

## CLINICAL REVIEW

### Clinical Review Section

to calculate the primary efficacy endpoint (i.e. the change from baseline in percentage "OFF" during waking hours). The protocol did not specify how many 24 hour diaries were to be completed at baseline and post-treatment. However, it was subsequently clarified by the sponsor that when data to be averaged were missing, available data would be averaged. If the only data available were from a single time or period, then that data would be used to represent the average of the data that should have been collected.

Secondary assessments of efficacy would be based upon the actual reduction in "OFF" hours, the motor and ADL subscales of the UPDRS (i.e. motor sub-scale for "OFF" and "ON", and ADL sub-scale for "OFF" and "ON"), the physician-rated Clinical Global Impression Improvement (i.e. CGI-I) Scale and the patient-rated Global Impression Improvement (i.e. PGI-I) Scale.

UPDRS motor subscale scores for "OFF" were to be collected by the patient withholding treatment with LD and study medication until being assessed at the beginning of the Visit. UPDRS motor subscale scores for "ON" were to be collected after dosing with LD and study medication. However, the time for collecting efficacy data after dosing was not specified, thus data would not be consistently collected at the same time after dosing. UPDRS subscales for historic ADL during "OFF" and "ON" would be collected at the end of the Visit.

#### Planned Statistical Analyses

The primary population to be analyzed for the primary efficacy analysis was the ITT population after a protocol amendment. The ITT population was defined as all patients who were randomly assigned to study medication and for whom baseline and on-treatment percentage "OFF" time measurements were available for at least 1 day. Initially, the LOCF ITT population was to be included in primary efficacy analysis according to the original protocol. Although the sponsor did not clearly identify which specific dataset of the ITT population would be analyzed for the primary analysis of the primary efficacy endpoint in the Statistical Analysis Plan (SAP), my interpretation of the SAP and all other documents suggested that the LOCF dataset of the ITT population should comprise the primary analysis of the primary efficacy endpoint.

According to the final study report, efficacy analyses were performed on the observed case (OC) data at each timepoint for all efficacy parameters. Although the protocol did not specify that the OC ITT would be part of the primary efficacy analysis, the protocol did note that one of the datasets to be analyzed would be the "visit-wise" dataset in which valid observations at each visit would be analyzed. Subsequently the sponsor clarified that the OC ITT is the same as the "visit-wise" ITT dataset. The OC ITT population included 140 patients (94-ZS and 46-placebo). Two patients assigned to placebo were excluded from the ITT analysis. One patient (Z37) did not have on-treatment efficacy data and one patient (Y51) was determined to have unreliable baseline efficacy data.

In addition, two different supportive analyses of two different populations of data were performed. One supportive analysis was performed on the last observation carried forward (LOCF) data set for efficacy parameters of the ITT population. The LOCF ITT population is the

## CLINICAL REVIEW

### Clinical Review Section

ITT population for which missing data were replaced with existing preceding on-study medication data. However, the protocol specified that LOCF dataset would be composed of patients who withdrew prematurely from the study and their last valid observation would be carried forward to missed visits. The protocol did not appear to specify how missing data would be handled and analyzed for patients who did not withdraw from the study. In such instances, the patient could have missed a study visit or data collected could have been lost. It was subsequently clarified by the sponsor that according to the Statistical Analysis Plan (SAP) that when data to be averaged were missing, available data would be averaged. If the only data available were from a single time or period, then that data would be used to represent the average of the data that should have been collected.

A second supportive analysis was conducted for the Per Protocol (PP) population by analyzing only observed data at each timepoint for the efficacy parameters. According to the protocol, the PP population was comprised of patients who did not violate study entry criteria, who were at least 80 % compliant with study medication, and who completed at least 6 weeks treatment. The PP population included a total of 131 patients (87-ZS and 44-placebo) at week 6 and a total of 122 patients (80-ZS and 42-placebo). The PP population was determined prior to breaking the blind. Prior to breaking the blind, the Clinical Project and Statistical managers reviewed a preliminary list of patient status with regard to PP population and decided to accept or reject potential patient exclusions based upon clinical judgement. The primary reasons for exclusion from the PP analysis was withdrawal (6 total patients) prior to week 6 and failure (6 total patients) to titrate to ZS 2.5 mg/d at week 6.

