

## CLINICAL REVIEW

### Clinical Review Section

#### 14.8. Clinical Laboratory Findings

##### 14.8.1. Approach to Clinical Laboratory Abnormalities

Clinical laboratory evaluations (e.g. clinical chemistry, hematology, urinalysis) were conducted in the double-blind placebo-controlled studies (Z/SEL/97/025 and Z/SEL/97/026), one randomized parallel group, controlled study (Z/SEL/95/008), and the extension studies (Z/SEL/97/027 and Z/SEL/95/008E). A central laboratory performed testing in studies Z/SEL/97/025, Z/SEL/97/026 and Z/SEL/97/027. It was not clearly specified whether the same central laboratory was used for study Z/SEL/95/008 and its extension. However, the presentation of the same normal reference ranges as for the double-blind studies would suggest that the same central laboratory was used for all these studies. Laboratory examinations were collected at screening, baseline, and at 4 and 12 weeks after treatment in the controlled studies. Tests were also collected at various times in the extension studies and were presented as occurring between 12 and 39 weeks and at  $\geq 40$  weeks. Analyses (tables and listings) conducted by the sponsor were descriptive in nature and consisted of summary statistics (mean, SD, min, med, max over time), shift tables (showing frequency of low, normal or high laboratory results at baseline and after treatment), and the incidence of particular severity of abnormality. However, the sponsor did not present a descriptive summary of analyte results for the extension studies.

The sponsor described the particular types of laboratory abnormality (e.g. potentially clinically significant - PCI, clinically significant - CS, or substantially abnormal (SA). Results of laboratory data and analyses were presented in tables and listings. PCI laboratory abnormalities were generally mild to moderate in severity relative to the normal reference range and **began at arbitrarily defined cutoff point below and above the normal reference range**. Specification of PCI abnormalities is shown in Table 75 along with the normal reference range for clinical chemistry, hematological, and urinalysis parameters. The designation CS was an arbitrary one used by investigators when they thought that the laboratory abnormality was "clinical significant" but no guidance was provided by the sponsor to help with consistency in applying this designation. I found this approach for designating CS so arbitrary and unsystematic in nature as not to be useful and thus did not attach much significance to CS designated abnormalities nor did I focus on analyzing CS abnormalities. A categorization of the most severe laboratory abnormality was SA and the definitions of SA (relative to lower limit of normal - LLN or upper limit of normal, ULN) for relatively, few, selected analyte abnormalities are shown in Table 76.

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**Table 75 Potential Clinically Important (PCI) Laboratory Abnormalities relative to Normal Reference Ranges for Study Reports and ISS**

Table 1. Comparison of Laboratory Normal Ranges and Criteria for Potentially Clinically Important (PCI) Laboratory Abnormalities - Clinical Study Reports (CSR)

Analyte Name	Gender (B=both) & Age Range	025/026/027 CSR Lab Normals	025/026/027 PCI Criteria	Difference Between CSR Normal Ranges vs PCI	Units
<b>CHEMISTRY</b>					
Sodium	B, 13-120	135-147	130-150	-5, +3	mMol/L
Potassium	B, 0-120	3.5-5.2	3.0-5.5	-5, +3	mMol/L
Chloride	B, 0-120	95-110	90-115	-5, +5	mMol/L
Calcium	B, 12-50	2.12-2.62	2.0-2.75	-12, +13	
	M, 51-120	2.12-2.62	2.0-2.75	-12, +13	mMol/L
	F, 51-120	2.18-2.66	2.0-2.75	-18, +09	
Phosphate	M, 15-60	0.80-1.45	.646-1.615	-.154, +.165	
	M, 61-120	0.74-1.26	.646-1.615	-.094, +.355	mMol/L
	F, 15-50	0.80-1.45	.646-1.615	-.154, +.165	
	F, 51-120	0.84-1.52	.646-1.615	-.194, +.095	
Carbon Dioxide - Total	B, 0-120	23-31	20-33	-3, +2	mMol/L
Creatinine	M, 10-120	60-125	44.2-159.1	-15.8, +34.1	µMol/L
	F, 10-120	50-110	44.2-159.1	-5.2, +49.1	
BUN	B, 18-120	2.5-8	NA-8.9	NA, +9	mMol/L
Uric Acid	M, 0-120	230-480	NA-501.5	NA, +21.5	
	F, 0-50	150-390	NA-501.5	NA, +111.5	µMol/L
	F, 51-120	210-450	NA-501.5	NA, +51.5	
Total Protein	B, 0-60	60-85	55-87	-5, +2	G/L
	B, 61-120	59-79	55-87	-4, +8	
Albumin	B, 0-120	35-50	30-55	-5, +5	G/L
Globulin	B, 0-120	10-50	None Specified		G/L
Total Bilirubin	B, 0-120	0-22	NA-22	NA, 0	µMol/L
Alkaline Phosphatase	M, 19-60	35-110	NA-130	NA, +20	U/L
	F, 18-60	35-110	NA-130	NA, +20	

Table 1. Comparison of Laboratory Normal Ranges and Criteria for Potentially Clinically Important (PCI) Laboratory Abnormalities - Clinical Study Reports (CSR)

Analyte Name	Gender (B=both) & Age Range	025/026/027 CSR Lab Normals	025/026/027 PCI Criteria	Difference Between CSR Normal Ranges vs PCI	Units
ALT	B, 61-120	0-175	NA-130	NA, +5	
	B, 0-120	5-40	NA-60	NA, +20	U/L
AST	B, 0-120	10-40	NA-60	NA, +20	U/L
GGT	M, 0-120	0-65	NA-80	NA, +15	U/L
	F, 0-120	0-40	NA-80	NA, +40	
Random Glucose	B, 0-120	3.6-7.8	2.5-9	-1.1, +1.2	mMol/L
Total Cholesterol	B, 0-120	0-6.2	None Specified		mMol/L
Triglycerides	M, 20-29	No data	None Specified		
	M, 30-39	0.55-3.3			mMol/L
	M, 40-49	0.6-3.6			
	M, 50-120	0.7-3.2			
	F, 20-29	No data			
	F, 30-39	0.55-2.2			
	F, 40-49	0.6-2.6			
	F, 50-120	0.7-2.75			
Serum Ferritin	F, 0-120	0-5	None Specified		µU/L
<b>HEMATOLOGY</b>					
Hemoglobin	M, 18-120	135-180	125-NA	-10, +NA	G/L
	F, 18-120	115-165	110-NA	-5, +NA	
Hematocrit	M, 18-120	0.40-0.54	0.40-0.54	No diff.	%
	F, 18-120	0.35-0.47	0.35-0.47	No diff.	
MCH	B, 0-120	27-33	None Specified		pg
MCV	M, 0-120	80-100	NA-100	NA, +0	fL
	F, 0-120	75-100	NA-100	NA, +0	
MCHC	B, 0-120	310-360	300-NA	-10, +NA	G/L
RBC	M, 18-120	4.5-6.5	None Specified		X 10 <sup>9</sup> /L

Table 1. Comparison of Laboratory Normal Ranges and Criteria for Potentially Clinically Important (PCI) Laboratory Abnormalities - Clinical Study Reports (CSR)

Analyte Name	Gender (B=both) & Age Range	025/026/027 CSR Lab Normals	025/026/027 PCI Criteria	Difference Between CSR Normal Ranges vs PCI	Units
	F, 18-120	4.0-5.5			
WBC	B, 18-120	4.0-11.0	2-12	-2, +1	X 10 <sup>9</sup> /L
Platelet Count	B, 0-120	150-400	100-500	-50, +100	X 10 <sup>9</sup> /L
Neutrophils	B, 18-120	2.0-7.5	None Specified		X 10 <sup>9</sup> /L
Bands	B, 10-120	0-7	None Specified		X 10 <sup>9</sup> /L
Basophils	B, 0-120	0-2	None Specified		X 10 <sup>9</sup> /L
Lymphocytes	B, 10-120	1.0-3.5	None Specified		X 10 <sup>9</sup> /L
Eosinophils	B, 11-120	0-4	None Specified		X 10 <sup>9</sup> /L
Monocytes	B, 2-120	0-8	None Specified		X 10 <sup>9</sup> /L
Other (differential)	B, 0-120		None Specified		
<b>URINALYSIS</b>					
Protein	B, 0-120	Negative	Negative	No diff.	
Blood	B, 0-120	Negative	Negative	No diff.	
Glucose	B, 0-120	Negative	Negative	No diff.	
Specific Gravity	B, 0-120	1.001-1.030	None Specified		
PH	B, 0-120	5-8	None Specified		
Ketone	B, 0-120	Negative	None Specified		
Bilirubin	B, 0-120	Negative	None Specified		
RBC	M, 0-120	0-2	None Specified		
	F, 0-120	0-0			
WBC	B, 0-120	0-5	None Specified		
Epithelial Cells	B, 0-120	0-5	None Specified		
Bacteria	B, 0-120	Negative	None Specified		

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**Table 76 Sponsor's Criteria for Substantially Abnormal (SA) laboratory Results**

Criteria for Laboratory Values to be Substantially Abnormal		
Parameters	Criteria (1)	Units
WHITE BLOOD CELL COUNT	<= 0.75 of LLN	10E9/L
PLATELET COUNT	<= 0.75 of LLN	10E9/L
NEUTROPHILS	<= 0.75 of LLN	10E9/L OR PERCENTAGE
HEMOGLOBIN	<= 0.75 of LLN	G/L
TOTAL BILIRUBIN	>= 5 of ULN >= 8 of ULN	UMOL/L
ALKALINE PHOSPHATASE	>= 5 of ULN >= 8 of ULN	U/L
ALANINE TRANSAMINASE (ALT)	>= 5 of ULN >= 8 of ULN	U/L
ASPARTATE TRANSAMINASE (AST)	>= 5 of ULN >= 8 of ULN	U/L
GAMMA GLUTAMYL TRANSFERASE (GGT)	>= 5 of ULN >= 8 of ULN	U/L

At the pre-NDA meeting (11/7/01), DNDP told the sponsor that its plan for presenting 3 categories of laboratory abnormalities (e.g. for low values) might be too fine and weighted toward relatively mild to moderate abnormalities. DNDP further noted that the categorization in each direction should not exceed 3 categories and should include "abnormal (any result outside the reference range such as LLN), potentially clinically important (or analogous term to represent some more severe abnormality you define such as  $< 0.75 \times \text{LLN}$ ), and perhaps "panic" value to represent a very severe, potentially life-threatening abnormality such as an absolute neutrophil count  $< 500$ , total platelet count  $< 25,000$ , serum potassium  $\leq 2.5$  or  $\geq 6.5$ , or  $\leq 120$  or  $\geq 160$  that you define."

After noting that the sponsor did not seem to follow DNDP recommendations provided at the pre-NDA meeting, I told the sponsor about these shortcomings related to not presenting the incidence of any laboratory abnormality (relative to the normal reference range) and not having a categorization of moderate to severe abnormalities (both low and high) for all analytes. The sponsor responded that it did not think that it would be useful to show all mild abnormal results and wanted to review data initially to assess what differences might be observed if all abnormal laboratory results were presented. The sponsor submitted a response (8/30/02 letter date) showing the differences between the normal reference range and PCI values for all analytes, the incidence of abnormal laboratory results vs PCI abnormal results for each analyte, listings of all abnormal results that were not considered PCI, and a table of criteria for a new category (i.e. "markedly abnormal") of moderate to severe laboratory abnormalities for each analyte. This latter category was added based upon my recommendation and input about defining "markedly abnormal" criteria and has subsequently been revised according to my additional input. I had noted to the sponsor that the SA abnormalities defined in Table 76 were only specified for relatively few analytes, and were only applicable for a "more severe" abnormality in one direction (i.e. low or high). I had also noted that according to their criteria for SA results, other more severe abnormalities of other important analytes such as serum potassium, sodium, calcium, BUN, and creatinine would not be specified, the cut-off for low hematological abnormalities was relatively modest (e.g.  $< 0.75$  of LLN), and very high hematological analytes would not be specified. Thus, the sponsor's most severe abnormal

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**laboratory designation (i.e. SA) was very limited and restricted in scope for identifying outliers (both high and low) for analytes of important clinical relevance.** After this submission, the criteria for "markedly abnormal" were further modified. Presentation and analyses of the incidence of "markedly abnormal" results and shift tables utilizing these generally more severely abnormal criteria (both low and high) were eventually submitted. I reviewed this submission and have incorporated a presentation of relevant, markedly abnormal results in my review. The shift tables consisted of categories including : not markedly abnormal, any markedly abnormal, markedly abnormal low, and markedly abnormal high.

The sponsor's analyses (8/30/02 submission) of determining the frequency of laboratory abnormalities (combining results from placebo and ZS treated patients in studies Z/SEL/97/025, Z/SEL/97/026 and Z/SEL/97/027) that were not considered at least PCI revealed that a substantial proportion of abnormalities were not presented when the sponsor neglected presenting all laboratory abnormalities as DNDP had requested at the pre-NDA meeting. More specifically, the sponsor's analyses of the frequency of less severe abnormalities revealed that 529 abnormal individual observations (~ 41 % of all abnormalities) were not presented for clinical chemistry analytes, that 511 abnormal individual observations (~ 48 % of all abnormalities) were not presented for clinical hematological analytes, and that 166 abnormal individual observations (~ 34 % of all abnormalities) were not presented for urinalysis analytes. However, the presentation of the number of abnormal observations (~ 511) that did not meet the PCI criteria plus the total number of PCI abnormalities (660) for hematology did not add up to the total number of abnormal observations (i.e. estimated at 1050). Similar discrepancies were noted for analytes for chemistry and urinalysis. When I inquired of the sponsor's representative as to explanation for these apparent discrepancies, I was told that a specific analysis had not been conducted but merely an estimate of these numbers had been made. I then asked (11/8/02) that an analysis be conducted to provide this information based upon actual numbers (not estimates) from the respective datasets. This requested analysis based upon actual numbers (not estimates) from the respective datasets was recently submitted (12/02) but was received too late to be reviewed and included in this review.

**After reviewing the various analyses/presentations of laboratory data in the ISS, cause for additional concerns about the sponsor's analyses and presentations of analyses surfaced.**

- Review of a Shift Table 5.7 in the ISS (Volume 56, page 48) for total WBC in extension study Z/SEL/95/008E showed that the total number of patients who had received ZS (10 mg daily) was 2. However, Shift Table 5.7 in the ISS (Volume 56, page 49) for % neutrophils in extension study Z/SEL/95/008E showed that the total number of patients who had received ZS (10 mg daily) was 20. **When I inquired from a representative of the sponsor as to the reason for this discrepancy, I was told that Elan considered the data for study Z/SEL/95/008E and its extension (Z/SEL/95/008E) incomplete.** These data had been obtained by Elan from a previous sponsor (Scherer). I have not found any presentation of this information in the NDA and was told that there might be some mention of this problem in the SAS data codes. When I asked the representative what other data in the NDA were considered incomplete by the sponsor but had not clearly been identified as such, I was told

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that she thought that this problem might only relate to studies Z/SEL/95/008 and Z/SEL/95/008E but she was not certain.

I conducted an additional survey of results for total WBC, total neutrophil count, and % neutrophils in the various studies to assess for possible discrepancies among related analytes. My assumption was that because total neutrophil count would be based upon a computation of multiplying total WBC by % neutrophils, that one would not expect the number of subjects with % neutrophils to exceed the number of subjects with a total neutrophil count. Also one would not expect the total number of subjects with a total neutrophil count to exceed the total number of subjects with a total WBC. Table 77 shows a comparison of total number of subjects with total WBC, total neutrophil count, and % neutrophils for the same treatment group at the same time in the same study. Study Z/SEL/95/008 (randomized, controlled trial) shows that the number of patients with % neutrophils always exceeds the number of patients with total neutrophil counts suggesting that there are missing data for this important hematological analyte. Study Z/SEL/95/008E (extension of Z/SEL/95/008) also shows a similar phenomenon. In contrast, the number of patients with total WBC and total neutrophil count are identical for studies Z/SEL/97/025 and Z/SEL/97/026 (combined randomized, double-blind, placebo controlled trials) suggesting that data for these trials may be complete because there is no apparent discrepancy.

I have asked that the sponsor submit a response as to what type of data (efficacy and various safety- laboratory, VS, ECGs, etc) are considered complete and incomplete and for which studies in the NDA. This finding raises suspicions about the integrity of all data in the NDA, particularly when the sponsor did not describe this potential problem but it was only discovered by chance after a careful review of particular data of interest. At the least, if the sponsor confirms my impression of missing/incomplete safety data in studies Z/SEL/95/008 and Z/SEL/95/008E, this raises the question as to the utility of incorporating incomplete data from these studies into the ISS. A response was submitted (12/02) too late to be reviewed and included in this review.

