starting on Study Day 9, subjects will undergo evaluations for orthostatic hypotension starting after the morning dose. The tyramine challenge tests (as described above) will be repeated in the **clinical trials unit for Study Days 11 – 16, with one additional tyramine dose.** The additional dose will be lower than the previous tyramine doses and will be given on Study Day 11, as outlined in the following table:

Study Day	Tyramine Dose
11	12.5 mg
12	25 mg
13	50 mg
14	100 mg
15	200 mg
16	400 mg

One dose of tyramine will be given each day. In total, each subject could potentially undergo a maximum of 11 tyramine challenge tests, each lasting approximately 3 hours in a clinical trials unit.

**Orthostatic Blood Pressure Evaluations:**

On Study Day-6 through Study Day-5 and on Study Day 9 through Study Day 10, vital signs (systolic and diastolic blood pressure and heart rate will be recorded at rest after the subject has been supine for 5 minutes (using a validated automatic blood pressure machine [Welch-Allyn Vital Signs Monitor] at the brachial artery) and then again after the subject has been standing at rest for 2 minutes. These vital signs will be recorded pre-dose, and 0.5, 1, 2, 4, 6, 8, 10 and 24 hours after the morning dose of study medication. Heart rate will also be obtained from the blood pressure machine. Throughout the study, the same arm will be used for blood pressure measurements in each subject.

**Vital Signs**

Vital signs will be taken after subjects have rested in a supine position for at least 5 minutes. Heart Rate and Blood Pressure will be repeated after at least two minutes in a standing position. The normal ranges for vital signs are:

Sign	Normal Range
Oral body temperature	Between 35.0 and 37.5 °C
Systolic Blood Pressure	Between 100 -140 mmHg
Diastolic Blood Pressure	Between 60 - 85 mmHg
Heart Rate	Between 50-100 bpm

Vital signs will be obtained at Screening and Study Day -7 through Study Day 16, and at Discharge. The actual time of vital signs measurements will be recorded.

**Pharmacokinetic Evaluation:**

Blood samples will be obtained for analysis of selegiline concentration at 11 time points during the collection interval. These samples will be analyzed to identify peak and delayed concentrations to allow verification and to assess any correlation between tyramine challenge response findings with selegiline blood concentrations.

On Study Days 10 through 11, a total of 11 blood samples will be collected following the morning dosing for pharmacokinetic analysis: pre-dose (0), and post-dosing at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours for analysis of selegiline concentration.

**Analysis:** The primary safety concern is that while on steady-state clinical doses of Zelapar<sup>®</sup>, ingestion of tyramine could lead to an accelerated hypertensive episode. Thus, the primary analysis will be based upon a comparison of the mean blood pressure response for each treatment group of Zelapar versus placebo and a positive control non-specific MAO inhibitor (Nardil<sup>®</sup>).

Efficacy analyses will be conducted for two populations: intent-to-treat and per protocol. Descriptive statistics will be presented for the observed blood and heart rate values, but analysis will be performed on change from baseline. Endpoint is defined as the effect measured following the highest tyramine dose administered during randomized treatment. For analyses conducted on results obtained at the scheduled visits, missing values in the ITT population will be imputed using the last observation carried forward (LOCF) method; missing values will not be imputed for the per protocol population. No adjustment will be made for multiple comparisons.

Summaries of baseline variables by treatment group will be presented with appropriate descriptive statistics.

**Primary Outcome Measures:** Three primary analyses will be conducted:

- In the first analysis, change from baseline in peak SBP response at endpoint will be compared among the four active treatment groups and placebo.
- In the second analysis, the log tyramine dose required to produce a 30 mmHg increase in peak SBP response will be compared between the Zelapar<sup>®</sup> and Nardil<sup>®</sup> treatment groups.
- In the third analysis, systolic and diastolic blood pressures both lying and after standing for 2 minutes will be recorded and the change in systolic and diastolic blood pressure after standing for 2 minutes (orthostatic blood pressure) will also be recorded. These blood pressure measure will be compared among the four active treatment groups and placebo.

**Secondary Outcome Measures:** The secondary outcomes will be

- The blood pressure response to tyramine challenge will be compared to peak blood concentrations of selegiline
- tyramine ED<sub>25</sub>, ED<sub>50</sub> and ED<sub>75</sub>
- relative potency
- change from baseline in peak SBP at each tyramine dose

- log tyramine dose required to produce a 20, 25, or 30 mmHg increase in peak SBP response
- ratio of doses producing a 20, 25, or 30 mmHg increase in peak SBP response (TPR)
- change from baseline in mean SBP (measured over the 2-hour observation period)
- change from baseline in peak and mean DBP and pulse rate
- factorial response surface
- safety and tolerance via routine monitoring of adverse events (AEs) and other safety assessments, e.g., clinical laboratory testing.
- Secondary analyses will be conducted for the intent to treat (ITT) and per protocol (PP) populations. In addition, descriptive analyses will be presented to examine the effect of gender and age at endpoint.

### Statistical Analysis:

#### Primary Effect Analysis

Three primary analyses will be conducted.

**1. Change from baseline in peak systolic blood pressure (SBP) response at endpoint:**

On any day that a dose of tyramine is given, SBP is measured at ten minute intervals for 120 minutes and at fifteen minute intervals for 60 minutes for a total of sixteen measurements. The largest of these sixteen measurements is called *peak systolic blood pressure*. From the peak systolic blood pressure the pre-dose systolic blood pressure is subtracted and called the *change from pre-dose peak SBP*. For this analysis the response measure is the difference between the *change from pre-dose peak SBP* for the largest dose of tyramine during steady state and the *change from pre-dose peak SBP* for the corresponding dose of tyramine during baseline, ie. a difference of differences. For a subject that completes the full range of tyramine dosing, this would be the *change from pre-dose peak SBP* on day 16 minus his *change from pre-dose peak SBP* on day -1.

The statistical model is the one-way classification model. Each of the active treatments will be compared to placebo using a contrast statement in SAS proc mixed.

**2. The log tyramine dose required to produce a 30 mmHg increase in peak SBP response will be compared between the Zelapar and Nardil treatment groups:**

For each subject, the four-parameter logistic function will be used to model peak SBP as a function of log-dose tyramine. Data from study Days 11 through 16 will be used to fit the curve using SAS proc nlmixed. Then the log tyramine dose required to produce a 30 mmHg increase in peak SBP response will be calculated from the curve and will be the response measure for this analysis. In the event that some subjects do not achieve a 30-mmHg increase in peak SBP response, 20 mmHg or 25 mmHg will be used.

The statistical model for this response is the one-way classification model. The group comparisons are: 1 versus 5, 2 versus 5, and 3 versus 5.

The dose-response curve relating SBP to log-dose tyramine is known to have a sigmoid shape from historical studies. The four-parameter logistic function was selected because of its flexibility and interpretation.