Secondary efficacy endpoints were to be analyzed similarly as the primary efficacy endpoint.

The study report did not present results of analysis of the "completer" dataset that was supposed to be analyzed according to the protocol and SAP. The "completer" dataset was equivalent to the "visit-wise"/observed case dataset for all patients who completed the study.

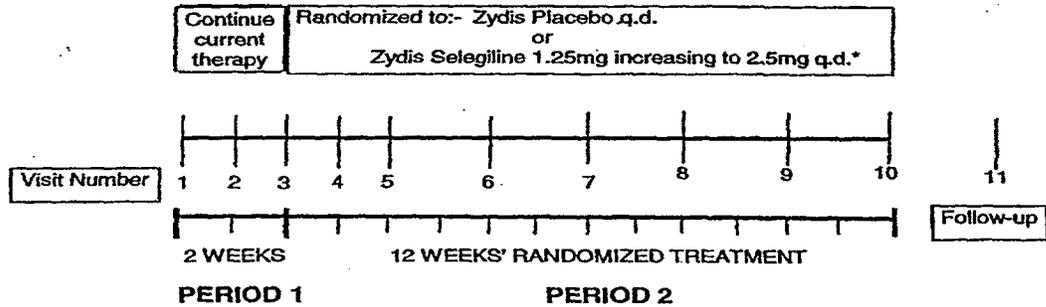
Analysis of safety and tolerability of treatment would be based upon vital signs, routine laboratory test results, adverse events and oropharyngeal examinations.

Appears This Way  
On Original

# CLINICAL REVIEW

## Clinical Review Section

**Figure 8 Schematic Diagram of Study**



\*During Period 2, patients will initially be randomized to receive either Zydys Selegiline 1.25mg q.d. or Zydys Placebo q.d (i.e. 1 tablet q.d.). After 6 weeks of study treatment, a patient's daily dose of Zydys Selegiline will be increased to 2.5mg q.d. (or Zydys Placebo equivalent; i.e. 2 tablets q.d.). This treatment regimen will then be maintained for the remainder of the study.

Appears This Way  
On Original

# CLINICAL REVIEW

## Clinical Review Section

**Table 29 Schedule of Assessments / Events**

**ATTACHMENT II - STUDY ASSESSMENTS TABLE**

ASSESSMENT	Visit 1 Day -14	Visit 2 Day -7	Visit 3 Day 0	Visit 4 Day 7	Visit 5 Day 14	Visit 6 Day 28	Visit 7 Day 42	Visit 8 Day 56	Visit 9 Day 70	Visit 10 Day 84	Visit 11 Day 98 Follow up*
Informed consent taken	X										
Check entry criteria	X										
Patient demographics	X										
Vital signs	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X		X							X	
Medical History	X										
Physical examination	X									X	
Mini Mental State examination	X										
Swallowing Assessment	X										
Clinical Global Impression Scale	X	X	X	X	X	X	X	X	X	X	
Patient's Global Impression Scale				X	X	X	X	X	X	X	
Motor and ADL UPDRS		X	X				X			X	
Oropharyngeal exam.			X							X	
Patient diary card issued	X	X	X	X	X	X	X	X	X		
Diary card review		X	X	X	X	X	X	X	X	X	
Modify levodopa dosage according to signs & symptoms				X	X	X	X	X	X		
Check concomitant medications	X	X	X	X	X	X	X	X	X	X	
Blood samples for population pharmacokinetics						X				X	
Hematology/biochemistry and urinalysis	X		X			X				X	
Medication dispensed			X	X	X	X	X <sup>‡</sup>	X	X	X <sup>‡‡</sup>	
Medication compliance check				X	X	X	X	X	X	X	
Adverse Event check		X	X	X	X	X	X	X	X	X	X

\*only to be performed for those patients who **do not enter** extension study Z/SEL/97/027

<sup>‡</sup> During Period 2, patients will initially be randomized to receive either Zydys Selegiline 1.25mg q.d. or Zydys Placebo q.d. (i.e. 1 tablet q.d.). After 6 weeks of study treatment, a patient's daily dose of Zydys Selegiline will be increased to 2.5mg q.d. (or Zydys Placebo equivalent; i.e. 2 tablets q.d.). This treatment regimen will then be maintained for the remainder of the study.