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**Table 77 Total Number of Patients with Specific Analyte Test Results in Different Studies (Bold Numbers Emphasize Discrepant Results)**

Study	Treatment	Time	Total WBC	Total Neutrophils	% Neutrophils
Z/SEL/95/008	ZS 1.25 mg	week 4	<b>60</b>	<b>17</b>	<b>43</b>
“	“	week 12	<b>49</b>	<b>14</b>	<b>35</b>
“	ZS 10 mg	week 4	<b>57</b>	<b>14</b>	<b>43</b>
“	“	week 12	<b>48</b>	<b>11</b>	<b>37</b>
“	Eldepryl 5 mg BID	week 4	<b>65</b>	<b>16</b>	<b>49</b>
“	“	week 12	<b>58</b>	<b>15</b>	<b>43</b>
Z/SEL/97/027 Z/SEL/95/008E	ZS 1.25/2.5 mg	week 12-39	<b>281</b>	<b>257</b>	<b>44</b>
“	“	week $\geq$ 40	<b>250</b>	<b>234</b>	<b>18</b>
“	ZS 10 mg	week 12-39	<b>24</b>	<b>2</b>	<b>20</b>
“	“	week $\geq$ 40	<b>21</b>	<b>0</b>	<b>19</b>
Z/SEL/97/025 Z/SEL/97/026	ZS 1.25/2.5 mg	week 4	175	175	0
“	“	week 12	157	157	0
“	Placebo	week 4	92	92	0
“	“	week 12	86	86	0

- The sponsor has not conducted an analysis of PCI abnormalities nor of any laboratory abnormalities across studies for the ISS to provide this much desired presentation of such data in tabular format in the ISS.** PCI abnormalities (i.e. a major focus of analysis of laboratory analyses in this NDA) are only presented in the ISS in data listings, a format that makes it difficult to analyze and understand what happened to patients with respect to PCI abnormalities. PCI laboratory abnormalities are tabulated in individual studies but this approach should be incorporated into the ISS to integrate findings across studies. Furthermore, when individual study reports tabulate total PCI and CS abnormalities, they are not broken down further to indicate the incidence of high and low PCI and CS abnormalities. I asked the sponsor to conduct an analysis of PCI abnormalities for all laboratory analytes across studies for presentation in the ISS. The sponsor submitted such an analysis and this analysis was reviewed and included in this review.
- The shift tables only show the number of patients with a low, high, normal or missing analyte result at baseline and after treatment at a particular time or period. The sponsor does not show the percentage for these categories. Because the number of patients in treatment group may vary among treatment, it is not easy to discern when shift results might suggest an effect possibly related to ZS treatment. To make valid comparisons, it is important to consider the incidence ( of the particular categorical shifts after treatment. I have asked the sponsor to calculate and present also percentages next to numbers of patients in the various categories. The sponsor submitted such an analysis and this analysis was reviewed and included in this review.

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- In general, the description, presentation and discussion of analyses of laboratory abnormalities in the ISS frequently notes that there were “no clinically significant trends” in chemistry, hematology, or urinalysis results according to descriptive statistics and /or shift table analyses. The sponsor did not perform any statistical analyses of laboratory data in the NDA. Neither did the sponsor appear to make any systematic attempt to ascertain any potential trends in laboratory abnormalities that might suggest a treatment effect of ZS. The response from the sponsor’s consultant to my direct question as to whether there had been any systematic attempt to analyze for possible laboratory abnormalities caused by ZS was no. Abnormalities that might be ZS related were considered by “eyeballing” results. **Overall, my impression is that the sponsor did not appear to conduct a serious, sophisticated, critical analysis of data looking for possible laboratory abnormalities that might suggest an effect from ZS treatment.**

I reviewed chemistry, hematology, and urinalysis analytes according to descriptive summary statistics (e.g. mean, SD, median, min, max) and shift tables over time (pre-treatment, weeks 4 and 12 for the controlled studies; and week 12-39 or week  $\geq 40$  for the extension studies) for different treatments. I gave special attention to results of the controlled, short term studies and in particular to results of double-blind placebo controlled studies for which placebo results could be compared with those for ZS (1.25 and 2.5 mg combined). In the double-blind placebo-controlled trials, I focused on results when the incidence of an abnormality in the ZS groups appeared to be greater than the incidence in the placebo group and especially when this difference appeared to be greater at week 12 or appeared at week 12 (possibly suggesting a ZS treatment effect related to longer treatment duration or higher ZS dose). In the randomized controlled trial investigating low (1.25 mg) and high (10 mg) dose ZS and Eldepryl (5 mg BID), I focused on results when the incidence of an abnormality in the low dose ZS group appeared to be greater than the incidence in the Eldepryl group, when the incidence of an abnormality in the high dose ZS group appeared to be greater than the incidence in the low dose group or Eldepryl group, and also when an apparent difference in a ZS group appeared to be greater at week 12 or appeared at week 12.

During review of the shift tables for the short term studies, I focused on determining when a shift in a ZS treatment group appeared to raise the possibility of a ZS treatment effect. A ZS treatment effects was suspected when there may have been an increase (for ZS vs placebo or Eldepryl, or for high dose vs low dose ZS) in the percent of patients with a low or high abnormality (relative to the normal reference range) of an analyte of potentially clinical relevance. When such a phenomenon was suggested, I calculated the percentage of patients showing an abnormal shift. This percentage of patients showing an abnormal shift was equal to :

the # of patients with a treatment shift from normal at baseline to abnormally low or high result  
the # of patients without a treatment shift who remained in the normal range as at baseline.

For the extension studies, I focused on results when the shift tables suggested a substantial increase in the incidence of a shift to an abnormally low or high category at the later period ( $\geq 40$  weeks) and especially if this occurred at high dose ZS (i.e. 10 mg).

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#### 14.8.2. Review of Clinical Laboratory Findings

The sponsor did not note in the ISS whether any patients discontinued from the study because of a laboratory abnormality. Although I did not find any instances in which a patient appeared patients to withdraw from a study because of a laboratory abnormality, I specifically asked this question of the sponsor. I was told that no patients withdrew from a study because of a laboratory abnormality.

I did not find any suggestions of laboratory abnormalities (chemistry, hematology, urinalyses) possibly related to ZS with the exception of impairment of renal function.

In the double-blind placebo controlled studies, there were no suggestions of mean changes from baseline for ZS compared to placebo for any chemistry or hematological analyte.

Results from the randomized controlled trial (SEL/95/008) and the extension trials (Z/SEL/97/027 and Z/SEL/95/008E) raised the question of impairment of renal function (i.e. reflected by apparent increments in serum BUN and creatinine) related to ZS. In the double-blind placebo controlled trials, there did not appear to be any increment in mean serum BUN or creatinine after treatment compared to baseline. Nor did there appear to be an increased shift from normal to abnormal high in the ZS group (1.25 or 2.5 mg) vs placebo. Although there was no increment in mean serum BUN for 1.25 mg ZS or Eldepryl (5 mg BID) at 4 and 12 weeks compared to baseline, the high dose ZS (10 mg) group showed a 4.2 % increment above baseline at 4 weeks and a 11.2 % increment above baseline at 12 weeks. For serum creatinine, low dose ZS (1.25 mg) showed a 3.2 % and 1.8 % mean increment above baseline at 4 and 12 weeks respectively, and high dose ZS (10 mg) showed a 2.9 % and 6.9 % mean increment above baseline at 4 and 12 weeks respectively. There was no mean increment above baseline for the Eldepryl group at 4 or 12 weeks. Shift tables showed the number of patients who exhibited shifts from normal to abnormal high for the short term controlled studies (Z/SEL/97/25, Z/SEL/97/026 and Z/SEL/95/008). I created Table 78 from End of Text Table 5.2.1c for serum BUN and creatinine in the ISS. Table 78 shows that there was an increased shift from normal to abnormal high for both serum BUN and creatinine for high dose ZS (10 mg) compared to placebo, low dose ZS (1.25/2.5 mg), or Eldepryl (5 mg BID). Although the percent shift for serum BUN for Eldepryl was similar to that for placebo and low dose ZS, the percent shift for serum creatinine for Eldepryl appeared to be higher than that for both groups but was lower than the percent shift for high dose ZS. These results suggest some impairment of renal function by the 10 mg ZS and raise the question of a slight renal impairment also by the conventional dose of Eldepryl. Table 79 shows that there was an increased shift from normal to abnormal high for both serum BUN and creatinine for high dose ZS (10 mg) compared to low dose ZS (1.25/2.5 mg). There were no consistent changes in urinalyses of any treatment groups, particularly for the high dose ZS group. Although these results did not suggest any impairment of renal function with low dose ZS (1.25 or 2.5 mg), they did suggest that a high dose (10 mg) of ZS impairs renal function. The highest dose that the sponsor would like to market is 2.5 mg ZS daily.

In view of these findings I believe that PK must be studied in patients with renal impairment to characterize the PK and tolerability of subjects with various degrees of renal impairment.

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Patients who are treated with ZS and have renal impairment could generate high PK levels after 2.5 mg ZS that could mimic levels obtained high dose ZS (10 mg) and these high levels could further impair renal function or result in increased toxicity. This information is important for dosing considering that excretion of ZS is believed to occur mainly via the kidney and that high dose ZS appears to impair renal function.

**Table 78 Percent Shift of Normal to Abnormal High / Normal Remaining Normal From Baseline After Treatment in the Short Term Controlled Studies for Renal Function Analytes (Serum BUN, Creatinine)**

Renal Function Analyte	Week	Placebo N = 98	ZS 1.25/2.5 mg N = 259	ZS 10 mg N = 62	Eldepryl 5 mg BID N = 70
Serum BUN	4	8.2 %	7.9 %	24.1 %	8.1 %
“ “	12	8.7 %	6.9 %	38.1 %	7.5 %
Serum creatinine	4	0 %	1.9 %	9.0 %	5.4 %
“ “	12	1.3 %	1.6 %	18.2 %	8.3 %

**Table 79 Percent Shift of Normal to Abnormal High / Normal Remaining Normal From Baseline After Treatment in the Extension Studies for Renal Function Analytes (Serum BUN, Creatinine)**

Renal Function Analyte	Week	ZS 1.25/2.5 mg	ZS 10 mg
Serum BUN	12 - 39	18.5 %	45.5 %
“ “	≥ 40	28.7 %	37.5 %
Serum creatinine	12 - 39	4.3 %	28.0 %
“ “	≥ 40	6.7 %	25.0 %

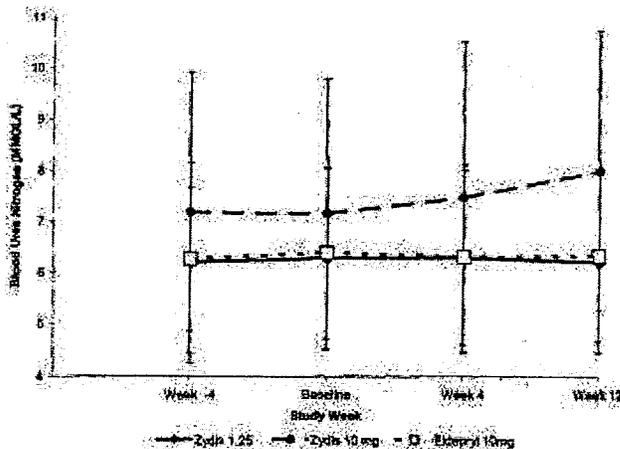
In response to my request, the sponsor plotted and submitted serum BUN and creatinine results of various treatment groups over time in various studies. Figure 16, Figure 17, Figure 18, and Figure 19 show that mean serum BUN and creatinine appear to increase over time in patients treated with high dose ZS (i.e. 10 mg daily) in the randomized, controlled study and its extension phase. But there does not appear to be any increase in patients treated with low dose ZS (i.e. 1.25 mg daily) or Eldepryl (5 mg BID) in these same studies. In contrast, Figure 20 and Figure 21 show that there does not appear to an increase in mean serum BUN and creatinine over time in patients treated with low dose ZS (1.25 mg daily over weeks 1-6 and then 2.5 mg daily over weeks 7-12) in the double-blind, placebo controlled studies. These data further support the impression that high dose ZS (i.e. 10 mg daily) is associated with mild-modest impairment of renal function. Of significant interest, there was no instances of a shift from not-markedly abnormal results to markedly high abnormal results (i.e. serum BUN  $\geq$  24 mMol/L, ULN = 8 mMol/L; serum creatinine  $\geq$  375  $\mu$ Mol/L, ULN = 125  $\mu$ Mol/L) in any of the three controlled studies or two extension studies. The sponsor submitted additional presentation of outlier results

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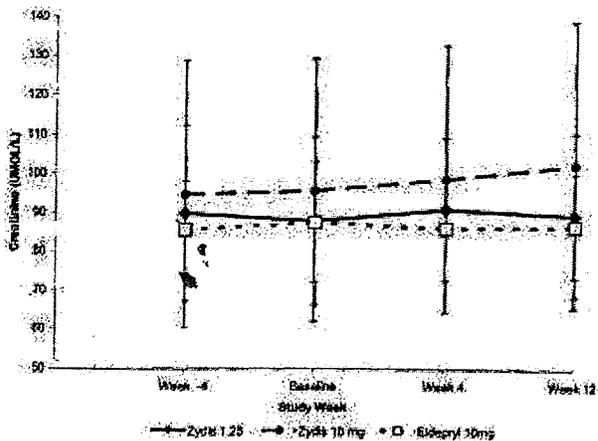
## Clinical Review Section

in response to my request (see Table 83). These observations suggest that the impairment of renal function that occurs with high dose ZS (i.e. 10 mg daily) appears to be limited, is not progressive in nature, and did not result in any instances of renal failure. The sponsor did not note that any patients discontinued from study because of abnormal laboratory result for serum BUN or creatinine. However, the caveat should be noted that there were significant numbers of missing values (i.e. serum BUN and creatinine results) in the controlled study and its extension phase involving treatment with high dose ZS (i.e. 10 mg daily).

**Figure 16** Serum BUN in Randomized, Controlled, Open-Label Study (Z/SEL/95/008) Comparing Low and High Dose ZS with Eldepryl



**Figure 17** Serum Creatinine in Randomized, Controlled, Open-Label Study (Z/SEL/95/008) Comparing Low and High Dose ZS with Eldepryl



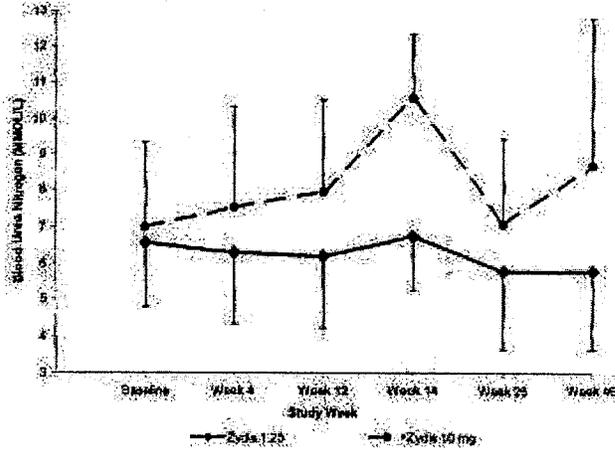
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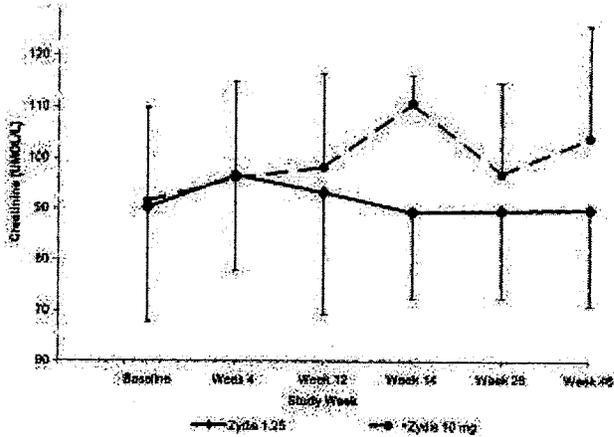
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**Figure 18** Serum BUN in Extension Study (Z/SEL/95/008E) Comparing Low and High Dose ZS with Eldepryl



**Figure 19** Serum Creatinine in Extension Study (Z/SEL/95/008E) Comparing Low and High Dose ZS with Eldepryl



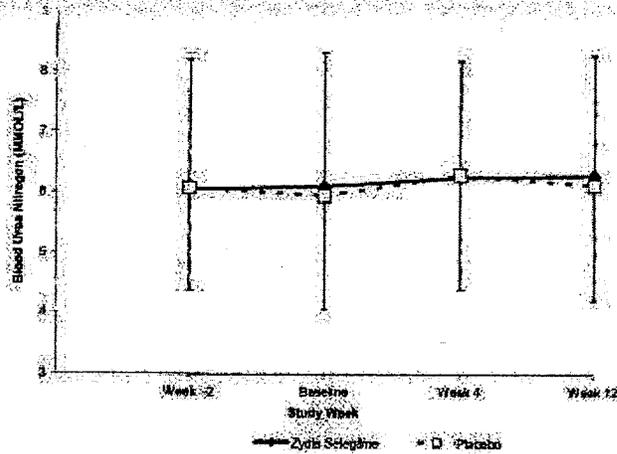
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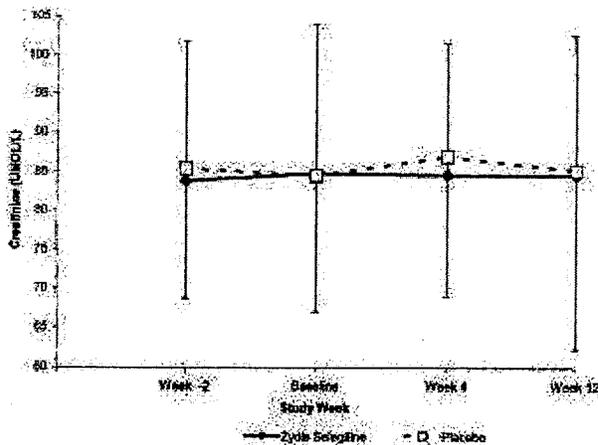
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**Figure 20 Serum BUN in Double-Blind, Placebo-Controlled Studies Comparing ZS with Placebo**



**Figure 21 Serum Creatinine in Double-Blind, Placebo-Controlled Studies Comparing ZS with Placebo**



### 14.8.3. Analyses of Laboratory Outliers

The sponsor did not provide any analyses of laboratory outliers except the analyses and presentation of SA abnormalities (Table 76). I have noted the severe limitations and shortcomings of this designation (e.g. relatively few analytes in this category, other important analytes not designated SA, not always severe level of abnormality, and no designation of both high and low abnormalities of clinical interest). Based upon my recommendation to define and determine the frequency of markedly abnormal laboratory results, the sponsor created such a definition, conducted an analysis and submitted this analysis. I reviewed this submission and have incorporated relevant comments about this analysis in my review.