**3. Systolic and diastolic blood pressure (DBP) both lying and after standing for 2 minutes and the change in systolic and diastolic blood pressure after standing for 2 minutes (orthostatic blood pressure):**

Toward the end of dosing to steady state (Day 9), each subject will have orthostatic blood pressure and heart rate measurements. Systolic and diastolic blood pressures both lying and after standing for 2 minutes will be recorded and the change in systolic and diastolic blood pressure after standing for 2 minutes (orthostatic blood pressure) will also be recorded. These same quantities are also calculated during **baseline (Day -6). The difference between the Day 9 values and the Day -6 values are the response variables** for this analysis. The one-way classification model is assumed for the orthostatic change in SBP, DBP, and heart rate. Each active treatment group will be compared to placebo.

The proportion of subjects exhibiting clinically significant orthostatic hypotension (decrease in SBP  $\geq 20$  mmHg or DBP  $\geq 10$  mmHg) will be calculated. Each of the active treatment groups will be compared to placebo with respect to **orthostatic hypotension using Fisher's exact test**.

## Secondary Analyses

**Correlation of blood pressure response to tyramine challenge with the peak blood concentrations of selegiline:** On Study Day 10, eleven blood samples are taken from each subject in groups 1, 2, and 3 for the analysis of selegiline concentration. The largest of the eleven concentrations is called the peak concentration of selegiline. The peak concentration of selegiline and blood pressure elevations induced by the highest dose of tyramine constitute a bivariate response. The correlation coefficient of these responses will be calculated across subjects. It should be noted that this measures linear association only.

**Tyramine ED<sub>25</sub>, ED<sub>50</sub> and ED<sub>75</sub>:** The analysis here is similar to the second primary analysis --- the difference being that the emphasis is on a percentage of the range of responses rather than a fixed specified response. Two parameters of the four-parameter logistic function represent the lower and upper bounds for the response. ED<sub>50</sub> is the dose that produces a response equal to (1-0.5) times the lower bound plus 0.5 times the upper bound. ED<sub>25</sub> and ED<sub>75</sub> are analogously defined. Tyramine ED<sub>25</sub>, ED<sub>50</sub> and ED<sub>75</sub> will be calculated for the response peak SBP for each subject. Each active treatment will be compared to the placebo separately for each ED. A one-way classification model is assumed.

**Relative potency:** Here relative potency is quantified by the ratio of the group average ED<sub>50s</sub>. Relative potency of each of the selegiline groups to the positive control will be calculated.

**Change from baseline in peak SBP at each tyramine dose:** The change from baseline in peak SBP at each tyramine dose will be calculated for each subject ie. peak SBP at day 12 minus peak SBP at day -5 and similarly for Days 13 and -4, 14 and -3, 15 and -2, and 16 and -1. Each of these differences will be analyzed separately. Assuming a one-way classification model, all active treatments will be compared to placebo.

**Change from baseline in mean SBP (measured over the 2-hour observation period):** Change from baseline in mean SBP (measured over the 2-hour observation period) will be calculated for each subject. This will be calculated for the end point tyramine dose. Assuming a one-way classification model, all active treatments will be compared to placebo.

**Change from baseline in peak and mean DBP and pulse rate:** Change from baseline in peak DBP, mean DBP, and pulse rate will be calculated for each subject. This will be calculated for the end point tyramine dose. All active treatments will be compared to placebo separately for each of these measures. The one-way classification model is assumed.

#### **Analysis of Safety and Adverse Events**

All patients who completed informed consent and received at least one dose of double-blind test medication will be included in the analysis of safety.

Patient safety will be assessed through the monitoring and reporting of any adverse events that occur during the study and other safety parameters obtained at baseline and post-treatment, including physical examinations, clinical labs, ECGs, vital signs, and body weight.

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### Study Activities

	Days -28 - -3	Day -7	Day -6	Day -5	Days -4 to -1	Days 1-10	Days 1-10	Days 1-10	Day 9	Day 10	Days 11-16	Discharge
	Screen	Study Admittance	Orthostatic BP	Tyramine Challenge Baseline		Selegiline Dosing to Steady State	Nardil® Dosing to Steady State	Orthostatic BP	pK Sample Collection	Tyramine Challenge at Steady State		
Informed Consent	X											
Med History	X											
Inclusion/Exclusion Criteria	X											
Physical Exam	X											X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X
Safety ECG	X	X										X
Exercise Stress ECG (readable)	X											
Clinical Lab Tests	X	X										X
HIV, Hepatitis B/C	X											
Blood alcohol and urine screen	X	X										
Pregnancy Test (hCG)	X	X										X
Overnight stay		X	X	X	X	X	X	X	X	X	X	
Orthostatic BP			X	X <sup>a</sup>				X	X <sup>a</sup>			
Randomization						X						
	Screen	Day -7	Day -6	Day -5	Days -4 to -1	Days 1-10	Days 1-10	Days 1-10	Day 9	Day 10	Days 11-16	Discharge



## RECOMMENDATION

The following comments regarding protocol RNA-ZEL-B21-102 should be conveyed to the sponsor:

- Since peak concentrations of selegiline are reached within 10-15 minutes post dose, it is recommended to include a 5 and 10 minute blood sampling time point in addition to the predose, 15 and 30 minute, 1, 2, 3, 4, 6, 8, 12, 24 hours blood sampling time proposed in the protocol.
- It is recommended to take trough samples on Days 8 and 9 as well to assure that steady state has been reached at the time of tyramine challenge.
- Section 5.8 of the protocol describes the vital signs measurements, but does not give the details of when the vital signs would be measured in relation to the dosing during the tyramine challenge days and the frequency of these measurements. No details have been provided in the Table summarizing the study activities in Appendix I. These details should be included in the protocol.
- Nardil<sup>®</sup> is marketed as tablets. It is not clear from the protocol whether the sponsor intends to encapsulate the Nardil<sup>®</sup> tablets. If the sponsor intends to do that for blinding purposes, in vitro dissolution studies should be conducted to show similarity between the encapsulated Nardil<sup>®</sup> and the Nardil<sup>®</sup> tablets using f2 comparisons.

Veneeta Tandon, Ph.D.  
Pharmacokineticist  
Division of Pharmaceutical Evaluation I

Team Leader: Ramana Uppoor, Ph.D. \_\_\_\_\_

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Veneeta Tandon  
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Ramana S. Uppoor  
8/11/04 10:12:07 AM  
BIOPHARMACEUTICS

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## Clinical Pharmacology/Biopharmaceutics Review

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PRODUCT (Generic Name): ZYDIS® Selegiline HCl

PRODUCT (Brand Name): ZELAPAR ODT

DOSAGE FORM: Orally Disintegrating Tablets (ODT)

DOSAGE STRENGTHS: 1.25 mg

NDA: 21-479

INDICATION: Adjunct treatment for the management of Parkinson's disease in patients who are exhibiting deterioration of response to levodopa/carbidopa therapy

NDA TYPE: 505(b)(2)

SUBMISSION DATE: 3/29/02, 6/10/02, 6/21/02, 7/26/02, 8/29/02

SPONSOR: Elan Pharmaceuticals Inc.

REVIEWER: Veneeta Tandon, Ph.D.