<sup>‡‡</sup>only to those patients **who are entering** extension study Z/SEL/97/027

Amendment No. 5 -- 05 March 1999

### Protocol Amendments

There were five protocol amendments during the study, an amendment to the statistical analysis

## CLINICAL REVIEW

### Clinical Review Section

plan, and a post-hoc analysis of statistical robustness of efficacy.

- Protocol Amendment 1 ( 12/9/97)

Significant revisions for this amendment related to the inclusion and exclusion criteria.

- An inclusion criterion was changed to require treatment with immediate release LD  $\pm$  DDCI for 6 weeks instead of 3 months prior to Visit 1.
- The requirement for females of childbearing potential to use birth control was changed from an exclusion criterion to an inclusion criterion.

- Protocol Amendment 2 ( 2/4/98)

Significant revisions for this amendment related a change in dosing and the statistical analyses.

- The protocol was revised so that the daily ZS dose for **all** patients would increase to 2.5 mg/d at 6 weeks after treatment. Previously, the investigator had the option to increase ZS from 1.25 mg/d to 2.5 mg/d if the patient did not exhibit a  $\geq 20\%$  reduction of average daily "OFF" time at 6 weeks post-treatment.
- The sample size estimate (based upon unequal randomization with one-third of patients receiving placebo and two-thirds of patients receiving ZS) was revised to detect a difference of 11% (SD = 18.5) between treatment groups (equivalent to a treatment groups difference of approximately 1.75 hrs "OFF") with 90 % power using a two-sided test at the 5 % significance level. Previously the estimate assumed a 20 % difference (SD = 1.25 hrs "OFF") between treatment groups resulting in 80 % power for a 5 % statistical significance.
- Statistical analysis was amended to change the primary population for analysis as the intention-to-treat (ITT) population. Previously, the protocol was to conduct the primary analysis of the ITT last observation carried forward (LOCF) population.
- The primary efficacy variable was changed to calculate the percentage reduction in total daily "OFF" time **during waking hours** (derived from patient/caregiver diaries) instead of total diary time including sleep.

- Protocol Amendment 3 ( 4/1/98)

Significant revisions for this amendment related to the inclusion/exclusion criteria.

- Patients using controlled release formulations of LD  $\pm$  immediate release LD could enroll in the study. Previously, patients using controlled release formulations of LD were excluded.
- Patients using a dopamine agonist at study entry could enroll. Previously, patients using any dopamine agonist were excluded.

- Protocol Amendment 4 ( 11/27/98)

Significant revisions for this amendment related to the transfer of responsibility for medical monitoring and regulatory reporting of serious adverse event information from Scherer DDS to a contract research organization

- Protocol Amendment 5 ( 3/5/99)

Significant revisions for this amendment related transferring overall responsibility and ownership

b(4)

## CLINICAL REVIEW

### Clinical Review Section

of the study between commercial sponsors, incorporating some protocol language according to the new sponsor's templates, extending study enrollment, and allowing for the option of additional study sites.

- Scherer DDS transferred overall responsibility (including medical monitoring and regulatory reporting of serious adverse event information) and ownership of the study to Elan Pharma International.
- Some protocol language was changed to conform to templates of the new sponsor (Elan).
- Study enrollment would continue until 135 patients (available at ZS 2.5 mg/d) was ensured.
- The new sponsor had the option of adding 5 additional study sites.

- Amendment to the Statistical Analysis Plan ( 12/22/99)

The Statistical Analysis Plan was amended at the request of FDA with regard to methods for continuous endpoints. The amendment provided that a non-parametric approach would include the center-stratified Cochran-Mantel-Haenzel mean test score with the change from baseline to endpoint as the response if the hypothesis of normality is rejected at the 5 % level of significance. Previously, the sponsor had not designated a single non-parametric approach.