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The sponsor presented SA results for the double-blind placebo-controlled studies (Table 80), the randomized, controlled, open-label study (Z/SEL/95/08) (Table 81), and the extension studies (Table 82). However, the sponsor did not present nor analyze these outlier results according to the treatment emergent concept (i.e. new appearance of this SA abnormality or worsening of the SA laboratory after study treatment). In contrast, the sponsor also presented SA results that were present before study treatment and did not become "significantly" worse after study treatment. I analyzed the sponsor's SA results as treatment emergent when the SA results appeared after treatment or became "significantly" more abnormal. I defined "significantly" more abnormal as a > 25 % worse, change from baseline after study treatment. Applying these criteria, 4 of the 7 SA results in the double-blind, placebo controlled studies were treatment emergent. These SA results (Table 80) included decreased hemoglobin (patient 002-A63), decreased platelets (patient 018-B61), decreased neutrophils (patient 108-Y32, and increased serum ALT (patient 112-Y76). Of these SA results, the treatment emergent decrease in hemoglobin, platelets, and neutrophils observed at week 4 (ZS 1.25 mg daily dose) showed significant improvement (i.e. > 25 % change) at a later timepoint (e.g. week 12) after longer exposure to ZS and a higher dose (i.e. 2.5 mg daily dose). I interpret these observations as not suggesting that ZS produced a significant risk in producing these SA laboratory results. However, the increase in serum ALT in patient 112-Y76 occurred at week 12 was a new development and was noted to be "continuing at the end of study." Although the sponsor did not specify if this patient or any patient discontinued from further study because of a laboratory abnormality, it was not clear if this patient enrolled into the extension trial. It was not clear that the sponsor obtained appropriate follow-up on this adverse event/laboratory abnormality to show that it had resolved or at least stabilized. After requesting additional follow-up information on this patient from the sponsor, I learned that the hepatic abnormality eventually improved and did not result in a severe problem or hepatic failure (see my analyses of markedly abnormal laboratory abnormalities and section 14.21.4 Clinical Laboratory Findings of Safety Update).

For study Z/SEL/95/08, only 1 (decreased hemoglobin, patient Kelly-062 SA result) (Table 81) out of 5 SA results was treatment emergent. This SA abnormal result that occurred at week 4 also was associated with significant improvement despite continued ZS exposure to very high dose ZS (i.e. 10 mg daily). The very marked increment in serum ALT (939) and AST (368) that appeared to occur in one patient (Mondial-003) at week 4 after high dose ZS (i.e. 10 mg daily) seemed to be a spurious laboratory error because repeat testing on the same day showed only a minimally elevated ALT (57) and a normal AST (32).

In the extension studies, only 2 (out of 8 total SA results presented) were treatment emergent. These SA results (Table 82) were both for decreased hemoglobin (patients 002-A27 and 108-Y28 and occurred at the end of the study after  $\geq 2.5$  years treatment with low dose ZS (i.e. 1.25/2.5 mg daily).

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**Table 80 SA Laboratory Results in Double-Blind Placebo-Controlled Studies**

Patient Age (Sex)	Lab Test (Units)	Lower to High Limit (S. Criteria)	Visit (Week)	Collection Date	Lab Value	PCI	CS	Comments
002-A63 93 (M)	Hemoglobin (G/L)	135-180 (≤0.75 of LLN)	V1 (W-2)	30Mar99	141	No		Patient had mild, unrelated colitis (anemia secondary to diverticulosis with rectal bleeding).
			V3 (Baseline)	13Apr99	141	No		
			V6 (W4)	11May99	93	Yes	1	
			V10 (W12)	13Jul99	130	No	1	
117-Z33 58 (M)	Hemoglobin (G/L)	135-180 (≤0.75 of LLN)	V1 (W-2)	18Feb99	92	Yes	1	
			V3 (Baseline)	2Mar99	90	Yes	1	
			V6 (W4)	1Apr99	88	Yes		
			V10 (W12)	10Aug99	92	Yes		
012-B83 70 (F)	Platelets (x10 <sup>9</sup> /L)	150-400 (≤0.75 of LLN)	V1 (W-2)	2Nov98	124	No	1	
			V3 (Baseline)	13Nov98	111	No	1	
			V6 (W4)	7Dec98	117	No	1	
			V10 (W12)	16Feb99	112	No	1	
018-B61 81 (M)	Platelets (x10 <sup>9</sup> /L)	150-400 (≤0.75 of LLN)	V1 (W-2)	20Jan99	142	No	1	
			V3 (Baseline)	3Feb99	128	No	1	
			V6 (W4)	3Mar99	93	Yes	3	
			V10 (W12)	30Apr99	165	No		
108-Y31 74 (F)	WBC (x10 <sup>9</sup> /L)	4-11 (≤0.75 of LLN)	V1 (W-2)	5Jan99	3.4	No	1	
			V3 (Baseline)	19Jan99	3.4	No	1	
			V6 (W4)	17Feb99	3.3	No	1	
			V10 (W12)	16Apr99	3.0	No	1	
108-Y32 69 (F)	Neutrophils (x10 <sup>9</sup> /L)	2.0-7.5 (≤0.75 of LLN)	V1 (W-2)	11Jan99	2.4	No		
			V3 (Baseline)	26Jan99	2.1	No		
			V6 (W4)	23Feb99	1.5	No	1	
			V10 (W12)	22Apr99	2.2	No		
112-Y76 42 (M)	ALT (U/L)	5-40 (≥5 of ULN)	V1 (W-2)	9Dec98	56	No		SGPT increased reported as a moderate, unrelated adverse event on 30Mar99 that was continuing at end of study
			V3 (Baseline)	6Jan99	56	No	1	
			V6 (W4)	3Feb99	62	Yes	1	
			V10 (W12)	30Mar99	208	Yes		

Protocols Z/SEL/97/025 and Z/SEL/97/026

Data Source: Listings 2.2 and 9.2

S. Criteria = Criteria for Substantially Abnormal Value

PCI = Value of Potential Clinical Importance, defined as values outside the normal range (See Listing 6)

CS = Clinical Significant codes assessed by investigator: 1 = Not clinically significant; 2 = Clinically significant, related to underlying condition; 3 = Clinically significant, probably not related to underlying condition. Blank codes means no code was reported.

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**Table 81 SA Laboratory Results in the Randomized, Controlled, Open-Label Study (Z/SEL/95/08)**

Patient Age (Sex)	Lab Test (Units)	Lower to High Limit (S. Criteria)	Visit (Week)	Collection Date	Lab Value	PCI	CS	Comments
Zydis Selegiline 1.2/2.5 mg								
Tanner-284 70 (F)	Platelets (x10 <sup>9</sup> /L)	150-400 (≤0.75 of LLN)	V1 (W-4)	29Jul97	31	Yes	1	
			V3 (Baseline)	26Aug97	40	Yes	1	
			V5 (W4)	24Sep97	38	Yes	1	
			V9 (W8)	22Oct97	39	Yes	1	
Zydis Selegiline 10 mg								
Kelly-062 76 (F)	Hemoglobin (G/L)	135-180 (≤0.75 of LLN)	V1 (W-4)	16Jun97	100	Yes	3	Patient had severe, unrelated anemia reported on 8Aug97 that was continuing at study end.
			V3 (Baseline)	10Jul97	93	Yes	3	
			V5 (W4)	7Aug97	68	Yes	3	
			V9 (W12)	2Oct97	87	Yes	1	
Selzer-160 67 (F)	Platelets (x10 <sup>9</sup> /L)	150-400 (≤0.75 of LLN)	V1 (W-4)	24Feb97	47	Yes	3	
			V3 (Baseline)	25Mar97	49	Yes	1	
			V5 (W4)	22Apr97	46	Yes	1	
			V9 (W12)	13Jun97	NR			
			V9 (W12 retest)	13Jun97	207	No		
Sergay-191 83 (M)	Platelets (x10 <sup>9</sup> /L)	150-400 (≤0.75 of LLN)	V1 (W-4)	4Jun97	73	Yes	2	Patient had mild, unrelated refractory anemia (sideroblastic anemia) reported on 26Sep97 that ended on 18Sep97.
			V1 (W-4 retest)	4Jun97	137	No	1	
			V3 (Baseline)	2Jul97	104	No	2	
			V5 (W4)	30Jul97	94	Yes	2	
			V5 (W4 retest)	30Jul97	101	No	2	
			V9 (W12)	26Sep97	210	No		
Mondal-003 78 (M)	ALT (U/L)	7-56 (≥5 of ULN)	V1 (W-4)	20Mar96	29	No		Patient had a severe, probably related adverse event of LFT abnormal reported on 15May96 that ended 29May96.
			V3 (Baseline)	17Apr96	26	No		
			V5 (W4)	15May96	939	Yes	3	
			V5 (W4 retest)	15May96	57	No	1	
				V9 (W12)	10Jul96	29	No	
	AST (U/L)	5-40 (≥5 of ULN)	V1 (W-4)	20Mar96	23	No		
			V3 (Baseline)	17Apr96	21	No		
			V5 (W4)	15May96	368	Yes	3	
			V5 (W4 retest)	15May96	32	No		
			V9 (W12)	10Jul96	26	No		

Protocol Z/SEL/95/008

Data Source: Listings 2.2, 2.3, 9.2, and 9.3

NR = Not Recorded

S. Criteria = Criteria for Substantially Abnormal Value

PCI = Value of Potential Clinical Importance

CS = Clinical Significant codes assessed by investigator: 1 = Not clinically significant; 2 = Clinically significant, related to underlying condition; 3 = Clinically significant, probably not related to underlying condition. Blank codes means no code was reported.

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**Table 82 SA Laboratory Results in Extension Studies**

Patient Age (Sex)	Lab Test (Units)	Lower to High Limit (S. Criteria)	Visit (Week)	Collection Date	Lab Value	PCI	CS	Comments			
<b>Zydis Selegiline 1.2/2.5 mg</b>											
002-A27 68 (M)	Hemoglobin (G/L)	135-180 (≤0.75 of LLN)	PV3 (Baseline)	14May98	134	No	1				
			PV6 (W4)	11Jun98	135	No					
			PV10 (W12)	12Aug98	130	No	1				
			V3 (W24)	5Nov98	130	No	1				
			V5 (W52)	18May99	119	Yes	1				
			V6 (Y1.75)	4Nov99	122	Yes	1				
			V7 (Y2.25)	18Apr00	116	Yes	1				
			V8 (Y2.75)	3Oct00	106	Yes					
			V9 (Y3.25)	5Apr01	98	Yes	1				
108-Y28 73 (M)	Hemoglobin (G/L)	135-180 (≤0.75 of LLN)	PV10 (Baseline)	1Dec98	158	No					
			V3 (W12)	23Feb99	154	No					
			V5 (W40)	25Sep99	141	No					
			V6 (Y1.5)	7Mar00	144	No					
			V7 (Y2)	7Sep00	146	No					
			V8 (Y2.5)	8Mar01	99	Yes					
			<b>108-Y21 74 (M)</b>								
			Platelets (x10 <sup>9</sup> /L)	150-400 (≤0.75 of LLN)	PV10 (Baseline)	29May98	137	No	1		
V3 (W12)	25Aug98	112			No						
Rescreen	4May99	137			No	1					
V6 (Y1.5)	4Nov99	138			No	1					
V7 (Y2)	9May00	149			No	1					
V8 (Y2.5)	7Nov00	134			No	1					
V9 (Y3)	8May01	143			No	1					
<b>104-Y92 53 (M)</b>											
WBC (x10 <sup>9</sup> /L)	4-11 (≤0.75 of LLN)	PV10 (Baseline)	6Oct98	3.4	No	1					
		V3 (W12)	21Dec98	4.7	No						
		V5 (W40)	7Jul99	3.0	No						
		V6 (Y1.5)	5Jan00	5.7	No						
		Study End	3Apr00	4.0	No						
<b>108-Y31 74 (F)</b>											
WBC (x10 <sup>9</sup> /L)	4-11 (≤0.75 of LLN)	PV3 (Baseline)	19Jan99	3.4	No	1	Patient had mild, unrelated blood dyscrasia (ie, abnormal hematology) reported on 27Jan00 that resolved, but no end date was recorded.				
		PV6 (W4)	17Feb99	3.3	No	1					
		PV10 (W12)	16Apr99	3.0	No	1					
		V3 (W24)	6Jul99	4.2	No						
		V5 (W52)	27Jan00	2.8	No						
		V5 (Retest)	17Feb00	3.5	No						
		V6 (Y1.75)	27Jul00	3.7	No	1					
V7 (Y2.25)	30Jan01	3.8	No	1							
<b>Kelly-225 67 (F)</b>											
GGT (U/L)	6-38 (≥5 of ULN)	V9 (Baseline)	6Nov97	183	Yes	1	Patient had severe, unrelated cholelithiasis and gastritis as well as moderate, unrelated hepatitis reported from 21Dec97 to 27Dec97.				
		V10 (W2)	19Nov97	192	Yes	1					

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Patient Age (Sex)	Lab Test (Units)	Lower to High Limit (S. Criteria)	Visit (Week)	Collection Date	Lab Value	PCI	CS	Comments		
<b>Zydis Selegiline 10 mg</b>										
Sergay-191 83 (M)	Hemoglobin (G/L)	135-180 (≤0.75 of LLN)	V3 (Baseline)	2Jul97	119	Yes	1			
			V5 (W4)	30Jul97	113	Yes	1			
			V5 (W4 retest)	30Jul97	108	Yes	1			
			V9 (W12)	26Sep97	109	Yes	1			
			V10 (W14)	8Oct97	111	Yes	1			
			V13 (W26)	27Mar98	88	Yes	3			
			V17 (W46)	30Sep98	114	Yes	1			
			Platelets (x10 <sup>9</sup> /L)	150-400 (≤0.75 of LLN)	V3 (Baseline)	2Jul97	104	No	2	Patient had mild, unrelated refractory anemia (sideroblastic anemia) reported on 26Sep97 that ended on 18Sep97. Chronic myelocytic leukemia was reported on 17Jun98. On 30Sep98, moderate, unrelated abnormal platelets (decreased platelet count) was reported and continued at study end
					V5 (W4)	30Jul97	94	Yes	2	
					V5 (W4 retest)	30Jul97	101	No	2	
					V9 (W12)	26Sep97	210	No		
					V10 (W14)	8Oct97	152	No		
					V13 (W26)	27Mar98	153	No		
V17 (W46)	30Sep98	79	Yes	3						

Protocols Z/SEL/95/008 Extension and Z/SEL/97/027  
 Data Source: Listings 2.2, 2.3, 9.2, and 9.3  
 PV = Previous visit from original protocol (ie, Z/SEL/97/025 or Z/SEL/97/026 for Z/SEL/97/027 and Z/SEL/95/008 for the Z/SEL/95/008 extension.  
 S. Criteria = Criteria for Substantially abnormal Value  
 PCI = Value of Potential Clinical Importance  
 CS = Clinical Significant codes assessed by investigator: 1 = Not clinically significant; 2 = Clinically significant, related to underlying condition; 3 = Clinically significant, probably not related to underlying condition. Blank codes means not code was reported.