PHARMACOMETRICS REVIEWER: Andre Jackson, Ph.D

TEAM LEADER: Ramana Uppoor, Ph.D.

PHARMACOMETRICS TEAM LEADER: Joga Gobburu, Ph.D.

OCPB DIVISION: DPE I, HFD 860

OND DIVISION: HFD 120

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B inhibition is the urinary concentration of phenylethylamine (PEA), which increases with the inhibition of MAO-B. The clinical model for assessing MAO-A inhibition is the Tyramine Challenge Test, which is an assessment of safety of MAO-inhibitors. Selegiline is known to inhibit MAO-A at higher doses. Inhibition of MAO-A leads to cardiovascular effects such as hypertension (called 'Cheese Reaction' to ingested dietary tyramine). Other markers although not as sensitive as the tyramine test, include the measurement of plasma 3-methoxy-4 hydroxyphenyl glycol (MHPG) levels and urinary excretion of 5-hydroxy indole acetic acid (5-HIAA), both of which decrease with the inhibition of MAO-A.

Disintegration specifications have been provided in lieu of dissolution specifications for this NDA as a quality control test for assessing the quality of Zydis selegiline product, because dissolution of the product was very rapid in all three media ( \_\_\_\_\_ ). The disintegration specifications for the Zydis tablets are 'not more than \_\_\_\_\_'. All tablets from pivotal biobatches disintegrated in less than \_\_\_\_\_.

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The clinical pharmacology and biopharmaceutics findings from the review of this NDA are discussed under the section 'Overall summary of Clinical Pharmacology and Biopharmaceutics Findings' on page 6.

## RECOMMENDATIONS

The Clinical Pharmacology and Biopharmaceutics section of NDA 21-479 is acceptable, provided the sponsor addresses the following comment regarding drug metabolism, urinary excretion, food effect and gender effect and the labeling changes recommended on pages 24-27. In addition to these comments, there is lack of information on the pharmacokinetics of Zydis selegiline in special populations. The sponsor needs to address these issues as Phase 4 Commitments.

### COMMENTS TO THE SPONSOR:

Regarding Drug Metabolism: In the labeling for Zydis selegiline, the sponsor has included a section on 'Cytochrome P450 enzymes' under 'DRUG INTERACTIONS'.

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\_\_\_\_\_ A literature search conducted by the reviewer revealed that this was not a comprehensive list of isoenzymes responsible for the metabolism of selegiline. Various conflicting literature articles have been published regarding the metabolism of selegiline. The sponsor has referenced only one literature article. The sponsor should either conduct a thorough literature search and update the proposed label or conduct in vitro metabolism studies (if inadequate information is available in literature) to evaluate the CYP 450 isoenzymes responsible for the metabolism of selegiline and update the label based on results of these studies. The sponsor should also characterize the inhibition/induction potential of selegiline by conducting in vitro studies or obtain from literature if available.

Additional drug-drug interaction studies may need to be considered depending on the information gathered on the metabolism of selegiline.

Regarding urinary excretion: The sponsor states in Volume 1, page 154, that the urinary excretion of selegiline and its metabolites is 86% of the oral dose with 59% being recovered as L-methamphetamine and 26% recovered as L-amphetamine. The sponsor also provides references associated with this sentence. The reviewer could not locate this information in the literature. Please highlight in the referenced article, the section from which this information was obtained. It appears that only 44-58% of the dose has been recovered in the urine based on Shin's article.

Regarding Food Effect: It is unclear why an opposite food effect is observed in Study Z/SEL/96/008 as that known for approved product Eldepryl. The sponsor should explain the results obtained.

Regarding Gender Effect: The sponsor should conduct a meta-analysis to characterize the effect of gender on the pharmacokinetics of Zydys selegiline and include appropriate information in the labeling of the product.

Phase 4 Commitments:

- The sponsor should conduct a pharmacokinetic study in subjects with hepatic impairment.
- The sponsor should conduct a pharmacokinetic study in subjects with renal impairment since selegiline is excreted mostly renally (although mostly as metabolites, these contribute to the activity of the drug to some extent).

Veneeta Tandon 1/17/03

Primary Reviewer:

Veneeta Tandon, Ph.D.  
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 1/17/03

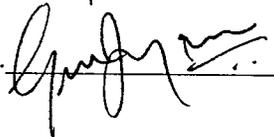
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Team Leader: Ramana Uppoor, Ph.D.

 01/17/03

Pharmacometrics Team Leader: Joga Gobburu, Ph.D.



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**OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS FINDINGS**

**QUESTION BASED REVIEW**

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## (A) GENERAL ATTRIBUTES

### I) DRUG/DRUG PRODUCT INFORMATION

**Dosage Form:** Zydis®, Orally Disintegrating Tablet (ODT) to be placed on the tongue. Zydis is a rapidly dissolving oral dosage form consisting of an open matrix of water soluble \_\_\_\_\_  
\_\_\_\_\_ This formulation dissolves quickly in the saliva on the tongue and does not require added water to aid disintegration.

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**Indication:** As an adjunct treatment for management of symptoms in patients with Parkinson's disease who are exhibiting deterioration of their response to levodopa (L-DOPA)/carbidopa therapy.

**Dosage and administration (Sponsor's Proposed):**  
1.25 and 2.5 mg (2x1.25 mg) as adjunctive therapy in combination with levodopa. Choice of dose should be based on individual basis. Zydis® ODT should be taken in the morning before breakfast and without liquid \_\_\_\_\_  
\_\_\_\_\_ should avoid ingesting food or liquids 5 minutes before and after taking the drug.

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**Pharmacologic Class:** Enzyme activated irreversible inhibitors, also referred to as "suicide" substrates. Selegiline selectively and irreversibly inhibits monoamine oxidase Type B (MAO-B)

**Chemical Name:** phenylisopropyl-N-methylpropylamine hydrochloride

**Physical Characteristics:** open matrix of water soluble \_\_\_\_\_  
\_\_\_\_\_ dissolves in the saliva on the tongue. It is a lyophilized tablet. Solubility of selegiline: 333 mg/mL.

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**Mechanism of action:** In the brain, L-DOPA is converted to dopamine by decarboxylation. Dopamine is further metabolized through deamination by MAO- B. Selegiline as a selective inhibitor blocks the deamination of dopamine produced by L-DOPA, extending the duration of action of a given dose of L-DOPA/dopamine. Selegiline binds to the MAO-B active site and forms a covalent bond with the flavin moiety after deamination, thus inactivating the MAO-B enzyme. The net result is a reduction in the ability of MAO-B to oxidize (degrade) amine neurotransmitters and neuromodulators, such as dopamine and phenylethylamine.

**Foreign marketing history:** Selegiline is available in US as Tablets (NDA 19-334) and Capsules (NDA 20-647) under the tradename "Eldepryl®"

(Sponsor: Somerset Pharmaceuticals) to be administered as a 10 mg total daily dose, but not as orally dissolving Tablet. Zydis selegiline was first approved for marketing in UK in 1998. Since then it has been approved in 9 European countries, pending approval in one. Zydis selegiline has been approved as adjunctive therapy with levodopa or as monotherapy for Parkinson's disease in these countries.