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**Table 83 Criteria for Markedly Abnormal Laboratory Results**

Laboratory Panel Laboratory Test	Age Range (years)	Sex	Normal Range	Markedly Abnormal Range	Units
<b>Chemistry</b>					
ALANINE TRANSAMINASE (ALT)	0-120	BOTH	5 - 40	>=120	U/L
ALBUMIN	0-120	BOTH	35 - 50	<=28 - >=60	G/L
ALKALINE PHOSPHATASE	19-60 18-60 61-120	MALE FEMALE BOTH	35 - 110 35 - 110 0 - 125	>=330 >=330 >=330	U/L U/L U/L
ASPARTATE TRANSAMINASE (AST)	0-120	BOTH	10 - 40	>=120	U/L
BLOOD UREA NITROGEN (BUN)	18-120	BOTH	2.5 - 8	>=24	MMOL/L
CALCIUM	12-50 51-120 51-120	BOTH MALE FEMALE	2.12 - 2.62 2.12 - 2.62 2.19 - 2.66	<=1.85 - >=2.95 <=1.85 - >=2.95 <=1.85 - >=2.95	MMOL/L MMOL/L MMOL/L
CARBON DIOXIDE - TOTAL	0-120	BOTH	23 - 31	<=18 - >=36	MMOL/L
CHLORIDE	0-120	BOTH	95 - 110	<=85 - >=119	MMOL/L
CHOLESTEROL	18-29 30-120	BOTH BOTH	0 - 5.7 0 - 6.2	>=8.6 >=9.3	MMOL/L MMOL/L
<b>Chemistry</b>					
CREATININE	10-120 10-120	MALE FEMALE	60 - 125 50 - 110	>=375 <50 - >=330	UMOL/L UMOL/L
GLOBULIN	0-120	BOTH	10 - 50	<10 - >=65	G/L
GLUCOSE-RANDOM	0-120	BOTH	3.6 - 7.8	<=2.5 - >=11.2	MMOL/L
GAMMA GLUTAMYL TRANSFERASE (GGT)	0-120 0-120	MALE FEMALE	0 - 65 0 - 40	>=195 >=120	U/L U/L
PHOSPHATE	15-60 61-120 15-50 51-120	MALE MALE FEMALE FEMALE	0.80 - 1.45 0.74 - 1.26 0.80 - 1.45 0.84 - 1.52	<=0.60 - >=1.75 <=0.57 - >=1.55 <=0.60 - >=1.75 <=0.62 - >=1.80	MMOL/L MMOL/L MMOL/L MMOL/L
POTASSIUM	0-120	BOTH	3.5 - 5.2	<=2.7 - >=6.0	MMOL/L
PREGNANCY (SERUM HCG)	0-120	FEMALE	0 - 5	>5	IU/L
SODIUM	13-120	BOTH	135 - 147	<=125 - >=157	MMOL/L
TOTAL BILIRUBIN	0-120	BOTH	0 - 22	>=66	UMOL/L
<b>Chemistry</b>					
TOTAL PROTEIN	0-60 61-120	BOTH BOTH	60 - 85 59 - 79	<=45 - >=100 <=44 - >=94	G/L G/L
TRIGLYCERIDES	20-29 20-29 30-39 30-39 40-49 40-49 50-120 50-120	MALE FEMALE MALE FEMALE MALE FEMALE MALE FEMALE	0.50 - 2.55 0.50 - 1.90 0.55 - 3.30 0.55 - 2.20 0.60 - 3.60 0.60 - 2.60 0.70 - 3.20 0.70 - 2.75	>=5.1 >=3.8 >=6.60 >=4.40 >=7.20 >=5.20 >=6.40 >=5.5	MMOL/L MMOL/L MMOL/L MMOL/L MMOL/L MMOL/L MMOL/L MMOL/L
URIC ACID	0-120 0-50 51-120	MALE FEMALE FEMALE	230 - 480 250 - 390 210 - 450	>=650 >=560 >=620	UMOL/L UMOL/L UMOL/L
<b>Hematology</b>					
HEMATOCRIT	18-120 18-120	MALE FEMALE	0.40 - 0.54 0.35 - 0.47	<=0.30 - >=0.60 <=0.28 - >=0.54	% %
HEMOGLOBIN	18-120 18-120	MALE FEMALE	135 - 180 115 - 165	<=100 - >=200 <=85 - >=185	G/L G/L
<b>Hematology</b>					
MCH	0-120	BOTH	27 - 33	<=22 - >=38	PG
MCHC	0-120	BOTH	310 - 360	<=285 - >=400	G/L
MCV	0-120 0-120	MALE FEMALE	80 - 100 75 - 100	<=70 - >=110 <=65 - >=110	FL FL
PLATELET COUNT	0-120	BOTH	150 - 400	<=100 - >=500	X10E9/L
RED BLOOD CELL COUNT	18-120 18-120	MALE FEMALE	4.50 - 6.50 4.00 - 5.50	<4.00 - >=7.2 <4.00 - >=5.5	X10E12/L X10E12/L
WHITE BLOOD CELL COUNT	18-120	BOTH	4.0 - 11.0	<=3.0 - >=15.0	X10E9/L
<b>Differential</b>					
(A) BANDS	10-120	BOTH	0.0 - 0.7	>=1.1	X10E9/L
(A) BASOPHILS	0-120	BOTH	0.0 - 0.2	>=0.5	X10E9/L
(A) EOSINOPHILS	11-120	BOTH	0.0 - 0.4	>=1.0	X10E9/L
(A) LYMPHOCYTES	10-120	BOTH	1.0 - 3.5	<0.6 - >=5.5	X10E9/L
<b>Differential</b>					
(A) MONOCYTES	2-120	BOTH	0.0 - 0.8	>=1.3	X10E9/L
(A) NEUTROPHILS	10-120	BOTH	2.0 - 7.5	<=1.5 - >=12.0	X10E9/L

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I conducted additional outlier analyses based upon the sponsor's presentation of analyses markedly abnormal results (Table 83) that were submitted in response to my request for a more comprehensive presentation of outlier abnormal laboratory results. These presentations/analyses of data from the same studies (double-blind, placebo-controlled; randomized, controlled; extension) that were analyzed for SA results by the sponsor included shift tables showing results (absolute patient numbers and percentages) of baseline categorization (markedly low, not markedly abnormal, markedly high, or missing) and the same categorization after treatments. The sponsor also provided listings of markedly abnormal results and figures showing mean chemistry and hematology laboratory parameters over time according to treatment group. However, the sponsor did not submit any description, summary, or interpretation of these results.

My analysis of the markedly abnormal (MA) results initially focused on evaluating the incidence of MA results in the double-blind, placebo-controlled trials by comparing the incidence in the ZS vs placebo groups particularly after treatment. Although there were isolated MA results for many parameters, there did not appear to be a significantly increased incidence (i.e.  $\geq 2\%$  difference for ZS group vs placebo control group) of MA laboratory results after ZS treatment for any chemistry or hematological parameters except for MA low RBC counts. However, because the increased incidence of this MA result in the ZS group was present at all timepoints (i.e. screening, baseline, 4 and 12 weeks on treatment) and because it was not associated with an increased incidence of MA low hemoglobin and hematocrit results, I cannot attach much clinical significance to this observation. Neither did my review of shift results for these same parameters suggest that ZS was producing a substantial shift to markedly low or high results.

Whereas the sponsor's review of SA results noted that serum ALT was increased in patient 112-Y26, my review also revealed that one patient (randomized # 124 in study Z/SEL/97/026) exhibited a MA increased serum ALT (208) and MA increased serum AST (141) at week 12. The patient had the same identifying number (i.e. Y76) at screening and thus appears to be the same patient. The sponsor's presentations are further confusing because this same patient is listed as exhibiting a MA increased serum ALT and AST at week 12 in listings for both the double-blind placebo-controlled study (Z/SEL/97/026) and its extension study (Z/SEL/97/026). This patient also showed a mildly elevated serum ALT at screening (56), baseline (56), and week 4 (62). Serum AST at screening (39), baseline (39), and week 4 (38) was normal (10-40). Serum AST increased at week 4 (62) and further increased at week 12 (208). Serum glutamyl transferase (GGT; normal  $\leq 65$ ) was elevated at screening/week -2 (146) and baseline (76) did not increase further with treatment over 12 weeks. There was no associated increase in serum total bilirubin nor alkaline phosphatase over the 12 weeks of treatment. Thus, this patient did not exhibit MA increased serum GGT, alkaline phosphatase, or bilirubin during treatment.

I also reviewed the incidence of MA laboratory results, shift tables for MA results, MA result listings and figures of mean laboratory parameters over time according to study treatment in the randomized, controlled, open-label study, and both extension studies. I utilized a similar analytical approach as described above for the double-blind, placebo controlled studies. Although I focused, especially on reviewing for hepatic, renal, and certain hematological results (e.g. WBC, neutrophil count, platelets, hemoglobin, hematocrit, I did not find any additional

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laboratory (chemistry or hematology) results that met the criteria for MA and I deemed worthy of presentation or discussion.

#### 14.9. Vital Signs (VS)

VS consisting of oral temperature, ventilatory rate, and **supine, sitting and standing** systolic and diastolic blood pressure and pulse were collected randomly with respect to study treatment dosing in the double-blind, placebo controlled studies (Z/SEL/94/026, Z/SEL/94/025, and their extension trial - Z/SEL/94/027). In the randomized, controlled study (Z/SEL/95/008) and its extension trial (Z/SEL/95/008E), VS collected consisted of **sitting** systolic and diastolic blood pressure and pulse collected randomly with respect to study treatment dosing. **None of these trials collected VS data with regarding to dosing so that one could potentially see if there was a particular response occurring at a particular time after dosing.** VS were considered Potentially Clinically Important (PCI) when : 1) systolic blood pressure was > 160 or < 100 mm Hg; 2) diastolic blood pressure was > 100 or < 60 mm Hg; 3) pulse was > 110 or < 60 beats per minute; 4) oral temperature was > 39 or < 35 ° C ; and 5) ventilatory rate was > 23 or < 14 ventilations per minute. Changes in VS from sitting to standing were considered PCI when : 1) systolic blood pressure increased or decreased by > 20 mm Hg; 2) diastolic blood pressure increased or decreased by > 10 mm Hg; and 3) pulse increased or decreased by > 15 beats per minute.

In the double-blind, placebo controlled trials, the incidence of a PCI decrement in oral temperature was 4.6 % for ZS (1.25/2.5 mg) and 0 % for placebo. The treatment difference incidence (i.e. treatment incidence – baseline incidence) for PCI increments in systolic blood pressure was greater (6.2 %) for ZS than placebo (1.0 %). However, the treatment difference incidence for PCI decrements in systolic blood pressure, any PCI change in diastolic blood pressure, any PCI change for pulse or ventilatory rate for the ZS group was not greater than that for the placebo group.

When results of all short term controlled trials were combined, ZS appeared to produce a dose-dependent increase in the incidence of PCI increments in systolic blood pressure. Whereas the treatment difference incidence for placebo was minimal (1.0 %), the treatment difference incidence for low dose ZS (1.25/2.5 mg) was higher (5.4 %), and the treatment difference for high dose ZS (10 mg) was even greater (8.1 %) than that for low dose ZS. The treatment difference incidence of PCI increments in systolic blood pressure for Eldepryl (5 mg BID) was even greater (11.3 %) than that (8.1 %) for high dose ZS. The treatment difference incidence for PCI decrements in systolic blood pressure and PCI changes in pulse for any selegiline treatment was not greater than respective treatment difference incidence for the placebo group.

In the extension studies, there was no suggestion of a treatment difference incidence for any PCI VS change for low dose vs high dose ZS.

Table 84 (created by this reviewer and derived from End of Text Tables 7.3 and 7.3a in ISS) shows results of PCI changes in orthostatic VS (sitting to standing) during treatment (i.e.

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throughout the entire period on study drug) in the double-blind, placebo controlled trials. The incidence shows the frequency of patients who exhibited at least one episode of "increased" or "decreased" pulse or blood pressure (according to the cut-off changes) during the positional change. **Patients who experienced the changes beyond the defined threshold were counted once for the incidence calculations.** This analysis does not allow one to assess the total number of VS changes beyond the define threshold cut-off. There was no treatment difference in the incidence of PCI changes for either ZS dose compared to the treatment difference incidence for the placebo group.

**Table 84 Treatment Difference Incidence (Treatment Incidence – Baseline Incidence) of PCI Changes for Orthostatic VS (Sitting to Standing) after Treatment with ZS in Double Blind Placebo Controlled Studies**

PCI VS Change	Placebo N = 98	ZS 1.25 mg N= 194	ZS 2.5 mg N = 178	ZS 1.25 or 2.5 mg N = 194
Systolic BP increase > 20	8.2 %	3.1 %	3.9 %	6.2 %
Systolic BP decrease > 20	16.3 %	11.4 %	11.1 %	19.6 %
Diastolic BP increase > 10	15.3 %	5.1 %	3.9 %	10.3 %
Diastolic BP decrease > 10	25.5 %	14.0 %	8.9 %	24.3 %
Pulse increase > 15	10.2 %	10.9 %	8.1 %	16.0 %
Pulse decrease > 15	6.1 %	1.1 %	3.6 %	5.2 %

VS changes of blood pressure and pulse may be significant in Parkinson's disease patients by virtue of their age and disease state. Furthermore, antiparkinsonian medications (e.g. especially drugs enhancing dopaminergic tone) frequently increase the risk for pulse and blood pressure changes, especially orthostatic hypotension. My impression of the sponsor's analyses and presentations was that relatively little was done compared to what may have been analyzed and presented according to the data collected. The sponsor's plan for exploring data analyses did not seem to be very comprehensive. Of particular concern, the sponsor had only analyzed and presented orthostatic VS changes from sitting to standing positions. There were no analyses that would look at potentially maximal orthostatic changes that could occur by changing from supine to standing position. Whereas, changes from sitting to standing might be minimal or modest, changes from supine to standing could potentially be much greater.

**Considering these important shortcomings, I asked the sponsor to submit additional combined (studies Z/SEL/97/025 and Z/SEL/97/026) analyses and presentations of VS data (i.e. blood pressure, pulse, orthostatic responses when collected) according to study treatment and position and over time. These additional analyses include : 1) tables/figures**

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showing the mean (SD) absolute data ; 2) tables/figures showing the mean (SD) change from baseline; 3) tables/figures showing the changes from one position to another (including all combinations, supine-standing, supine-sitting, sitting-standing); and 4) shift tables showing all combinations of positional changes using the sponsor's PCI criteria and also applying more severe criteria (e.g. increment or decrements of  $> 40$  for systolic blood pressure,  $> 20$  for diastolic blood pressure, and  $> 30$  for pulse) of orthostatic changes.

I will present relevant results. **Review of these requested analyses showed that there were statistically significant decrements ( $p < 0.05$ ) for the frequency of abnormal blood pressure decrements (i.e.  $> 20$  mm Hg systolic and  $> 10$  mm Hg diastolic) while changing from supine to standing positions at week 8 for ZS (2.5 mg/d) compared to the placebo group.** The percentage of patients with abnormal systolic blood pressure decrements was higher ( $p = 0.008$ ) for ZS (21.1 %) than for placebo (9.2 %). A statistically significant ( $p = 0.038$ ) treatment difference (i.e. mean ZS change – mean placebo change; - 4.6 mm Hg) related to ZS was also noted for the mean systolic blood pressure change from baseline after standing from a supine position. Similarly, the percentage of patients with abnormal diastolic blood pressure decrements was higher ( $p = 0.03$ ) for ZS ( 11.9 %) than for placebo (4.1 %). Similar analyses of these data applying more markedly abnormal VS changes (e.g. systolic BP change  $> 40$ , diastolic BP change  $> 20$ , pulse change . 30) did not reveal any increase these abnormalities due to ZS. Results from these new analyses suggested that the occurrence of orthostatic hypotension was more prominent soon after starting the 2.5 mg daily dose of ZS.

These additional analyses also showed that ZS produced statistically significant ( $p < 0.05$ ) lower mean changes of systolic blood pressure from baseline while changing from sitting to standing position at weeks 2 and 6 than those observed in placebo patients. The mean treatment difference (i.e. mean ZS result – mean placebo result) in blood pressure was approximately - 4 to - 5 mm Hg. At weeks 8 and 12 ZS effects trended ( $0.05 > p < 0.1$ ) toward statistical significance. ZS also produced statistically significant ( $p < 0.05$ ) lower mean changes of diastolic blood pressure from baseline at weeks 1, 2, and 4 than those observed in placebo patients. The mean treatment difference in diastolic blood pressure was approximately - 2 to - 3 mm Hg. At week 12 ZS effects trended ( $0.05 > p < 0.1$ ) toward statistical significance for a lower mean treatment difference in diastolic blood pressure.

There did not appear to be a treatment difference in the frequency of orthostatic hypotension based upon my analysis (Table 84) of orthostatic hypotension while changing from sitting to supine position . However, I noted the limitation of this analysis above when patients exhibiting orthostatic hypotension are counted once in such incidence analyses regardless of the number of episodes of orthostatic hypotension or when they occurred. Based upon the sponsor's requested analyses of data I created Table 85 that shows the number of abnormal decrements in blood pressure /patient while changing from supine to standing position during different treatment periods. These data were derived by counting the total number of episodes of abnormal decrements in blood pressure and dividing each group's total by 194 patients (ZS) or 98 patients (placebo).

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This analysis shows that number of episodes of abnormal decrements in systolic blood pressure per patient is higher with ZS treatment (0.54) than with placebo treatment (0.37) during the latter half of the study while on ZS 2.5 mg daily. The number of episodes of abnormal decrements in diastolic blood pressure per patient was also higher with ZS treatment than with placebo treatment throughout the study during treatment with both 1.25 and 2.5 mg daily doses.