**Formulation:**

Ingredient	Purpose of Ingredient	Amount (mg) 1.25 mg tablets
Selegiline HCl	Active ingredient	1.25
Gelatin		
Mannitol		
Glycine		
Aspartame		
Citric acid		
Grape Fruit flavor		
Yellow		
Total		

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**II) EFFICACY AND SAFETY**

**What were the Phase 3 efficacy and safety studies?**

The Phase 3 efficacy and safety of Zydis® selegiline 1.25 mg and 2.5 mg/day (as 2x1.25 mg) was assessed in two identical double blind, placebo controlled studies (Study Z/SEL/97/025 and 026) in patients with parkinson's disease taking L-DOPA (with or without DOPA-decarboxylase inhibitor) who experienced deterioration in the quality of their response to this therapy. In each study, 194 subjects were randomized to Zydis® selegiline and 98 to placebo. Subjects were given 1.25 mg Zydis® selegiline or placebo for 6 weeks, then dose increased to 2.5 mg/day for additional 6 weeks. The key efficacy parameter was % daily OFF time at week 12.

Therapeutic equivalence was assessed in an active-controlled study (Study Z/SEL/95/008) in which subjects were randomized to either Eldepryl® 10 mg, given as 5 mg BID (N=71), Zydis selegiline 10 mg QD (N=62) or Zydis® selegiline 1.25 mg QD (N=64) for 12 weeks in patients stabilized on L-DOPA and Eldepryl® 5 mg BID. The key efficacy parameter was response on the Unified Parkinson's Disease Rating Scale (UPDRS) at the end of 12 weeks.

Study 025 did not show any statistical difference between the two treatment groups (p=0.467), where as Study 026 did show statistical difference in the % reduction of OFF Time (p<0.0001). The sponsor also conducted a combined evaluation of the two studies and significant difference between the treatment groups was observed (p=0.003). For Study 008 significant differences between the three treatment groups on UPDRS scores

could not be detected. The sponsor concluded that it was suggestive of therapeutic equivalence.

Effectiveness of Zydis selegiline was not affected by patient age, sex, or changes in L-DOPA dose in these studies.

The most common side effects are: motor effect (Dyskinesias), psychiatric effects (hallucinations, nightmares, psychoses, delusions, anxiety, akathisia, confusion, cognitive impairment, daytime sleepiness, dizziness) or cardiovascular effects (hypotension, orthostatic hypotension or hypertension) and others like abdominal pain.

### **(B) GENERAL CLINICAL PHARMACOLOGY**

**What were the biomarkers used in the clinical pharmacology studies for evaluating pharmacodynamics (efficacy and safety) and how were they measured?**

Monoamine oxidases (MAOs) are intracellular enzymes widely distributed throughout the body and exist as two isoenzymes-MAO-A and MAO-B. In humans, intestinal MAO is predominantly Type A, while that in the brain is Type B. At lower concentrations, selegiline acts as a selective inhibitor of MAO-B, while at higher concentrations, it inhibits both isoenzymes. Hence, it is important to assess the inhibition of both isoenzymes by selegiline.

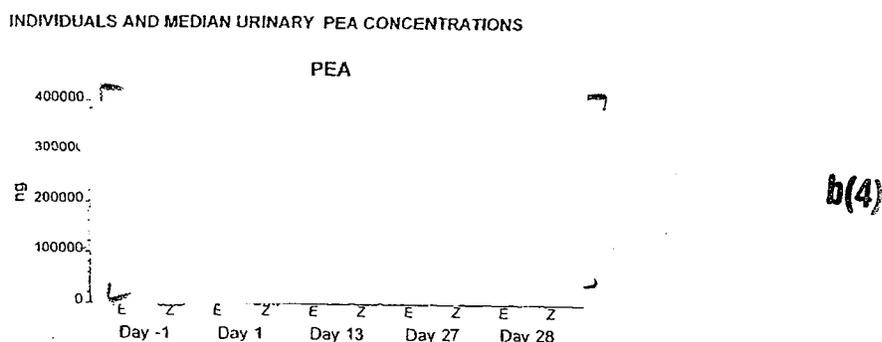
#### Markers for MAO-B inhibition:

- **Urinary phenylethylamine (PEA):** MAO-B primarily degrades dopamine and phenylethylamine (PEA). PEA 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, and it is excreted unchanged in the urine. Therefore if selegiline 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.

In general single dose of Zydis selegiline 1.25 mg showed an increase in post dose PEA amounts as compared to pre-dose PEA amounts. Single dose of Eldepryl® 10 mg showed higher amounts of PEA (> 40%) in the urine as compared to the Zydis formulation. The exposure to selegiline was 58% higher and C<sub>max</sub> was 2-fold higher with Zydis than Eldepryl® 10 mg in this Study 95/023. In study 95/003 the PEA parameters of Zydis selegiline 1.25 mg were comparable to Eldepryl® 10 mg. In study 96/008 urinary PEA excretion was greater after Zydis formulation as compared to Eldepryl®. In a steady state study (Study 101), amount of urinary PEA excreted

with Zydis 1.25 mg selegiline treatment group was half that of Eldepryl® 5 mg BID. Study 96/014 also showed greater excretion of PEA with the Eldepryl regimen at steady state. Hence, these variable results show the unreliability in concluding superiority of selective MAO-B inhibition with either formulation. The sponsor has concluded that higher amounts of PEA are excreted in the urine with the Zydis formulation as the Zydis dose is increased and the degree of MAO-B inhibition is similar to Eldepryl® and in some cases better than Eldepryl®. Due to cross study differences this conclusion cannot be made reliably. The most clinically relevant comparison would be from Study 101, where Eldepryl® was given as 5 mg BID.

Representative Figure showing urinary PEA concentrations from Study 014 is shown below:



Because selegiline's inhibition of MAO-B is irreversible, it is impossible to predict the extent of MAO-B inhibition from steady state plasma levels and is also not possible to predict the rate of recovery of MAO-B activity as a function of plasma levels or using the PEA information. The relationship between MAO-B inhibition and the clinical effect is not yet established, hence, the clinical relevance of measuring these biomarkers for establishing clinical effect is also very limited.

#### Markers for MAO-A inhibition:

- Tyramine Threshold Test: The clinical model for testing MAO-A inhibition is oral tyramine threshold test (Tyramine Challenge Test) that detects the pressor response to tyramine. In the periphery epinephrine is a substrate for MAO-A. Peripheral activity of MAO-A, particularly in the gut, is of great interest in relation to safety of selegiline, as it inactivates dietary pressor amine and protects against excessive cardiovascular responses to ingestion of tyramine rich food (also called Cheese Effect). Inhibition of MAO-A in the gut leads to increased sensitivity to dietary amines that act to release norepinephrine, which subsequently increase blood pressure after ingestion.

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"). This test is conducted for presenting the 'worst case scenario' for cheese

reactions as an assessment of safety. Sensitivity to tyramine is assessed by measuring blood pressure at baseline with increase in tyramine dose and after administration of selegiline with increasing doses of tyramine. The tyramine dose that causes an increase in blood pressure of 30 mmHg is called the tyramine threshold dose. The ratio of pre-treatment tyramine threshold dose/during treatment tyramine threshold dose is called the tyramine pressor ratio (or tyramine sensitivity factor, TSF)

From study 101 (1.25, 2.5 & 5 mg QD Zydis vs. 5 mg BID Eldepryl) it was observed that,

- Although all Zydis® and Eldepryl® formulations showed greater sensitivity to tyramine suggestive of MAO inhibition, there was no clear dose dependent relationship with increasing doses of selegiline. The TSF 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: range 1.25-24, 2.76 range: 1-12, 4.76: range 1.5-12 respectively) were less than 5 mg BID Eldepryl® (6.78 range: 1-20). 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. Moreover, these results are contrary to that published in the literature. At a similar dose of selegiline, 5 mg BID the TSF was 1.7 (Ref: NDA 21-336 for Eldepryl®).
- 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 C<sub>max</sub> 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 and high concentrations of selegiline. Hence, the relationship between PK parameters and the tyramine pressor ratios is inconclusive.

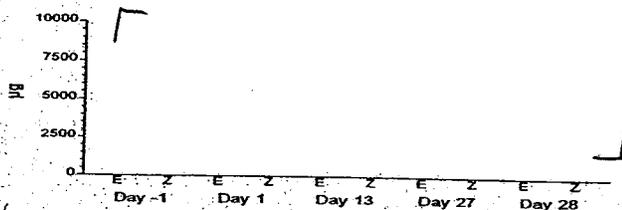
From Study 014 (1.25 mg QD Zydis vs. 10 mg Eldepryl) it was observed that,

- The mean TSF after a 1.25 mg Zydis dose was 2.83 (range 0.6-14) and that after Eldepryl® 10 mg (not given in divided dose) was 3.37 ( range 1-16). The mean TSF from 1.25 mg Zydis dose is less than that obtained from study 101.

The risk assessment would be done by the Reviewing Medical Officer.

- Urinary 5-HIAA: 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. Hence, urinary excretion of 5-HIAA is also used as a marker for assessing MAO-A inhibition, but is not considered as sensitive as a tyramine challenge test.

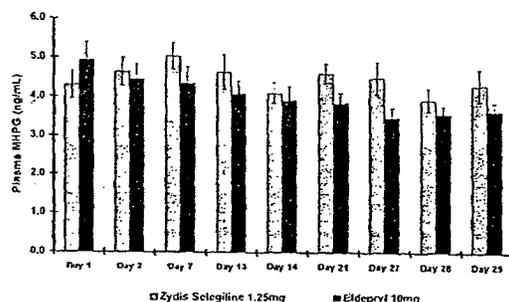
Excretion of 5-HIAA did not change in either treatment. Representative figure showing the pre and post dose 5-HIAA distribution with Eldepryl® and Zydis is provided below (from Study 014):



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- Plasma MHPG: 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.

Representative figure showing the pre and post dose MHPG distribution with Eldepryl® and Zydis® is shown in the following figure (from Study 014):



- For Zydis selegiline the plasma MHPG showed no clear trend from Study 014.

It was observed from Study 101 that:

- 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%↓). For all other doses 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.

**Is there a scientific basis for dose selection for the Zydis® selegiline formulation? Are clinically relevant dose/dosage regimen and mode of administration adequately evaluated in pharmacokinetic studies?**

Early pharmacokinetic studies conducted with the Zydis formulation and conventional tablets of selegiline at equal doses showed that the Zydis formulation had 5-8 times higher selegiline plasma concentrations as compared to the conventional oral tablets. Based on this information the sponsor selected a dose range of 1.25-2.5 mg to potentially provide similar efficacy and safety results.

The sponsor has evaluated the pharmacokinetics of selegiline and its metabolites given as a single dose or after multiple doses of 1.25 and 2.5 mg for 10 and 28 days.

The dosing instructions in the 'Dosage and Administration' section of the label state that the Zydis Tablets should be placed on the top of the tongue where it will dissolve in seconds. ~~\_\_\_\_\_~~ should avoid ingesting food or liquids 5 minutes before and after taking the tablet. The tablet should be taken in the morning before breakfast without liquid.

b(4)

None of the pharmacokinetic studies conducted give the same dosing instruction of ~~\_\_\_\_\_~~ In most studies no water was allowed 30 minutes before and after dosing with Zydis selegiline. In study Z/SEL/95/001 subjects were allowed to swallow after 1 minute. This study showed that at equal doses of Zydis and Eldepryl® 10 mg, the exposure from the Zydis formulation was 16-fold higher than that after Eldepryl®. In study AN17933-101 subjects were asked to refrain from swallowing, the Zydis tablets were administered after an overnight fast and breakfast was served 30 minutes post dose. The protocol also stated that subjects were not allowed to eat or drink at least 5 minutes before dosing and after administration of the Zydis tablets. This sentence is contrary to the previous instruction of fasting overnight and 30 minutes post dose. If this is true then the statement that they should not eat or drink at least 5 minutes before and after dosing does not make sense in the same protocol, as the protocol also states that food is allowed 30 minutes post dose. Hence, the dosing instructions proposed cannot be justified based on the PK studies.

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The Phase 3 efficacy studies were conducted with dosing instructions of no food or drink 5 minutes before and after dosing. No recommendations were made regarding not swallowing for 2 minutes after dosing.

**What are the general pharmacokinetic characteristics of Zydis® selegiline?**

- Zydis selegiline is rapidly absorbed with peak selegiline concentrations reaching within 10-15 minutes as opposed to 40-90 minutes with conventional selegiline tablets given QD and BID ~ 4 hours apart.
- There is some extent of pregastric absorption from the Zydis dosage form, resulting in higher concentrations of selegiline and lower concentrations of metabolites as compared to the conventional tablets (Study 023). From Study 001 which was conducted to evaluate buccal absorption, the Zydis not swallowed (Zydis NS) treatment arm showed that 40% of the starting dose was either absorbed from the oral

- mucosa or remained to be absorbed from the pregastric areas based on analysis of the mouth rinses.
- Based on a dose normalized basis the Zydis selegiline produces 3.7-6.9 times higher exposure to selegiline as compared to Eldepryl®. However, Study 003 showed that Zydis 1.25 mg produced similar selegiline concentrations to Eldepryl® 10 mg and lower concentrations of all metabolites as compared to Eldepryl®.
  - There is significant accumulation of selegiline upon multiple dosing after the administration of Zydis selegiline. At steady state the selegiline exposure is 3-9 fold higher than that obtained after single dose.
  - Selegiline (SEL) undergoes extensive metabolism in the liver. The major metabolites are N-desmethyl selegiline (NDMS), L-methamphetamine (L-MA) and L-amphetamine(L-AMP). Only NDMS is known to have MAO-B inhibiting activity. Concentrations of NDMS are 3-5 fold higher than parent selegiline after administration of Zydis selegiline. The concentrations of L-MA and L-AMP are 7-20 fold greater than that of selegiline. These metabolites interfere with dopamine re-uptake at the synapse and enhance release of neurotransmitters (e.g. norepinephrine, dopamine, serotonin). The extent to which these metabolites contribute to the effects of selegiline is unknown. For pathways of metabolism please refer to the section on "Extrinsic Factors"
  - About 44-58% of selegiline is eliminated mainly in the urine as metabolites, with up to 37% of the oral dose of selegiline given as conventional tablets recovered as L-MA<sup>1</sup>. Approximately 15% of the dose is also discharged in the feces. No unchanged selegiline has been detected in the urine<sup>2</sup>.
  - The t<sub>1/2</sub> of selegiline is 1-4 hours after a single dose. Under steady state conditions, the elimination half life increases to 10 hours suggesting capacity limited elimination.
  - About 85% of plasma selegiline is reversibly bound to proteins.
  - The pharmacokinetics of selegiline are highly variable. The variability appears to be less from the Zydis formulation (%CV ~40-75%), as compared to the conventional formulation (%CV ~75-106%).