**Table 85**      **Number of Abnormal Decrements in Blood Pressure/Patient from Supine to Standing During Different Treatment Periods in Double-Blind, Placebo-Controlled Studies (ZS n = 194; Placebo n = 98)**

Treatment Period	Weeks 1 – 6 (wks 1, 2, 4, 6)		Weeks 8 – 12 (wks 8, 10, 12)		Weeks 1- 12 (wks 1,2,4,6,8,10,12)	
	Placebo	ZS 1.25 mg	Placebo	ZS 2.5 mg	Placebo	ZS 1.25 or 2.5 mg
N	98	194	98	194	98	194
Systolic BP decrease > 20 mm Hg	0.67	0.64	0.37	0.54	1.02	1.20
Diastolic BP decrease > 10 mm Hg	0.20	0.34	0.22	0.30	0.43	0.64

Of interest, the PK/PD tyramine challenge study (AN17933-101) collected extensive orthostatic VS data (supine and standing blood pressure and pulse) with respect to dosing (ZS 1.25, 2.5, 5.0 mg and Eldepryl 5 mg BID) over a 24 hour period after initial dosing (day 1) and after PK steady state for ZS (e.g. day 10). The sponsor had presented tabulations of these data showing descriptive data (mean, SD, median, min, max) of study treatment groups over time on each of the two 24 hour study periods. However, there were no data analyses showing changes from the immediate pre-dosing value for a particular VS parameter over the 24 hour period for a particular position. Neither were there data analyses showing changes from baseline or for the maximal orthostatic maneuver (i.e. supine to standing). These data provide a unique opportunity to explore for potential orthostatic VS changes with regard to ZS dosing, data that were not collected in the clinical trials. The only significant shortcomings in these data are the facts that the data were not collected under double-blind conditions and there was no placebo group for comparison.

I requested the sponsor to submit tables and figures showing these changes from the pre-dosing value on day 1 and 10 for all orthostatic VS parameters. The sponsor submitted these presentations but did not conduct any statistical analyses. When I reviewed these presentations, I raised the question whether ZS produced a moderate increase in systolic blood pressure and a minimal rise in diastolic blood pressure, especially at later timepoints ( $\geq 10$  hrs) compared to Eldepryl that did not appear to increase blood pressure. These possible effects of ZS did not seem to be dose-dependent, different at PK steady state, nor clearly positionally related. In addition, both ZS and Eldepryl appeared to increase pulse but all ZS doses appeared to be more potent than Eldepryl. I have asked the sponsor to conduct statistical analyses of these data using a

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mixed effects model but the sponsor has not yet convened its team to discuss the statistical analyses that I desire.

In summary, I believe that these additional analyses that I requested were important in showing that ZS appears to exert pharmacological actions on VS resulting in orthostatic hypotensive actions. Not surprisingly, results from the studies of Parkinson's disease patients show that ZS produces orthostatic hypotensive effects that are most obvious when changing from supine to standing position. The greater abnormalities occurring during treatment with ZS 2.5 mg daily suggest a dose-dependent effect. It remains to be determined whether the possible changes (increase of systolic and diastolic blood pressure and pulse) that I suspect ZS produced in the PK/PD study of relatively young adult male healthy subjects are real or not.

#### 14.10. Electrocardiographic Analyses (ECGs)

Electrocardiograms (ECGs) were collected at the beginning (before treatment) and at the end of the short term studies (i.e. the double-blind placebo-controlled studies - Z/SEL/97/025 and Z/SEL/97/026, and the randomized parallel group, controlled study - Z/SEL/95/008). A single ECG was collected at baseline (instead of multiple ECGs that could be averaged) and this design could have contributed to results that are more subject to error because the baseline ECG is not a representative one for the patient. ECGs were characterized by an external reader, who was blinded to study treatment, as normal or abnormal, and if abnormal, as either clinically significant (CS) or not clinically significant (NCS). ECGs in study Z/SEL/97/026 were also analyzed for QT/QTc by the blinded reader after being manually digitized. The QT interval of 3 consecutive beats was measured and averaged and correcting using the Bazett and Fridericia correction formulae (i.e. QTcB and QTcF). The reproducibility of the system was  $1.4 \pm 2.2$  msec. The sponsor presented shift tables and data listings of CS abnormal ECG results for these short term controlled studies.

The sponsor also said that additional ECG analyses would be submitted but these have not yet been received as of 1/13/02. These additional ECG analyses would consist of QT/QTc data for study Z/SEL/97/025 and analyses of other ECG intervals (e.g. P-R, QRS, etc.) for both double-blind, placebo-controlled studies. I had requested that the sponsor conduct and submit the latter analyses. In the pre-NDA meeting, DNDP had requested that the sponsor address the issue of QTc prolongation with conventional oral selegiline via a search of the literature. The sponsor provided references relative to cardiovascular AEs the original submission, but initially did not note that it had searched the literature for QTc prolongation with conventional selegiline. I requested the sponsor to address this issue. In a subsequent submission in response to my request the sponsor noted that it had searched the literature for QTc prolongation with selegiline and was unable to find any information on this topic.

The sponsor recently submitted analyses of studies Z/SEL/97/025 and Z/SEL/97/027 for QTc changes in the 120 day Safety Update. I have reviewed these analyses and have included them in this review.

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I created a table (Table 86) to show mean QTc at baseline, mean QTc changes from baseline and outliers for QTc change from baseline. ECGs collected at baseline and at the end (week 12) of the study were compared. In study Z/SEL/97/025 there was a mild mean increment from baseline in QTc with ZS using both correction formulae but no mean QTc increment in the placebo group (Table 86). The treatment difference (i.e. ZS QTc – Placebo QTc) was approximately 7 msec. The percentage of outliers was higher for ZS for both moderate and more severe outliers using both QTc correction formulae. In contrast, there was no suggestion of QTc prolongation by ZS in study Z/SEL/97/026 when the mean QTc change from baseline for ZS was compared to placebo (Table 86). The percentage of outliers was greater for ZS only for moderate outliers for the QTcB correction method. No patient in either study developed a new QTc > 500 msec on treatment. One patient (# A63) who exhibited a very high baseline (534 msec QTcB and 521 msec QTcF) did not exhibit any increase at the end of the study after treatment with ZS.

**Table 86 QTcB and QTcF at Baseline, Change from Baseline, and Outlier Analyses in Double-Blind, Placebo-Controlled Trials**

Study	Z/SEL/97/025	Z/SEL/97/025	Z/SEL/97/026	Z/SEL/97/026
Treatment	Placebo	ZS 2.5 mg	Placebo	ZS 2.5 mg
N	42	78	38	79
Mean baseline QTcB	405	410	396	406
Mean baseline QTcF	397	401	390	397
Mean QTcB change from baseline	- 3.19	+ 4.32	+ 7.24	+ 1.51
Mean QTcF change from baseline	- 4.64	+ 2.24	+ 4.61	- 0.65
QTcB 30 – 60 msec	4 (10 %)	8 (10 %)	1 (3 %)	4 (5 %)
QTcF > 60 msec	0 (0 %)	1 (1 %)	1 (3 %)	0 (0 %)
QTcB 30 – 60 msec	0 (0 %)	6 (8 %)	2 (5 %)	3 (4 %)
QTcF > 60 msec	0 (0 %)	1 (1 %)	1 (3 %)	0 (0 %)

There did not appear to be any abnormally increased shift in the incidence of normal ECGs to abnormal ECGs for ZS vs placebo treatment in both studies. However, there was no definition of what constituted an "abnormal ECG." All shifts from normal to abnormal were characterized as NCS except for one ZS case (patient 108-Y27) in which the abnormal ECG was characterized as CS. This patient, who had received 2.5 mg ZS, developed frequent premature ventricular beats (VPBs) and also exhibited ventricular bigeminy, left ventricular hypertrophy (LVH), ST depression, and abnormal T waves. The ventricular bigeminy (that was reported as an AE) lasted for 33 minutes, was moderate in severity, and was considered unrelated to study drug. At baseline this patient had an abnormal ECG that was considered NCS.

The extension study (Z/SEL/97/027) for the placebo-controlled studies was also analyzed similarly as were the placebo-controlled studies. The baseline ECG for patients treated with ZS prior to entry into the extension study was the ECG obtained prior to treatment with ZS at the

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beginning of the placebo-controlled study. The baseline ECG for patients treated with placebo in either placebo-controlled study was the ECG obtained at the end of that study and immediately prior to entry into the extension study. ZS prior to entry into the extension study was the ECG obtained prior to treatment with ZS at the beginning of the placebo-controlled study. Baseline QTc, QTc change from baseline at 1 year and at the end of the study and outlier analyses for QTc using the Bazett and Fridericia correction formulae are shown in Table 87 created by the sponsor. Patients treated with ZS prior to entry into the extension phase did not show a QTc increment above baseline for QTcB or QTcF at 1 year or at their last visit. In contrast, patients treated previously with placebo showed a mild increment above baseline for QTcB (4 msec) and QTcF (2 msec) at 1 year. At the termination visit, the mean increment above baseline for previous placebo patient was considerable for QTcB (15 msec) and for QTcF (8 msec). Outlier analyses showed higher frequencies of outliers for nearly every category for patients who had received placebo compared to patients who had received ZS. One patient (Z17) who was initially randomized to ZS showed a 50 msec increment above baseline at 1 year to a value of 501 msec (QTcB). This patient also exhibited a QTcF of 435 msec at baseline that increased to 467 msec for a 32 msec increment.

**Table 87 QTcB and QTcF (msecs) at Baseline, Change from Baseline, and Outlier Analyses in Extension Trial (Z/SEL/97/027) for Double-Blind, Placebo-Controlled Trials**

	Prior Therapy with Placebo	Prior Zydys Selegiline Use
N	65	138
Baseline QTcB	400	407
Baseline QTcF	390	398
Change from Baseline		
At 1 year QTcB	4	0
At 1 year QTcF	2	-2
At End of Study QTcB	15	0
At End of Study QTcF	8	-4
At 1 year QTcB 30-60 msec	11 (17%)	13 (9%)
At 1 year QTcF 30-60 msec	8 (12%)	10 (7%)
At End of Study QTcB 30-60 msec	6 (30%)	3 (7%)
At End of Study QTcF 30-60 msec	3 (15%)	2 (4%)
At 1 year QTcB > 60 msec	1 (2%)	0
At 1 year QTcF > 60 msec	2 (1%)	2 (1%)
At End of Study QTcB > 60 msec	0	0
At End of Study QTcF > 60 msec	0	0

These results are puzzling because each placebo-controlled study was identical in design but each suggested a different result for QTc change from baseline. Furthermore, there are no reports in the literature suggesting QTc prolongation with conventional selegiline (i.e. Eldepryl) treatment. Whereas the treatment difference for ZS was negative and approximately - 6 msec (QTcB) and - 5 msec (QTcF) in study Z/SEL/97/026, the treatment difference for ZS was positive and approximately + 7 msec (QTcB and QTcF) in study Z/SEL/97/025. Outlier percentages were fairly similar in both studies with the exception of being greater for ZS for moderate outliers for the QTcB correction method. A possible explanation for the results

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suggesting QTc prolongation in the controlled trial could be that ECGs were collected by chance more frequently at particular times after ZS dosing when QTc prolongation occurs.

In the extension study, QTc increment above baseline was small (2-4 msec) at 1 year and larger (8-15 msec) at the end of the study for patients initially treated with placebo. In contrast, patients always treated with ZS showed no increment (-2 - 0) at 1 year or at the end of the study (-4 - 0). It is not clear why the results seemed so different when the main apparent difference were placebo vs ZS in the initial trial and a baseline collected for the extension trial 12 weeks later for placebo treated patients. Of interest, the outlier percentages seemed significantly higher for previously treated placebo patients. Conceivably, the results raising QTc prolongation questions in the extension trial could have occurred because ECGs were collected at study termination by chance in patients at a higher risk for expressing QTc prolongation. It may also be somewhat reassuring that one patient who had a very high QTc at baseline (> 500 msec) did not experience a further QTc increment or a serious arrhythmia on treatment with ZS.

**These puzzling results cannot be dismissed as reassuring safety and raise the question of QTc prolongation with ZS.** The sponsor's submission provides speculative reasons why there should not be a significant concern for QTc prolongation from ZS. **However, the sponsor's summary does acknowledge "a very small effect on cardiac repolarization cannot be entirely excluded."** Greater QTc changes and the development of a QTc increment to a value > 500 msec were observed when the Bazett correction formula was used vs the Fridericia correction. The sponsor's submission notes that the Bazett correction is less accurate than the Fridericia method. However, I know this to be the case mainly when a drug increases heart rate. The sponsor's submission does not note any effect of ZS on heart rate and the analyses of supine heart rate did not show any statistically significant changes from baseline for ZS treatment vs placebo. The sponsor did not conduct analyses/plots (in placebo and/or baseline patients) of the different QTc corrections vs heart rate to validate the selection of the correction formula. The sponsor should conduct analyses/plots of QT (using the different correction formulae) vs heart rate in placebo and/or baseline patients to see that the slope of the plot is 0 and there is no correlation between QTc and heart rate.

**Considering all findings, I conclude that additional study must be conducted to exclude or at least characterize QTc prolongation with ZS because QTc prolongation has been suggested and has not been excluded.** This could best be done in a clinical pharmacology, pharmacodynamic study such as one that needs to be repeated for tyramine challenge. In addition, the sponsor can conduct animal and/or in vitro studies to investigate effects of ZS on cardiac repolarization. Because ECGs were collected randomly without regard to dosing of study drug, there are no data to assess whether there might be any QTc prolongation changes related to particular times after dosing of ZS. It would be desirable to study ECGs at multiple specific times after dosing to exclude a QTc prolongation effect of ZS, especially considering that Cmax with ZS is much higher than that which occurs with Eldepryl.

**14.11. Special Safety Studies (Oropharyngeal exams)**

In the original database the previous sponsor (Scherer) imposed some manual coding for adverse events it thought could be considered related to the potential for oral toxicity of the Zydis formulation. The current Sponsor (Elan) thought that this process was over-inclusive and potentially misleading, and a review of all AEs potentially related to oral or skin toxicity were reviewed for proper assignment of COSTART Preferred Terms. During an evaluation of the preliminary results, Elan became aware of the conventions applied to the Adverse Event Coding for oral events by the previous sponsor (Scherer) and thought that they were inappropriate. Apparently, Scherer's intent was to maximize the likelihood of detecting any oral events associated with Zydis selegiline or placebo administration. Elan concluded that little thought or clinical insight had been applied to this process, resulting in inappropriate coding of numerous terms to the Preferred Term Stomatitis or to another inappropriate term.

The current sponsor (Elan) thought that a review of all adverse events potentially involving the oral cavity should be reviewed by a qualified oncologist experienced in the evaluation of oral lesions, and that a consistent set of conventions ought to be applied for assigning preferred AE terms. Therefore, the procedure the sponsor employed for this re-review was systematized and recording was performed. After this review and "correction" process was completed, AE tables and listings were re-created. Once again, no collapsing of Preferred Terms was performed in the generation of the AE tables and listings. All grouping or collapsing of Preferred Terms was done in the ISS Text discussion and in-text tables. This review, "correction" process, and the changes imposed, were made without regard to treatment allocation by the oncologist who was blinded to treatment during this reclassification.

**Risks Associated with Contact Irritation**

Irritant contact stomatitis of the oral cavity is another potential risk associated with Zydis selegiline, arising from direct irritation from the grapefruit flavor, from aspartame, or other components of the dosage form. Distinguishing irritation from hypersensitivity is difficult in the oral cavity and the two may overlap. Irritation may also occur in the oral cavity due to mechanical trauma, e.g., from poorly fitting dentures, or from ingestion of food at elevated temperature. Stomatitis, irritation, and mouth ulceration are not infrequently occurring symptoms in the general population and may occur at increased rates in older individuals. The prevalence of irritant contact stomatitis was estimated range between 1% to 10% with significant underreporting assumed. The sponsor noted that concurrent conditions such as dry mouth and denture wear in older individuals is associated with stomatitis rates of approximately 13% and poorly fitting dentures can increase this frequency considerably. In addition, the sponsor noted that patients with Parkinson's disease have been shown to exhibit oral mucositis at higher rates than control groups, a factor that may also contribute to the incidence of stomatitis.

Oropharyngeal (OP) examinations were conducted in both Phase 3 studies in the clinical development program for ZS. These examinations were conducted by a qualified rater (typically

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a dentist or oral surgeon) blinded to the treatment assignments of the individual patients. Specific areas of the oral cavity were rated for the presence or absence of single or multiple areas of focal reddening, inflammation, or ulceration. Each patient was examined at baseline, after completion of 12 weeks of therapy, and at 6-12 month intervals during extension treatment. Patients exhibiting positive findings on the OP exam had these findings recorded on the examination page, and in addition these findings were captured as adverse events such as stomatitis, cheilitis, pharyngitis, mouth ulceration, tongue disorder, leukoplakia, and other related oral terms. No effort was made to assign relatedness to study drug or to patient factors such as dry mouth or use of dentures. Stomatitis in particular, defined as "single or multiple areas of focal reddening", was selected as a potential early indicator of mucosal irritation associated with Zydis selegiline. The incidence of stomatitis varied across studies, reported in the 12-week double-blind, placebo controlled trials at 5.2% for ZS and 4.1% for PLA. In the 12-week open-label randomized trial stomatitis was reported at 12.3% for ZS (1.25 mg), at 17.7% for ZS (10 mg), and at 8.5% in the Eldepryl group. In long-term extension studies encompassing up to 3 years of observation, stomatitis was reported at 7.8% in the ZS 1.25/2.5 mg group and at 12.5% in the ZS 10 mg group. Although the incidence of stomatitis varied across ZS studies, the rates observed seemed to approximate those reported in the published literature as expected for a population of this age, medication use, and general health. These data do not appear to indicate an increased risk of oral irritation from the Zydis dosage form of selegiline (i.e. ZS). None of these occurrences were judged to be of sufficient severity to warrant biopsy or further workup.

Summary tables show the type and frequency of the findings in which there was an increase in the severity in oropharyngeal exam findings from baseline to the end of treatment for the double-blind, placebo-controlled studies (Table 88), open-label, controlled study (Table 89), and extension studies (Table 90).

#### Overall Summary of Oropharyngeal Examination Results

- In general, the nature of the oropharyngeal examination abnormalities were similar across all treatment Groups: Zydis Placebo, ZS 1.25/2.5 mg, ZS 5/10 mg, conventional selegiline 10 mg (e.g. Eldepryl)
- Discrete areas of focal reddening were reported in the majority of cases, with approximately equal distribution on the right and left cheeks, lower lip, and pharynx. Oropharyngeal examination abnormalities involving the tongue were reported for only a minority of cases and varied between discrete areas of focal reddening, multiple foci of reddening, and ulceration.
- Although some oropharyngeal examination abnormalities were also reported as AE, none were considered to be SAEs.
- A significant number of oropharyngeal examination abnormalities occurred with inactive study drug (Zydis Placebo) and/or prior to administration of active study drug. For those oropharyngeal examination abnormalities which occurred after administration of active study

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drug, there did not appear to be a clear temporal relationship between study drug start date and oropharyngeal examination abnormality onset date.

- The oropharyngeal examination abnormalities resolved in the vast majority of cases. There was no evidence of permanent damage or long-term clinical sequelae.
- Elderly patients seemed more sensitive to some oropharyngeal TEAEs.
- Stomatitis was clearly a dose-dependent TEAE occurring in 17.7 % of patients treated with 10mg/d ZS but only in 2.1 % and 3.4 % of patients treated with 1.25 mg/d and 2.5 mg/d respectively.
- An assessment of study drug relationship was made by the investigators for the majority of oropharyngeal examination abnormalities. In virtually all instances, the study drug was considered by the investigator to be probably unrelated or unrelated to study drug.
- In all cases, patients who experienced moderate to severe oropharyngeal examination findings were also receiving anti-Parkinson's medications with known oral irritancy side effects, as described in Table 91 (sponsor's Table 3.9.-1 in the Application Summary, Vol.1).

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**Table 88 Oropharyngeal Exam Findings in Double-Blind Placebo Controlled Studies**

**Table 11-A: Patients with an Increase in Severity in Oropharyngeal Exam Findings from Baseline to the End of Treatment – Double-Blind Placebo Controlled Studies**

	None to Mild		None to Moderate		None to Severe	
	ZP	ZS	ZP	ZS	ZP	ZS
<b>Swallowing Pain</b>	3 (3.2%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
<b>Mouth Pain</b>	0 (0.0%)	8 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<b>Discrete Areas of Focal Reddening</b>	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Left Cheek	0 (0.0%)	9 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Right Cheek	1 (1.1%)	5 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Upper Lip	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lower Lip	0 (0.0%)	5 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tongue Surface/Underside	0 (0.0%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pharynx	0 (0.0%)	3 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<b>Multiple Foci of Reddening</b>	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Left Cheek	0 (0.0%)	2 (1.1%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Right Cheek	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Upper Lip	0 (0.0%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lower Lip	0 (0.0%)	2 (1.1%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Tongue Surface/Underside	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pharynx	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
<b>Oedema</b>	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Right Cheek	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Left Cheek	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tongue Surface/Underside	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pharynx	0 (0.0%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<b>Ulceration</b>	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Left Cheek	1 (1.1%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)
Right Cheek	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)
Upper Lip	0 (0.0%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lower Lip	0 (0.0%)	5 (2.8%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)
Tongue Surface/Underside	0 (0.0%)	4 (2.2%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Pharynx	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Protocols Z/SEL/97/025 and Z/SEL/97/026

Data Source: End-of-Text Table 6.1a

ZP = Zydys Placebo and ZS = Zydys selegiline

Note: Percentages are calculated based on the number of patients who had oropharyngeal examination results recorded both at Baseline and End of Treatment. Ninety-three patients in the placebo group and 179 patients in the Zydys selegiline group had results recorded at both Baseline and End of Treatment.

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**Table 89 Oropharyngeal Exam Findings in Randomized, Open-label Controlled Study**

**Table 11-B: Patients with an Increase in Severity in Oropharyngeal Exam Findings from Baseline to the End of Treatment – Randomized Parallel Study**

	None to Mild			None to Moderate		
	ZS 1.25	ZS 10	SEL 10	ZS 1.25	ZS 10	SEL 10
<b>Swallowing Pain</b>	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<b>Mouth Pain</b>	1 (1.6%)	3 (4.8%)	0 (0.0%)	2 (3.1%)	0 (0.0%)	0 (0.0%)
<b>Discrete Areas of Focal Reddening</b>						
Left Cheek	1 (1.6%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Right Cheek	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)
Lower Lip	0 (0.0%)	2 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tongue Surface/Underside	1 (1.6%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pharynx	2 (3.1%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<b>Multiple Foci of Reddening</b>						
Lower Lip	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tongue Surface/Underside	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)
Pharynx	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<b>Oedema</b>						
Tongue Surface/Underside	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<b>Ulceration</b>						
Lower Lip	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tongue Surface/Underside	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)

Protocol Z/SEL/95/008

Data Source: End-of-Text Table 6.1b

ZS 1.25 = Zydys Selegiline 1.25 mg, ZS 10 mg = Zydys Selegiline 10 mg, and SEL 10 = Selegiline 10 mg

Note: Percentages are calculated based on the number of patients who had oropharyngeal examination results recorded at both Baseline and End of Treatment. Sixty-four, 62, and 71 patients in the Zydys selegiline 1.25 mg, Zydys selegiline 10 mg, and Selegiline 10 mg groups, respectively, had oropharyngeal examination results recorded at both Baseline and End of Treatment.

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**Table 90 Oropharyngeal Exam Findings in Extension Studies**

Table 11-C: Patients Receiving Zydys Selegiline 1.25/2.5 mg with an Increase in Severity in Oropharyngeal Exam Findings from Baseline to the End of Treatment – Extension Studies

	None to Mild	None to Moderate	None to Severe
<b>Swallowing Pain</b>	3 (1.0%)	0 (0.0%)	0 (0.0%)
<b>Mouth Pain</b>	4 (1.3%)	0 (0.0%)	1 (0.3%)
<b>Discrete Areas of Focal Reddening</b>			
Left Cheek	2 (0.7%)	0 (0.0%)	0 (0.0%)
Right Cheek	3 (1.0%)	0 (0.0%)	0 (0.0%)
Lower Lip	3 (1.0%)	0 (0.0%)	0 (0.0%)
Tongue Surface/Underside	2 (0.7%)	1 (0.3%)	0 (0.0%)
Pharynx	2 (0.7%)	1 (0.3%)	0 (0.0%)
<b>Multiple Foci of Reddening</b>			
Left Cheek	1 (0.3%)	0 (0.0%)	0 (0.0%)
Right Cheek	1 (0.3%)	0 (0.0%)	0 (0.0%)
Upper Lip	1 (0.3%)	0 (0.0%)	0 (0.0%)
Lower Lip	1 (0.3%)	0 (0.0%)	0 (0.0%)
Tongue Surface/Underside	1 (0.3%)	2 (0.7%)	0 (0.0%)
Pharynx	1 (0.3%)	1 (0.3%)	0 (0.0%)
<b>Oedema</b>			
Left Cheek	0 (0.0%)	1 (0.3%)	0 (0.0%)
Lower Lip	2 (0.7%)	0 (0.0%)	0 (0.0%)
Tongue Surface/Underside	1 (0.3%)	0 (0.0%)	0 (0.0%)
Pharynx	2 (0.7%)	0 (0.0%)	0 (0.0%)
<b>Ulceration</b>			
Right Cheek	1 (0.3%)	0 (0.0%)	0 (0.0%)
Upper Lip	0 (0.0%)	0 (0.0%)	1 (0.3%)
Lower Lip	0 (0.0%)	1 (0.3%)	1 (0.3%)
Tongue Surface/Underside	1 (0.3%)	0 (0.0%)	0 (0.0%)

Protocols Z/SEL/95/008 Extension and Z/SEL/97/027

Data Source: End-of-Text Table 6.3

Note: The initial dose of Zydys selegiline in the Extension Studies was 1.25 mg for 53 patients and 2.5 mg for 254 patients.

Percentages are calculated based on the number of patients who had oropharyngeal examination results recorded at both Baseline and End of Treatment. In the Zydys selegiline 1.25/2.5 mg group, 302 patients had oropharyngeal examination results recorded at both Baseline and End of Treatment.

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Of potential relevance to this NDA for ZS, the sponsor presented a summary (Table 91) of known oropharyngeal side effects for FDA approved anti-parkinsonian medications based upon the description of each drug's label in the 2002 Physicians Desk Reference.

**Table 91 Anti-Parkinson's Medications with Known Oropharyngeal Side Effects**

Anti-Parkinson's Medication	Oropharyngeal Side Effects
<b>Lodosyn</b> (carbidopa)	Pharyngeal pain, burning sensation of tongue, taste alterations, dysphagia, bullous lesions (including pemphigus-like reaction)
<b>Sinemet</b> (carbidopa-levodopa)	Pharyngeal pain, burning sensation of tongue, taste alterations, dysphagia, bullous lesions (including pemphigus-like reaction)
<b>Symmetrel</b> (amantidine HCl)	Dysphagia
<b>Mirapex</b> (pramipexole dihydrochloride)	Dysphagia (2%), pharyngitis ( $\geq 1\%$ ), taste perversions ( $\geq 1\%$ )
<b>Permax</b> (pergolide mesylate)	Dysphagia (frequent), periodontal abscess (infrequent), gingivitis (infrequent), aphthous stomatitis (rare), pharyngitis (frequent), laryngitis (infrequent), taste perversion (infrequent)
<b>Requip</b> (ropinirole HCl)	Pharyngitis (6%), gingivitis ( $\geq 1\%$ ), dysphagia (infrequent), periodontitis (infrequent), glossitis (infrequent), stomatitis (infrequent), ulcerative stomatitis (infrequent), tongue edema (infrequent)
<b>Eldepryl</b> (selegiline HCl)	Burning lips/mouth, throat burning, taste disturbance, dysphagia

Source: Physician's Desk Reference (56<sup>th</sup> edition). Montvale, Medical Economics Company, 2002.

The sponsor also conducted a preclinical toxicology study to address the potential for oropharyngeal toxicity with ZS in response to DNDP concerns. A study of hamster buccal toxicity was evaluated after 28 days of daily ZS in both abraded and nonabraded cheek pouches. ZS was given to hamsters far in excess of exposure expected in patients. The highest concentration of selegiline achieved in the highest dose group of hamsters was approximately 10 fold higher than that expected with ZS 2.5 mg daily in humans. There was no local toxicity in hamsters supporting the oropharyngeal safety of ZS in humans.

#### 14.12. Abuse Potential

There is a theoretical concern about abuse potential for ZS considering that its major metabolites are amphetamine-like metabolites including L-amphetamine, L-methylamphetamine, and N-

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demethylselegiline. However, there are several observations that suggest that the risk for abuse potential is very low. The stereospecific isomers for amphetamine and methylamphetamine are the L-form. In various studies, the L-forms of these molecules are less potent for drug abusing effects than the D-forms. In addition, the proportions and circulating levels of these amphetamine-like metabolites are much lower ( $\sim \geq 75\%$  lower) after  $\leq 2.5$  mg daily ZS than those generated from conventional selegiline (e.g. Eldepryl 5 mg BID) which experiences a major first pass hepatic effect. Other studies have investigated the reinforcing properties of selegiline in animals and found negative results. Furthermore, the extensive clinical use of conventional selegiline (e.g. Eldepryl) and limited use of ZS in other countries as antiparkinsonian therapy has not shown any significant abuse and confirmed the low potential for physical dependence and amphetamine-related abuse predicted by animal studies.

ZS via its inhibition of MAO-B activity could theoretically augment the behavioral effects of an abuse drug such as cocaine. However, there are studies that show that selegiline does not facilitate the self administration of cocaine or amphetamine suggesting low abuse potential. Of interest, there is at least one publication that describes how selegiline has been investigated as a treatment for cocaine dependence.

Although questions have been raised as to whether selegiline has effects as a performance/cognition enhancer and anti-aging drug, there is little reliable scientific data to support these considerations.

Overall, considering the past experience with conventional selegiline (e.g. Eldepryl) and what is known about ZS to date, I see no reason to consider that there will be a significant abuse potential for ZS.

#### 14.13. Overdose

A significant concern with overdose is the theoretical potential for increased non-selectivity of MAO inhibition (i.e. increased MAO-A inhibition) and consequently increased risk of "cheese reaction" from tyramine containing products. There are relatively infrequent spontaneous reports of hypertensive reactions with the approved dose of Eldepryl (i.e. 10 mg daily) and other cases of severe hypertensive reactions have been reported with increased doses (e.g. 20 or 40 mg daily) of conventional selegiline. As presented and discussed in the pharmacodynamic section of this review, a range of ZS doses (i.e. 1.25 -10 mg daily) were associated with a several fold increase in tyramine sensitivity and the new development of tyramine pressor threshold doses that were low ( $\leq 50$  mg) in a considerable proportion of subjects. Thus, it would not be surprising to expect that subjects who overdose ( $> 2.5$  mg daily) with ZS would be at increased risk for a "cheese reaction" consisting of significant hypertension or even hypertensive crisis.

A second area concern with ZS overdose is the potential that certain patient subsets may be at increased risk for developing cardiovascular AEs when exposed to overdoses of ZS. In an open label trial Z/SEL/95/008E, patients exposed to high dose ZS (10 mg daily) experienced some

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cardiovascular AEs (e.g. postural hypotension, hypotension, and hypertension) more frequently than patients treated with low dose ZS (1.25 mg daily).

In addition, two patients who had been receiving ZS 10 mg daily died during the 12 week controlled treatment period (study Z/SEL/95/008) from cardiovascular complications (e.g. coronary artery thrombosis and myocardial infarction). This contrasts with no patients who died in the controlled trial periods while receiving 1.25 or 2.5 mg daily of ZS and 1 patient who died from a ruptured abdominal aortic aneurysm during a controlled trial period while receiving conventional selegiline (10 mg daily). This observation further raises the question about the risk of taking an "overdose" of ZS (i.e. 2.5 mg daily).

There are no reported cases of overdose of ZS in the sponsor's post-marketing experience in the relatively few countries where this formulation has been approved and marketed. In this NDA, there was one case of a ZS overdose in the single-dose cross-over study taste preference study (Z/SEL/94/026). One patient experienced an SAE due to an overdose and developed hypotension and a brief episode of syncope in a single-dose cross-over taste preference study (Z/SEL/94/026). This patient mistakenly received both 10 mg of conventional Eldepryl (i.e. 5 mg BID) and ZS 5 mg on the same day. Although this patient recovered uneventfully, this experience supports the concern for adverse cardiovascular events with overdose of ZS.

Finally, I pointed out (Clinical Laboratory Findings section) the apparent decrease in renal function (e.g. increase in serum BUN and creatinine) associated with high dose ZS treatment (i.e. 10 mg daily). Consequently, it would not be unreasonable to expect that acute or chronic overdosing with ZS might be associated with impairment of renal function.

#### **14.14. Human Reproductive Considerations**

No pregnancies were reported during the studies comprising the ISS and that would have included primarily a population of older patients and particularly geriatric patients. Information on the potential of conventional selegiline for teratogenicity in humans is sparse. In a series of 24 pregnant women (involving 33 pregnancies) with Parkinson's disease who took "combination therapy" there appeared to be only one case involving conventional selegiline along with at least levodopa treatment. Although no complications were reported in this single case, details about the extent of selegiline use during pregnancy were not provided.

The label for conventional selegiline treatment (i.e. Eldepryl) includes a Pregnancy Category C. The Eldepryl label is shown below in italics.

*No teratogenic effects were observed in a study of embryo-fetal development in Sprague-Dawley rats at oral doses of 4, 12, and 36 mg/kg or 4, 12 and 35 times the human therapeutic dose on a mg/m<sup>2</sup> basis. No teratogenic effects were observed in a study of embryo-fetal development in New Zealand White rabbits at oral doses of 5, 25, and 50 mg/kg or 10, 48, and 95 times the human therapeutic dose on a mg/m<sup>2</sup> basis; however, in this study, the number of litters produced at the two higher doses was less than recommended for assessing teratogenic potential. In the rat*

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*study, there was a decrease in fetal body weight at the highest dose tested. In the rabbit study, increases in total resorptions and % post-implantation loss, and a decrease in the number of live fetuses per dam occurred at the highest dose tested. In a peri- and postnatal development study in Sprague-Dawley rats (oral doses of 4, 16, and 64 mg/kg or 4, 15, and 62 times the human therapeutic dose on a mg/m<sup>2</sup> basis), an increase in the number of stillbirths and decreases in the number of pups per dam, pup survival, and pup body weight (at birth and throughout the lactation period) were observed at the two highest doses. At the highest dose tested, no pups born alive survived to Day 4 postpartum. Postnatal development at the highest dose tested in dams could not be evaluated because of the lack of surviving pups. The reproductive performance of the untreated off-spring was not assessed.*

*There are no adequate and well-controlled studies in pregnant women. Selegiline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.*

There is no useful information available on the risk of using ZS in human during pregnancy.