**How do the pharmacokinetics of 1.25 mg Zydis® Selegiline compare to the marketed 10 mg Eldepryl® tablets/capsules?**

Comparative information on 1.25 mg Zydis selegiline and 10 mg Eldepryl® tablets can be obtained from Studies Z/SEL/95/023, Z/SEL/95/003, Study Z/SEL/96/014 and Study AN17933-101. In all studies pharmacokinetic parameters were obtained after a single dose, the drug was administered after an overnight fast. The Zydis tablet was to be placed on the tongue, with no water allowed 30 minutes before and after the drug administration. The comparison based on the pharmacokinetic parameters is shown in the following Tables:

<sup>1</sup> Shin. Metabolism of selegiline in humans, Drug Met and Disp., 1997; 25(6): 657-662

<sup>2</sup> Heinonen et al "Pharmacokinetic aspects of l-deprenyl (selegiline) and its metabolites"; Clinical Pharmacol 56: 742-9 (1994)

For AUC<sub>0-∞</sub> (ng.h/ml):

Treatment	Moiety	Study* Z/SEL/95/023 N=24	Study** Z/SEL/95/003 N=23	Study*** Z/SEL/96/014 N=12	Study***# AN17933-101 N=14
Zydis (1.25 mg)	SEL	0.525 (0.252)	1.31 (0.66)	0.70 (0.37)	1.49 (0.77)
	NDMS	1.649 (0.719)	2.4 (0.8)	2.89 (1.32)	2.07 (0.71)
	L-AMP	7.61 (2.27)	8.9 (6.6)	9.72 (4.53)	1.49 (1.54)
	L-MA	17.02 (9.26)	20 (6.8)	17.77 (6.43)	5.68 (2.44)
		US Product	UK Product	UK Product	US Product
Eldepryl (2 x 5 mg)	SEL	0.37(0.28)	1.42 (1.99)	1.09 (0.73)	1.93 (1.67)
	NDMS	35.168 (11.062)	47.8 (23.8)	67.89 (27.58)	64.03 (38.56)
	L-AMP	94.33 (23.59)	113.6 (27.8)	130.92 (46.29)	44.17 (8.28)
	L-MA	226.64 (63.39)	288.4 (67.3)	282.28 (72.87)	131.34 (21.83)

\*crossover study

\*\* incomplete crossover (each subject receiving 2 treatment in a 4 treatment study)

\*\*\* parallel group study

# Eldepryl given as 5 mg BID

- As can be seen from the above Table, inter-study differences in the parameter estimates SEL are quite variable. In spite of the 8-fold reduction in dose, Study 95/023, a crossover study showed that Zydis 1.25 mg produces 50-60% higher exposure as compared to Eldepryl® 10 mg Tablets. In this study Eldepryl® was administered as a 10 mg single dose. Study 101, which had a parallel design produced 29% lower exposure with the Zydis 1.25 mg single dose as compared to Eldepryl® 5 mg BID. In study 101 Eldepryl® was administered in divided doses as per the label.
- The metabolite NDMS, L-AMP and L-MA concentrations are drastically lower (> 15-fold ↓) with the Zydis formulation as compared to the conventional tablets, probably because the fast dissolving tablets escape first-pass metabolism due to pre-gastric absorption.
- The inter-study differences in metabolites L-AMP and L-MA are less significant as compared to the parent. NDMS shows greater inter-study variability.

For C<sub>max</sub> (ng/ml):

Treatment	Moiety	Study* Z/SEL/95/023 N=24	Study** Z/SEL/95/003 N=23	Study*** Z/SEL/96/014 N=12	Study***# AN17933-101 N=14
Zydis (1.25 mg)	SEL	1.12 (0.76)	2.36 (1.14)	1.44 (0.88)	3.34 (1.68)
	NDMS	1.19 (1.77)	1.19 (0.49)	1.55 (0.95)	1.22 (0.48)
	L-AMP	0.23 (0.10)	0.34 (0.21)	0.25 (0.08)	0.20 (0.09)
	L-MA	0.68 (0.31)	0.93 (0.39)	0.82 (0.26)	0.62 (0.23)
		US Product	UK Product	UK Product	US Product
Eldepryl (2 x 5 mg)	SEL	0.456 (0.48)	1.50 (2.38)	1.29 (0.87)	1.12 (1.48)
	NDMS	16.345 (4.11)	18.37 (9.13)	23.45 (6.44)	10.65 (5.09)
	L-AMP	3.44 (0.89)	3.6 (0.92)	3.53 (0.66)	2.69 (0.65)
	L-MA	10.49 (2.27)	12.92 (3.95)	12.97 (2.53)	8.37 (1.28)

\*crossover study

\*\* incomplete crossover (each subject receiving 2 treatment in a 4 treatment study)

\*\*\* parallel group study  
# Eldepryl given as 5 mg BID

- Inter-subject variability in SEL Cmax is quite high. Study 95/023 shows a >2-fold ↑ in Cmax with the 1.25 mg Zydis formulation. Study 101 showed a 3-fold higher Cmax with the Zydis formulation.

For Tmax (h):

Treatment	Moiety	Study* Z/SEL/95/023 N=24	Study** Z/SEL/95/003 N=23	Study*** Z/SEL/96/014 N=12	Study****# AN 17933-101 N=14
Zydis (1.25 mg)	SEL	0.236 (0.093)	0.17	0.20 (0.14)	0.17
	NDMS	0.927 (0.26)	0.88	0.88 (0.35)	1.0
	L-AMP	3.5 (2.7)	3.5	3.88 (3.18)	1.8
	L-MA	3.1 (2.4)	2	2.0 (1.13)	1.5
		US Product	UK Product	UK Product	US Product
Eldepryl (2 x 5 mg)	SEL	0.685 (0.284)	1.50	0.61 (0.23)	4.55
	NDMS	0.823 (0.26)	0.75	0.82 (0.25)	1.50
	L-AMP	4.10 (2.4)	4	4.75 (2.60)	8.0
	L-MA	2.4 (1.3)	2	2.63 (1.51)	8.0

\*crossover study

\*\* incomplete crossover (each subject receiving 2 treatment in a 4 treatment study)

\*\*\* parallel group study

# Eldepryl given as 5 mg BID

- Tmax is very rapid with the Zydis formulation. The Tmax with the Zydis formulation is 10-15 minutes and with Eldepryl® given as 10 mg single dose is 40-90 minutes. Study 95/023 shows >3-fold ↓ in Tmax with the Zydis formulation as compared to Eldepryl®. In study 101 where Eldepryl® was given in two divided doses of 5 mg each 4 hours apart, the Tmax was about 30 minutes (after the second dose) as compared to within 10-15 minutes with the Zydis formulation. In any case the Tmax is significantly rapid with the Zydis formulation as compared to Eldepryl®.