The sponsor also noted that an interaction (see Drug-Drug Interactions) between selegiline and female sex steroid hormones has been reported in which the metabolic conversion of selegiline to the N-desmethyl metabolite is decreased.

#### 14.15. Drug-Drug Interactions (DDIs)

**It is important to note that Elan did not conduct any drug interaction studies assessing the effects of ZS treatment on sympathomimetics, nasal decongestants (e.g. pseudoephedrine), hypertensive agents, ant-hypertensives, MAO inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) or alcohol.** Nevertheless, the sponsor addresses some of these potential drug combinations and resulting DDIs with ZS in various sections of the proposed label also describes some of these DDIs in the ISS. Although the ISS notes a generally cautious approach should be taken about using selegiline with many of these drugs, information nor advice about how to use these drugs with the potential for DDIs with ZS is frequently not clearly specified.

In the Contraindications section of the proposed labeling, the sponsor notes that meperidine is contraindicated with selegiline but it does not specify that meperidine is contraindicated with ZS. This labeling further notes that "..... Thus, it is not clearly specified that any drug is contraindicated with ZS.

b(4)

The proposed labeling Warnings section notes that severe CNS toxicity associated with hyperpyrexia and death has been reported with the use of tricyclic antidepressants and conventional selegiline. However, there is no clear instruction given about using tricyclic antidepressants with ZS. ~~.....~~

b(4)

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This is confusing because it seems to imply incorrectly that fluoxetine is a tricyclic antidepressant.

In the Precautions section of the proposed labeling, the sponsor notes that \_\_\_\_\_

b(4)

In the absence of studies assessing and characterizing risks of DDIs between ZS and various drugs with the potential for serious DDIs, it seems reasonable to follow as a minimum the guidelines provided in the label for Eldepryl when considering ZS use with drugs for which a serious DDI might be expected. The sponsor should conduct some studies to address these potential DDIs with ZS.

In the Drug Interactions section of the proposed label, the sponsor describes potential DDI between conventional selegiline and various other drugs (e.g. levodopa, \_\_\_\_\_ or drug classes (cytochrome P450 inhibitors, MAO inhibitors, tricyclic antidepressants, \_\_\_\_\_). However, it is not clearly specified how one should consider combined treatment with ZS and one of these drugs or drugs from the class mentioned. Because it is not known which cytochrome P450 enzymes are involved with metabolism of selegiline, it is not possible to know which drugs that alter cytochrome P450 enzymes might be associated with increased risk in conjunction with ZS treatment.

b(4)

The sponsor noted that an interaction between selegiline and female sex steroid hormones has been reported in which the metabolic conversion of selegiline to the N-desmethyl metabolite is decreased. The bioavailability of selegiline could increase from this drug-drug interaction. Although the sponsor did not specifically address whether this interaction might be expected with ZS, this reviewer thinks that it could be but it is not known if the interaction would be greater or lesser for ZS compared to conventional selegiline. Regardless, it is conceivable that the bioavailability of selegiline could increase during pregnancy, hormonal treatment for contraception or hormonal replacement therapy. Such patients should be monitored closely for changes suggesting increased dopaminergic stimulation and may need a reduction in levodopa or selegiline.

#### 14.16. Drug-Disease Interactions

The ISS notes ZS undergoes relatively little and much less hepatic metabolism than conventional selegiline (e.g. Eldepryl). Although the qualitative metabolic profile of ZS is similar to that of Eldepryl, the quantitative proportions of major selegiline metabolites (e.g. N-demethylselegiline, L-amphetamine, L-methylamphetamine) is much less with ZS. The ISS notes that the impact of hepatic impairment on the safety of ZS will be less than the impact on Eldepryl. However, this is

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a purely speculative statement without any empirical support. The sponsor did not conduct any studies assess the safety and PK in subjects with various degrees of hepatic impairment.

The ISS also notes that significant renal impairment could result in accumulation of the 3 major metabolites all of which are primarily excreted via the kidney. The fact that N-demethylselegiline is a weak MAO-B inhibitor and could increase with renal impairment might result in increased MAO-B inhibition. The pharmacological effects of L-amphetamine and L-methylamphetamine are less than their D-isomer. Nevertheless, the consequences of increased levels of increased circulation levels of L-amphetamine and L-methylamphetamine are unknown. This statement is based upon the facts that : 1) there are no data available about the specific levels that would result with various degrees of renal impairment; and 2) the actual concentrations necessary to produce unwanted amphetamine-like is not clear.

The proposed label (i.e. Precautions section- General) describes the fact that levodopa-associated

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b(4)

#### 14.17. Drug-Demographic Interactions

The sponsor did not conduct drug-demographic interactions for safety findings with the exception of TEAEs analyzing TEAEs according to age and gender. These analyses are presented in Analyses of other safety parameters would be ideal.

#### 14.18. Review of Medical Literature

I conducted a literature search of PUBMED for various general terms related to ZS (e.g. Zydis selegiline, zydis selegiline, buccal selegiline, transmucosal selegiline) but did not find any publications. I consulted a reference librarian at FDA for help with my search. The reference librarian also attempted to find any publications but did not find any.

The sponsor conducted an extensive review of the literature to explore safety issues for selegiline and summarized results of clinical trials in the literature. The sponsor noted that findings in the literature were consistent with the safety profile described for ZS in this NDA. The sponsor did not identify any full publications (i.e. not abstract) on ZS. In response to my direct question, a representative of the sponsor noted that the sponsor was not aware of any full publications in the literature concerning ZS.

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### 14.19. Post-Marketing Experience

The sponsor reviewed the post-marketing experiences that have been reported with ZS in countries where it has been approved and used. The sponsor noted that eight adverse events, including 3 SAEs (see Table 92) had been reported (between 11/98 and 8/01) in four patients treated with ZS. These experiences are consistent with the safety profile of ZS described and presented in this NDA and do not raise any significant new safety concerns.

**Table 92 Spontaneously Reported Adverse Events from Post-Marketing Experience**

**Table 8.9-2: Spontaneous Adverse Events Reported between November 1998 and August 2001**

MCN	Report source	Trade name	Country of occurrence	Reported term	COSTART term	Body system	Serious	Outcome	Dose text	Dose form	Dose route	Gender	Age
ZELA000010 (0)	Regulatory authority	Zelapar	United Kingdom	Short term memory loss	Amnesia	Nervous system	No	Recovered	1.25 mg daily	Tablets	Oral	Male	71 years
ZELA000025 (0)	Regulatory authority	Zelapar	United Kingdom	Agitation	Agitation	Nervous system	No		2.5 mg daily	Tablets	Sub-lingual	Female	72 years
ZELA000025 (0)	Regulatory authority	Zelapar	United Kingdom	Confusion	Confusion	Nervous system	No	Recovered	2.5 mg daily	Tablets	Sub-lingual	Female	72 years
ZELA000025 (0)	Regulatory authority	Zelapar	United Kingdom	Hallucinations	Hallucinations	Nervous system	No		2.5 mg daily	Tablets	Sub-lingual	Female	72 years
ZELA000042 (0)	Spontaneous	Zelapar	United Kingdom	Mouth ulcers	Mouth ulceration	Digestive system	No	Unknown	Unknown	Tablets	Oral	Female	
ZELA000070 (0)	Regulatory authority	Zelapar	United Kingdom	Joint swelling	Joint disorder	Musculo-skeletal system	Yes		1.25 mg daily	Tablets	Oral	Female	62 years
ZELA000070 (0)	Regulatory authority	Zelapar	United Kingdom	Insomnia	Insomnia	Nervous system	Yes		1.25 mg daily	Tablets	Oral	Female	62 years
ZELA000070 (0)	Regulatory authority	Zelapar	United Kingdom	Decreased mobility	Movement disorder	Nervous system	Yes	Recovered	1.25 mg daily	Tablets	Oral	Female	62 years

### 14.20. Melanoma with Antiparkinsonian Medical Therapies

The DNDP has initiated an investigation of a possible association of anti-Parkinson's disease medical therapies and malignant melanoma. Information (i.e. safety database search especially from trials) about such cases has been requested from sponsors of antiparkinsonian drugs. DNDP's collection of data and investigation is ongoing.

There was one patient who developed malignant melanoma during treatment with ZS. The patient was initially randomized to placebo and subsequently enrolled in an extension trial. Approximately 6 months after receiving ZS (while on 2.5 mg/d) the patient developed a lump in the neck and excisional biopsy revealed stage IV malignant melanoma two months later. There was no evidence for metastases immediately after the diagnosis nor at approximately 9 months later.

It is difficult to draw any conclusions about the development of melanoma in this patient and the treatment with ZS.

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#### 14.21. 120 Day Safety Update

The 120 Day (4 month) Safety Update was submitted very late (> 3 month delay, < 3 months before action date) and was not received until more than 7 months (near mid-November '02) after submission of this NDA. The organization of the Safety Update was similar to that in the original NDA. Information presented in the Safety Update consisted of : 1) new data collected from the ongoing extension study Z/SEL/97/027 (i.e. the only study that was ongoing) during the interval from the NDA data cut-off (6/30/01) and the data cut-off date for the Safety Update (12/31/01); 2) data from prior time periods that through procedural error, did not undergo data entry and integration into the original NDA databases; and 3) corrections to errors identified after the database was locked for the original NDA submission. Although not specified in the sponsor's description of the Safety Update organization, it appears that the sponsor also included some TEAE information (especially for new deaths) that occurred after the Safety Update database lock. New data were presented in in-text tables in boldface and were located immediately adjacent to original NDA data. Statistical methodology applied to the Safety Update was identical to that applied to the original NDA submission. Data included in the Safety Update were locked on 4/30/02. I will describe what I deem as noteworthy findings subsequent to my review.

##### 14.21.1. Deaths

There were four new deaths (Table 93) that occurred (between 1/16/02 and 5/16/02) after the Safety Update database cut-off (12/31/01). No deaths occurred during the interval of the data cut-off dates for the original NDA submission and the Safety Update. Narratives containing information available for these new deaths were presented.

According to the sponsor's and the investigator's assessments, none of these deaths were judged to be study related. Based upon information presented I agree with those opinions with the possible exception of patient C37. This patient appeared to have been taking ZS for over 3 year at the time of death. After arising, the patient complained of shortness of breath and dizziness and fell to the floor. The patient received cardiopulmonary resuscitation from a family member, was transferred to an emergency room where resuscitative efforts were unsuccessful. The narrative noted that the event was possibly related to the patient's cardiac history, that was not described. Although I have no specific information that would suggest that this death was related to ZS, I do not believe that the information presented allows one to exclude a contributory role from ZS.

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**Table 93 List of Post-Database Lock Deaths : Extension Study Z/SEL/97/027**

**Table 9-A.2b: List of Post-Database Lock Deaths: Extension Studies**

Protocol Patient ID (Dose)	Age (Sex)	Verbatim (Preferred)	Onset Date <sup>a</sup>	End Date	Intensity	Related
Z/SEL/97/027 Y34, site 018 (Z SEL 1.25/2.5 mg)	80 (M)	Hemorrhagic Stroke	1-8-02		Severe	No
Z/SEL/97/027 X25, site 103 (Z SEL 1.25/2.5 mg)	78 (M)	Heart Arrest	5-16-02		Severe	No
Z/SEL/97/027 X99, site 108 (Z SEL 1.25/2.5 mg)	78 (M)	Respiratory Arrest/End Stage Parkinson's Disease	5-14-02		Severe	No
Z/SEL/97/027 C37, site 011 (Z SEL 1.25/2.5 mg)	70 (M)	Dyspnea, Dizziness	4-5-02		Severe	No

b(6)

b(6)

b(6)

Protocol Z/SEL/97/027

Data Source: Elan Pharmaceuticals Safety Database

<sup>a</sup> The deaths listed above are not represented in the Safety Update listings because they occurred after database lock. Narratives are provided in Appendix 3, containing all available information at the time of submission of the Safety Update.

### 14.21.2. Serious Adverse Events (SAEs)

There were 9 new SAEs. None appeared to be that unusual and different from SAEs described in the original NDA submission. There was no substantive change in the incidence tables for SAEs.

### 14.21.3. Study Withdrawal Due to Adverse Events (AEs)

There were 6 new patients who withdrew from the study because of at least one AE and 8 AEs reported for these patients. These AEs did not appear to be that unusual and different from AEs prompting study withdrawal in the original NDA submission. There was no substantive change in the incidence tables for SAEs

### 14.21.4. Clinical Laboratory Findings

There were no new clinical laboratory findings that seemed remarkable one exception. Patient Y 76 (site 112) exhibited a transient substantially abnormal laboratory result consisting of a serum

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ALT (208; upper limit of normal = 40) that resolved at the next visit 3 months later. This patient was reviewed in section 14.8.3 Analyses of Laboratory Outliers).

#### 14.21.5. Other Presentations in Safety Update

There were no other remarkable findings in the rest of the Safety Update with the exception that the incidence of "abnormal" ECG (TEAE) in the extension studies increased from 3.3 % to 5.2 %. This change meant that "abnormal" ECG became a "common" TEAE by virtue of its occurrence in  $\geq 5$  % of patients.

#### 14.21.6. Conclusions of Safety Update

There did not appear to be any new findings in the Safety Update that altered my perspective of the safety profile of ZS derived from data contained in the original NDA submission.

### 14.22. Comments on Safety Findings

- The major organ systems involved with TEAEs after ZS treatment were the CNS, cardiovascular system, digestive system, and body as a whole. Overall, these findings are not dissimilar from descriptions within the label for Eldepryl and the literature. Within the body as a whole category, there were significant numbers of patients who exhibited accidental injury with ZS. Accidental injury was a more frequent TE-SAE with ZS (1.25 or 2.5 mg/d) than with placebo and TEAEs also occurred much more frequently with high dose ZS (10 mg/d) than low dose ZS (1.25 or 2.5 mg/d). However, it is not clear if this was because of somnolent effects and/or orthostatic hypotension related to ZS. It would be desirable for the sponsor to analyze the data to try to make this determination.
- The definition of SAE provided for investigators was a relatively conservative one that seemed predisposed toward assessing an AE as not related to study drug unless evidence was relatively strong for indicting the study treatment as a cause (see section 14.4.1 Definition and Approach to Serious Adverse Events). It is important to recall that an SAE that is unexpected must also be considered at least possibly related to study treatment before it meets the criterion of an SAE subject to expedited reporting to FDA. Thus, this approach may have contributed to under-reporting of AEs that should be considered SAEs.
- Dose-dependent effects of ZS on TEAEs were most evident when high dose ZS (i.e. 10 mg/d) was compared with "low dose" ZS (i.e. 1.25 or 2.5 mg/d). Whereas approximately 64 % and 60 % of patients treated with 1.25 or 2.5 mg daily respectively experienced at least one TEAE, almost all (e.g.  $\sim 92$  %) of patients treated with 10 mg daily of ZS experienced at least one TEAE. Among the most common (i.e. occurring in  $\geq 5$  % of patients) TEAEs, the incidence of accidental injury was much more frequent with 10 mg/d ZS (14.5 %) than with

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1.25 mg/d ZS (6.2 %) or 2.5 mg/d ZS (4.5 %). Stomatitis was clearly a dose-dependent TEAE occurring in 17.7 % of patients treated with 10mg/d ZS but only in 2.1 % and 3.4 % of patients treated with 1.25 mg/d and 2.5 mg/d respectively.

- There are some remarkable drug-demographic findings regarding TEAEs including oropharyngeal events (see Treatment Emergent Adverse Events (TEAEs) by Age and Treatment Emergent Adverse Events (TEAEs) by Gender). In the youngest age group ( $\leq 55$  years old), increased relative risks (i.e.  $\geq 2.0$ ) were observed for TEAEs for back pain, dyskinesia, rhinitis, metabolic and nutritional systems, and hemic and lymphatic systems. In the middle age group analyzed (i.e. 56 – 64 years old), increased relative risk was observed for TEAEs related to the skin and appendages system. The elderly subgroup (i.e.  $\geq 65$  years old) exhibited an increased relative risk for nausea, dizziness, and related to the skin and appendages system. In addition, elderly patients seemed more sensitive to some oropharyngeal TEAEs.
- No patients discontinued from study because of abnormal laboratory results. Review of clinical laboratory findings (e.g. clinical chemistry, hematology, urinalyses) did not suggest any abnormalities related to ZS with the exception of renal dysfunction. Patients treated with high dose ZS (i.e. 10 mg/d) showed a mild increment in serum BUN and creatinine compared to patients treated with “low dose” ZS (e.g. 1.25 or 2.5 mg daily) and an increased percentage patient shift from normal at baseline to increased on treatment in the open-label controlled study (Z/SEL/95/008). This is a new finding that has not been recognized with Eldepryl. Although the dose that the sponsor wants to market (i.e. 2.5 mg/d) does not seem to be nephrotoxic, it is likely that the vast majority of patients who received this dose did not have significant renal impairment. Considering that selegiline appears to be excreted mainly via the kidney, it seems possible that patients with various degrees of renal impairment would be at increased risk for developing higher than “normal” levels (e.g.  $C_{max}$  and AUC) of selegiline after ZS treatment. If this is true, these patients could have increased selegiline levels (approaching or higher than those that occur in patients treated with ZS 10 mg/d). Such a result could produce increase toxicity from ZS and/or further renal impairment.

I did not systematically analyze for TEAEs associated with renal dysfunction. However, in the Safety Update, one patient (X25), who developed an AE of aberrant sexual behavior/acute psychosis (new for this patient), also had a markedly increased serum BUN (62 mg/dl) and mildly increased serum creatinine (1.6 mg/dl). Previously, serum BUN was minimally elevated and serum creatinine was normal ZS was discontinued and this behavior was reported as not having changed 3 days later. On the next day, the patient died from “sudden cardiopulmonary arrest.” Although the narrative did not mention QTc results from an ECG near this event, this patient had a significant cardiac history including coronary artery disease, S/P coronary artery bypass graft (X 2), pacemaker implantation for heart block, and cardiomyopathy.

I think that it is important to study steady state PK of ZS in patients with various degrees of renal impairment to characterize the PK, assess the short-term safety risk/tolerability, and obtain important information relative to describing labeling for appropriate ZS dosing.

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- There was no serious suggestion of hepatic dysfunction based upon the data presented. Although there were some isolated cases of abnormal hepatic function (e.g. increased serum aminotransferases), there did not appear to be any clear cases of hepatitis. There was one SAE (patient 225/Kelly in study Z/SEL/95/008E) that was described by the sponsor as exhibiting hepatitis, but I disagree with the diagnosis of "hepatitis" in the absence of elevation of serum ALT or AST. There were no cases of hepatic failure and the cases with aminotransferase increments did not exhibit significant increments in serum bilirubin.
- There were no cases of medically serious hematological abnormalities such as aplastic anemia, severe neutropenia/granulocytopenia, or severe thrombocytopenia. There was one case of a patient who had a sideroblastic anemia and then developed chronic myelogenous leukemia but there is nothing to suggest that this was not related to chance. Overall, the h
- My review of additional analyses I requested from the sponsor suggested that ZS results in orthostatic hypotensive effects at doses of 1.25 and 2.5 mg daily. This was not surprising considering the experience with Eldepryl and that orthostatic hypotension is a relatively common finding in Parkinson's disease patients treated with medical therapies that enhance dopaminergic tone. Although the sponsor's analysis did not suggest an increased incidence of orthostatic hypotension, I do not believe that the sponsor conducted a critical analysis looking for this finding. Considering the number of patients with the TEAE of chest pain, it is interesting to speculate how many (if any) may have been precipitated by orthostatic hypotension. Furthermore, there are no data in Parkinson's disease patients in which the effects of ZS was studied for orthostatic effects at various times after dosing. Such data should be collected to characterize cardiovascular effects better.

It is of additional interest that the orthostatic VS data collected in the last PK/PD tyramine challenge study (AN17933-101) suggested (by my analysis of figures showing mean BP and pulse data) cardiovascular effects of mild increase of systolic blood pressure, minimal increase of diastolic blood pressure and moderate increments of pulse relative to the control group of Eldepryl subjects. These data have not yet been analyzed statistically. It should also be noted that these studies were conducted in relatively young healthy males and these data were not analyzed for orthostatic hypotensive effects in individual subjects by applying the same criteria as used for Parkinson's disease patients. Conceivably cardiovascular effects of ZS could be somewhat different depending on age, gender, and disease state (e.g. Parkinson's disease).

- The most significant finding related to ECGs is the question of QTc prolongation. Altogether the data do not indicate a clear signal for QTc prolongation. However, the results (mean QTc change from baseline and QTc outliers) of study Z/SEL/97/025 and those of one population in the extension study Z/SEL/97/027 study raise the question of QTc prolongation. A significant shortcoming in the ECG data collected was that effects of ZS were not studied with respect to dosing (i.e. at various times after dosing). A significantly different PK profile (e.g. much higher C<sub>max</sub>) for ZS compared to that with Eldepryl is consistent with the possibility that ZS could result in this cardiac effect that has not been observed with Eldepryl.

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In addition, a death (patient C37) in the Safety Update could potentially be related to an arrhythmia such as Torsades de pointes from QTc prolongation. Now that the possibility of QTc prolongation has been raised, the potentially most serious effect clearly should be excluded or characterized, if the findings are real. Studying ECGs at various times (over 24 hours) after dosing of subjects treated with various doses of ZS in a double-blind, placebo-controlled trial would seem to be the best approach to clarify this safety concern.

- There did not appear to be any cases of sudden "sleep attacks." Although sudden "sleep attacks" were first described with two non-ergot dopaminergic agonist (i.e. pramipexole and ropinirole), it is likely that they occur in varying frequencies with all drugs that enhance dopaminergic tone in Parkinson's disease patients. Most likely the phenomenon of sudden "sleep attacks" is a class effect of antiparkinsonian medical therapies.
- Although there were cases of rash and AEs related to the skin and appendages, there were no cases of medically serious skin reaction such as such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or erythema multiforme.
- There is some question if patients initiate a dose of 2.5 mg/d of ZS that there may be increased toxicity rather than titrating to 2.5 mg/d by starting at 1.25 mg/d for some period before taking the 2.5 mg/d dose. In the controlled trials, patients did not initiate dosing with ZS 2.5 mg/d. Consequently, there is no relevant experience in Parkinson's disease patients about the safety of starting with the 2.5 mg/d dose. In the sponsor's proposed labeling,

Although the sponsor notes ~~\_\_\_\_\_~~ I cannot concur with that view because the 1.25 mg/d dose was not studied at/near the end of 3 months. Thus, based upon the data collected and submitted, I cannot conclude that the 1.25 mg/d of ZS is an effective dose after long term treatment (e.g. ~ 3 months) However, considering the safety profile in healthy subjects in the last PK/PD study, it appears that healthy subject tolerated a starting dose of 2.5 mg/d of ZS (dosed for approximately 2 weeks) reasonably well.

b(4)

#### 14.23. Summary of Safety Data Review and Safety Conclusions

The safety database for ZS consisted of 578 unique patients. Whereas 283 patients had received ZS for  $\geq 6$  months, 227 patients had received ZS for  $\geq 12$  months. ZS was tolerated relatively well. Most side effects/ adverse events (AEs) observed during treatment with ZS were mainly those that are an exacerbation of side effects produced by LD (e.g. nausea, vomiting, orthostatic hypotension, lightheadedness, syncope, hallucinations, dyskinesia, headache). Furthermore, TEAEs observed with ZS treatment were generally similar to those that would be expected with Eldepryl treatment.

There were 8 deaths (7 ZS and 1 conventional selegiline/Eldepryl) in the original NDA submission reflecting deaths up to the data cut-off date. Four additional deaths that occurred after

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the cut-off date for the Safety Update were noted in the Safety Update. None of the deaths were thought to be related to ZS and these deaths were not necessarily unexpected in this patient population. There were 4 cases with a cardiovascular cause of death (i.e. coronary artery thrombosis, myocardial infarction, ruptured abdominal aortic aneurysm, cardiorespiratory arrest) One patient with sideroblastic anemia and chronic myelocytic leukemia died (specific details surrounding death were unknown) several days after surgical evacuation of bilateral subdural hematomas. Causes of death in the other 3 cases were lung cancer, complications from sigmoid volvulus, and natural. Of interest, 3 patients with cardiovascular causes of death and the patient with the subdural hematomas had been on high dose ZS (10 mg/d).

There were a few instances (accidental injury, chest pain, digestive disorder) in which serious adverse events (SAEs) were more frequent (i.e.  $\geq 1\%$ ) with ZS (1.25 mg or 2.5 mg daily) than the incidence in the placebo group. However, the incidence of these SAEs with ZS was very low (e.g. 1%) compared to placebo group (0%). AEs were the most common reason for discontinuation from study in the ZS group and occurred in 5.2 % of patients in the placebo-controlled trials vs 1.0 % in the placebo group. In the placebo-controlled trials, the most common ( $\geq 3\%$  incidence and  $\geq 1\%$  higher frequency than placebo) AEs with ZS treatment (either 1.25 or 2.5 mg daily) were dizziness, nausea, accidental injury, pain, insomnia, back pain, stomatitis, dyspepsia, dry mouth, pharyngitis, rash, asthenia, constipation, hallucinations, skin disorder, somnolence and tremor. In the open-label, randomized trial, the most common ( $> 6\%$  incidence and  $\geq 1\%$  higher frequency than comparator groups ZS 1.25 mg QD or Eldepryl 5 mg BID) AEs with high dose ZS treatment (10 mg/d) were stomatitis, tongue disorder, constipation, accidental injury, pain, dizziness, tremor, increased cough, syncope, and skin ulcer. In general the incidence of TEAEs were similar for 1.25 mg/d and 2.5 mg/d of ZS. However, the increased incidence of some TEAEs in patients treated with 10 mg/d ZS (e.g. high dose) suggested a dose-dependent effect of ZS.

There were various analyses of VS and no remarkable findings for temperature or ventilatory rate. Although orthostatic hypotension occurred in patients in various treatment groups, the analyses provided by the sponsor did not suggest a greater frequency of orthostatic hypotension during treatment with ZS in the placebo-controlled trials. However, review of additional analyses requested from the sponsor showed that ZS appears to exert pharmacological actions on VS resulting in orthostatic hypotensive actions. These orthostatic hypotensive effects from ZS were most obvious when changing from supine to standing position but were not characterized with respect to times after ZS dosing. The greater abnormalities occurring during treatment with ZS 2.5 mg daily suggest a dose-dependent effect.

Increments in systolic blood pressure occurred more frequently with ZS treatment vs placebo in short-term, controlled studies and appeared to be dose-dependent with this treatment difference occurring mainly with high dose ZS (10 mg/d). Of potential interest, changes in orthostatic blood pressure and pulse were evaluated at various times over 24 hours after dosing in one PK/PD study comparing several doses of ZS (1.25, 2.5, 5 mg daily) to Eldepryl. Although ZS appeared to produce increments in systolic and diastolic blood pressure and pulse compared to Eldepryl, the sponsor did not statistically analyze these changes. It remains to be determined whether the

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possible changes (increase of systolic and diastolic blood pressure and pulse) that I suspect ZS produced in the PK/PD study of relatively young adult male healthy subjects are real or not.

Review of clinical laboratory analytes (clinical chemistry, hematology, urinalyses) during treatment with ZS did not reveal any remarkable findings with the exception of mild to moderate increments in serum BUN and creatinine above baseline in patients treated with high dose ZS (10 mg/d). Whereas there was no mean increment above baseline in serum BUN with ZS 1.25 mg/d or Eldepryl (5 mg BID) at 12 weeks, the mean increment high dose ZS (10 mg/d) was 11.2 % at 12 weeks. Although there was no mean increment in serum creatinine at 12 weeks with Eldepryl, there was a minimal mean increment (1.8 %) with low dose ZS (1.25 mg/d) and a greater mean increment (6.9 %) with high dose ZS (10 mg/d). In extension trials there appeared to be a mild mean increments in serum BUN and creatinine above baseline, but these increments plateaued and were not progressive. Shift tables showing changes from normal at baseline to increments above the upper limit of normal for serum BUN and creatinine after treatment also showed increased shifts to abnormal values for patients treated with high dose ZS (10 mg/d). There were no instances of markedly abnormal values ( $\geq 3 \times \text{ULN}$ ) for serum BUN or creatinine and no cases of renal AEs with a serious outcome. Considering that excretion of ZS is believed to occur mainly via the kidney and that high dose ZS appears to impair renal function, it would be important to characterize the PK and tolerability of subjects with various degrees of renal impairment. Conceivably, patients with renal impairment could generate high PK levels after 2.5 mg ZS that could mimic levels obtained high dose ZS (10 mg) and these high levels could further impair renal function. This information is important for dosing.

**ECG analyses revealed conflicting results about QTc prolongation. However, they cannot be dismissed as reassuring the safety of ZS and raise the question of QTc prolongation with ZS.** Study Z/SEL/97/025 showed a treatment difference (ZS – placebo) of  $\sim 7$  msec QTc increment above baseline and one patients showed a QTc 50 msec increment above baseline to a value of 501 msec. In contrast, study Z/SEL/97/026 showed a treatment difference of  $\sim -5$  msec QTc increment above baseline and no outlier above 500 msec. In addition, an extension trial showed considerable outliers for QTc increments above baseline. The sponsor's submission provides speculative reasons why there should not be a significant concern for QTc prolongation from ZS. **However, the sponsor's summary does acknowledge "a very small effect on cardiac repolarization cannot be entirely excluded."** Greater QTc changes and the development of a QTc increment to a value  $> 500$  msec were observed with the Bazett correction vs the Fridericia correction. Nevertheless, I am left with the inescapable conclusion that additional study must be conducted to exclude or at least characterize QTc prolongation with ZS.

Special oropharyngeal examinations were conducted investigating for possible effects on ZS on this area. There were no significant findings that were remarkable to treatment with the proposed dose of ZS compared to other control groups.

There were no instances of hypertensive "cheese" reactions following intake of tyramine containing products. Neither were there any severe drug-drug interaction syndromes from the combined use of ZS and tricyclic antidepressants, selective serotonin reuptake inhibitors, or meperidine, drugs that were prohibited.

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There did not appear to be any new findings in the Safety Update that altered my perspective of the safety profile of ZS derived from data contained in the original NDA submission.

### Conclusions :

Although the safety review to date does not find reasons that preclude an approval for ZS, there are several safety issues that require clarification prior to approval. It is not clear if the safety issues (e.g. possible MAO-A inhibition, renal toxicity, QTc prolongation) that arose during the review of this NDA are completely specific to PK/PD relationships of ZS or if they also apply to Eldepryl (but had not been identified previously). Additional study should be conducted to characterize MAO-A inhibition, QTc prolongation, and PK and tolerability in subjects with various degrees of renal impairment. Finally, AEs/SAEs should be reviewed by the sponsor to collapse preferred terms systematically and group similar AEs/SAEs, especially those possibly reflecting orthostatic hypotension.

## 15. LABELING ISSUES

I have reviewed the sponsor's proposed label, have found several concerns, and have summarized these concerns.

- Many statements made regarding Pharmacokinetics in the Clinical Pharmacology section either appear to be inaccurate or speculative and not based upon "hard" data.

- It is not clear that patient variability is the reason why PK for selegiline does not appear to be dose proportional at PK steady state.

- [REDACTED] b(4)

- [REDACTED] b(4)

- The description of the food effect interaction on PK is inaccurate [REDACTED] b(4)  
[REDACTED] Results show that food does not alter the rate of absorption but rather decreases the extent of absorption. It is puzzling why there should be any food effect on the PK results if most ZS is absorbed in the mouth. Although it may be that in the specific food interaction PK study conducted that a greater than usual amount of ZS was swallowed (and possibly increased AUC of metabolites supports this hypothesis). It is still difficult to understand what occurred in the sponsor's food interaction PK study because food decreased the AUC of Eldepryl which is the

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conventional formulation of selegiline that is swallowed. This food effect on Eldepryl PK appears to contrast with results in the literature and label that suggest that food increases selegiline exposure. In the Eldepryl label it is noted that food can increase bioavailability 3 to 4 fold. It should also be noted that the results of the food interaction study of PK was obtained with 5 mg of ZS, not the 2.5 mg dose that the sponsor would like to market.

- Sufficient data are not available to state that there is no effect of age on PK. More, specifically, the sponsor did not conduct any studies to assess PK in elderly subjects (i.e.  $\geq 65$  years).
- b(4)
- b(4)

Because the 1.25 mg daily dose was not evaluated as a parallel dose group at 12 weeks, it is not possible to comment on its effectiveness toward the end of the double-blinded, placebo-controlled phase.
- There is also a concern in the Clinical Studies section about showing the figure that the sponsor has inserted in the label. b(4)

I do not believe that the sponsor made appropriate corrections in the statistical analyses with regard to multiplicity and multiple comparisons. This is potentially misleading to the prescriber and could give the impression that ZS 1.25 mg daily is also an effective dose when in fact the sponsor did not study this dose over the study period (e.g. 3 months) desired before allowing an efficacy claim.
- There is no basis for specifying in the Dosing section b(4)

am not aware of any data that support this recommendation.
- The proposed label does not contraindicate many drugs that could have serious DDIs (see Drug-Drug Interactions section) but often provides general precautions that do not seem very helpful for a prescribing physician.
- Specific efficacy results from the sponsor's primary efficacy analyses are provided in the Clinical Studies section. The new results of the analyses of the ITT LOCF datasets that DNDP required for the primary efficacy analyses should be provided.
- It is not clear whether the concomitant use of meperidine is contraindicated with the use of ZS as it is with Eldepryl.

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- It is not always clear when the label refers specifically to ZS if the information or recommendation is based upon results obtained from studying ZS or is extrapolated from results obtained during the study of conventional selegiline (i.e. Eldepryl).
- The sections dealing with DDIs, Warnings, Contraindications, and Precautions are often not clear to be useful for the prescribing physician (see Drug-Drug Interactions section).
- It may be useful to describe some specific information regarding the minimal experience obtained regarding "overdose" of ZS.

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this page is the manifestation of the electronic signature.**

/s/  
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Leonard Kapcala  
1/15/03 03:56:45 PM  
MEDICAL OFFICER

John, Here is my review of ZS for NDA  
21479. I look forward to your thoughts. Thanx.  
Len

John Feeney  
1/23/03 11:40:55 AM  
MEDICAL OFFICER

Dr.Kapcala has recommended an Approvable Action requesting further delineat  
of the safety profile of this drug. I  
agree; see my memo

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