**Do the pharmacokinetic parameters change with time following multiple dosing?**

Single dose studies do not predict multiple dose pharmacokinetics based on calculations for accumulation factor. Trough concentration at Day 8, 9 and 10 indicated that steady state is reached at least by Day 8.

There is significant accumulation of selegiline and N-desmethyl selegiline after multiple dosing. From Study 101 it was observed that steady state exposure of selegiline at Day 10 was 3-4 fold higher than that at Day 1 for Zydis 1.25 mg and 2.5 tablets. Study 96/014 showed that there was a 9-10-fold increase in AUC at steady state on Day 28 with Zydis 1.25 mg formulation. Please see pages 68-70 of the review for pharmacokinetic parameters at steady state.

In study 96/014 there was a 2-3 fold increase in Cmax on Day 28 as compared to Day 1. However, in Study 101 the Cmax at steady state was similar to that on Day 1.

Metabolite concentrations also increased by 3-9 fold at steady state. The mean exposure of metabolites from Zydis selegiline at steady state was lower than that of Eldepryl®, however, Cmax was higher after Eldepryl® administration.

The short t1/2 of selegiline (1- 4 hours) and that of NDMS (3-6 hours) fails to explain this accumulation. Literature suggests that the apparent reason for this accumulation could be saturation of the MAO-B binding sites in tissues as selegiline binding is irreversible. Decreased first pass metabolism could also be a reason because selegiline is a highly extracted drug<sup>3</sup>.

**Does dose proportionality exist after single and multiple doses of Zydis® selegiline?**

Although selegiline concentrations rose with the increase in dose with the Zydis formulation, the increase was not statistically dose proportional for selegiline. However true proportionality cannot be determined as the study had a parallel 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: C <sub>ss,max</sub>	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	0.0461
	5.0 vs 1.25 mg	<0.0001
	5.0 vs 2.5 mg	0.0231
AUCτ	2.5 vs 1.25 mg	0.2267
	5.0 vs 1.25 mg	0.0416
	5.0 vs 2.5 mg	0.3689
Day 10: C <sub>ss,max</sub>	2.5 vs 1.25 mg	0.0107
	5.0 vs 1.25 mg	<0.0001
	5.0 vs 2.5 mg	0.0138
AUCτ	2.5 vs 1.25 mg	0.0606

<sup>3</sup> Laine et.al. "Multiple dose pharmacokinetics of selegiline and desmethyl selegiline suggest saturable tissue binding" Clinical Neuropharmacology 23 (1) 22-27, 2000.

	5.0 vs 1.25 mg	<0.0001
	5.0 vs 2.5 mg	0.0132

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

**How does the pharmacokinetics of Zydis selegiline in healthy volunteers compare to that in patients with Parkinson's disease?**

The sponsor has conducted all the pharmacokinetic studies in healthy volunteers. Trough plasma samples were taken from pivotal Phase 3 studies (97/025 and 97/026) and the sponsor conducted a population pharmacokinetic analysis on this data. These results were evaluated by Dr. Andre Jackson and were found inadequate for inferring any conclusions from the results obtained. Hence, no information is available regarding the pharmacokinetics of Zydis selegiline in patients.

**(C) INTRINSIC FACTORS**

**Are there any pharmacokinetic differences in the special populations based on age, gender, race, hepatic and renal impairment for Zydis selegiline 1.25 mg and 2.5 mg and is there a need for dosage adjustment in any special population?**

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 older and the young subjects is shown in the following Table:

Treatment	Study No.	Mean Age	N	Day 1		Steady State	
				C <sub>max</sub>	AUC <sub>0-∞</sub>	C <sub>max</sub>	AUC <sub>0-24</sub>
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)
	101	28.1 years	15	3.34 (1.68)	1.49 (0.77)*	3.96 (1.90)	4.77 (2.29)
Zydis 2.5 mg	003	50.9 years	23	3.38 (2.44)	2.29 (1.16)	NA	NA
	101	28.6 years	16	4.47 (2.56)	2.44 (1.64)*	4.37 (1.83)	6.52 (2.09)

\*AUC<sub>0-t</sub>

- This Table shows that the young subjects between the ages 18-44 have higher C<sub>max</sub> and AUC as compared to the subjects between the ages 40-75. There is a lot of variability in the pharmacokinetic results across studies, hence it is not prudent to draw any conclusion regarding effect of age from this comparison.
- A population analysis was conducted by the sponsor to study the effect of covariates on the pharmacokinetics of selegiline. The analysis showed that the clearance decreased with the increase in age. The age range of their subjects was 39-93 years. Based on the population model to evaluate clearance, the following CL values were obtained for subjects aged 39 and 93 years.

$$CL = 866 + (-7.02*39) = 592 \text{ L/HR}$$

$$CL = 866 + (-7.02*93) = 213 \text{ L/HR}$$

Based on Study 014, an estimate of the clearance was 195 L/HR (AUC<sub>0-inf</sub> was 6.39 ng.hr/ml at a dose of 1.25 mg at steady state for 40-70 year old subjects, Calculation of CL based on  $CL=D/AUC_{0-inf}$ ). This is below the sponsor's lowest estimate based upon population analysis of 213 L/HR. Based on these observations no conclusions can be made regarding the effect of age on the pharmacokinetics of Zydis selegiline. Please refer to review of population analysis by Dr. Jackson on page 95.

Effect of Gender:

No studies have been conducted to evaluate the effect of gender on the pharmacokinetics of selegiline

Effect of Race:

No studies have been conducted to evaluate the effect of race on the pharmacokinetics of selegiline

Effect of Renal Impairment:

No studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of selegiline.

Effect of Hepatic Impairment:

No studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of selegiline

**(D) EXTRINSIC FACTORS**

**Is there an in-vitro basis to suspect drug-drug interactions with selegiline?**

The sponsor has not conducted any in vitro metabolism studies to characterize the metabolism of selegiline. The literature survey conducted by the sponsor on this subject is also not extensive and includes only one published article on selegiline metabolism by CYP P450 isoenzymes.

A literature search conducted by the reviewer revealed various conflicting reports regarding the metabolism of selegiline by CYP P450 isoenzymes. The various reports suggest that the enzymes responsible for metabolism include CYP 2B6, CYP 2C19, CYP 1A2, CYP 3A4/5, CYP 2C9, CYP 2E1<sup>4,5,6,7,8</sup>. No definite conclusion has been drawn regarding the isoenzyme(s) involved in the metabolism and the rank order of their role in the metabolism of selegiline.

~~\_\_\_\_\_~~ Based on the literature search this information seems incomplete and inadequate.

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**Are there any in vivo drug-drug interaction studies that indicate exposure and/or exposure-response are different when drugs were co-administered and if yes, is there a need for dosage adjustment?**

The sponsor has not conducted any pharmacokinetic drug-drug interaction studies with Zydys selegiline. Pharmacodynamic drug interactions based on clinical trials have been described in the package insert and will be evaluated by the reviewing Medical Officer.

<sup>4</sup> Hidestrand M et al, CYP2B6 and CYP2C19 as the major enzymes responsible for the metabolism of selegiline, a drug used in the treatment of Parkinson's disease, as revealed from experiments with recombinant enzymes, Drug Metab Dispos 2001 Nov;29(11):1480-4

<sup>5</sup> Laine et al, CYP2C19 polymorphism is not important for the in vivo metabolism of selegiline. Eur J Clin Pharmacol. 2001 May;57(2):137-42.

<sup>6</sup> Skivisto KT et al, selegiline pharmacokinetics are unaffected by the CYP3A4 inhibitor itraconazole. Eur J Clin Pharmacol. 2001 Apr;57(1):37-42

<sup>7</sup> Taavitsainen P et al, Selegiline metabolism and cytochrome P450 enzymes: in vitro study in human liver microsomes, Pharmacol Toxicol. 2000 May;86(5):215-21. (referenced by the sponsor)

<sup>8</sup> Bach et al. Metabolism of N,N-dialkylated amphetamines, including deprenyl, by CYP2D6 expressed in a human cell line, Xenobiotica. 2000 Mar;30(3):297-306.

**(E) GENERAL BIOPHARMACEUTICS**

**Is the assay validation adequate?**

Assay validation for the determination of selegiline, N-desmethylselegiline, L-amphetamine, L-methamphetamine in plasma, MHPG in plasma and 5-HIAA and PEA in urine are all acceptable. The methodology is given along with the individual study reports in this review.

Acceptability is determined based on accuracy, precision, linearity, stability, recovery, specificity. Acceptance criteria are based on validation parameters as ~~-----~~ from the theoretical value for the low controls and ~~-----~~ for the medium and high controls.

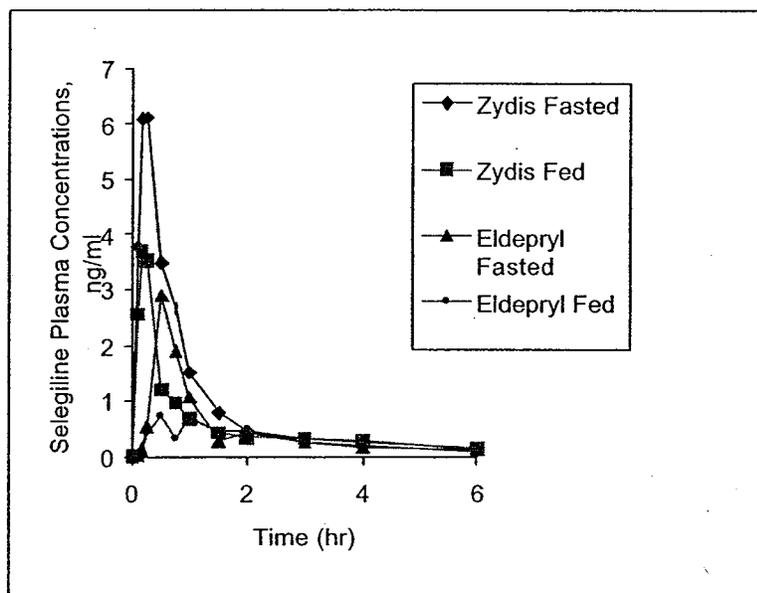
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**What is the effect of food on the bioavailability of selegiline from the Zydis dosage form? What dosing recommendation should be made, regarding administration of the product in relation to meals?**

- The food effect study was conducted with Zydis 5 mg, which is 2-4 fold higher than the to-be-marketed dose. With a 5 mg dose, 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 effect of food was greater on the Zydis® formulation than on the Eldepryl® formulation
- The NDMS AUC for 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.

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

Single Dose Plasma PK Parameter	Treatment Mean (% CV)				90% CI on Dose Normalized parameters	
	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 <sub>0-t</sub> (hr*ng/mL)	5.612 (41)	3.533 (91)	3.375 (188)	2.223 (156)	144-399	44-122
AUC <sub>0-inf</sub> (hr*ng/mL)	5.829 (43)	3.710 (87)	3.584 (189)	2.382 (152)	136-377	43-119
C <sub>max</sub> (ng/mL)	7.804 (54)	4.490 (62)	3.093 (160)	1.416 (95)	132-446	77-259
T <sub>max</sub> (hr)	0.208 (27)	0.202 (28)	0.688 (27)	1.604 (82)	-	-
T <sub>1/2</sub> (hr)	3.779 (47)	2.727 (36)	2.814 (79)	2.080 (75)	-	-



- 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. This difference cannot be explained. It has been reported that BID regimen produces higher exposure as compared to QD regimen and the T<sub>max</sub> is longer as well<sup>9</sup>.

**Are the dissolution conditions and specifications adequately developed to assure in vivo performance and quality of the product?**

The dissolution of Zydis selegiline is very rapid in all three media ~~as shown~~ as shown by the following representative dissolution profiles in one of the media (0.1M HCl). Due to this reason the sponsor chooses to have disintegration specification rather than dissolution specifications as quality control test for assessing the quality of their product.

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<sup>9</sup> Barrett et al. "The effect of dosing regimen and food on the bioavailability of the extensively metabolized, highly variable drug Eldepryl"; American Journal of Therapeutics 3, 298-313 (1996)

Time Point (mins)	% Release						Mean
	1	2	3	4	5	6	
2							103.5
6							103.7
10							103.8
15							104.2
20 <sup>1</sup>							103.7

After the 15 minute time point, the stirrer speed was increased to 200 rpm for 5 minutes.

Hence, in lieu of dissolution, the following disintegration method has been used in the specifications.

Disintegration method:

Two apparatuses are used with the same disintegrating mechanism, ~~\_\_\_\_\_~~ Apparatus A is used for units less than ~~\_\_\_\_\_~~ in diameter. This apparatus includes ~~\_\_\_\_\_~~ Zydis tablets are randomly selected to be tested. Disintegration time is recorded when the last tablet has disintegrated. Apparatus B is used for tablets ~~\_\_\_\_\_~~ in diameter. ~~\_\_\_\_\_~~

The disintegration of the tablets from the batches used in biostudies and the phase 3 studies is 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

The disintegration specification for the Zydis tablets are ~~\_\_\_\_\_~~

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       Trade Secret / Confidential (b4)

       Draft Labeling (b4)

✓ Draft Labeling (b5)

       Deliberative Process (b5)