- Post-hoc Analysis of Statistical Robustness of Efficacy

Markedly different results (i.e. no statistical difference for primary efficacy variable between treatments groups) in **another, identical** study (Z/SEL/97/025) prompted a review of the statistical robustness of study Z/SEL/97/026.

- Site effect was examined by including center groups in the ANCOVA. The center-by-treatment interaction would be removed from the ANCOVA model if the p-value was > 0.1. This analysis did not indicate a center effect.
- A descriptive analysis of the reduction in percentage "OFF" time by center was also performed. The ZS group showed a consistent trend in improvement in all centers.
- Baseline % "OFF" was compared and no differences were detected. The baseline value was included in the ANCOVA model as a covariate.
- Statistical assumptions for using ANCOVA were examined and both normality and equal variance assumption were met.
- Rank analysis of covariance was performed as a supportive analysis. The p-value obtained from rank analysis was nearly equal to the p-value obtained from ANCOVA.

#### 13.3.2. Results of Study Z/SEL/97/026 (Study Showing Efficacy)

##### Patient Disposition

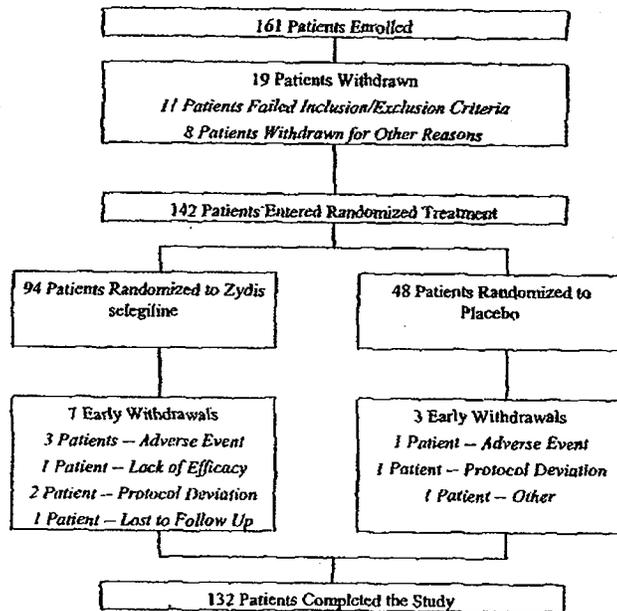
A total of 161 patients enrolled and 142 patients were randomized to one of two treatments in 16 U.S. medical centers. Of these patients, 94 received ZS and 48 received placebo. The number of patients completing the study was 132. Seven patients in the ZS and three patients in the placebo groups discontinued from the study prematurely for various reasons (i.e. adverse event, lack of

# CLINICAL REVIEW

## Clinical Review Section

efficacy, protocol deviation, lost to follow-up, “other”). The disposition of all patients is shown in Figure 2 (derived from sponsor’s Figure 5-1).

**Figure 9 Disposition of Patients**



Reference: End-of-Text Table 1.2

### Protocol Violations, Deviations, and Prohibited Concomitant Medications

The sponsor did not define what constituted a protocol violation and protocol deviation but appeared to use these terms interchangeably. Two patients (Z33, Z18) in the ZS group and one patient in the placebo group discontinued because of “protocol violations.” The patients received ZS for 91 and 31 days but it is not clearly specified why they were discontinued and for what protocol violations. One patient (Z37) randomized to placebo and having received placebo for 1 day was not included in any efficacy analyses because no post-treatment efficacy data were collected.

The protocol specified that scheduled visits were to occur within a 7-day window (e.g. visit day  $\pm$  3 days). There were several instances in which the scheduled visit occurred outside of the 7-day window. Table 30 (derived from sponsor’s Table 5-1) shows the number of visits outside this window for each treatment group.

# CLINICAL REVIEW

## Clinical Review Section

**Table 30 Visits Outside the Treatment Window**

Week <sup>a</sup>	Treatment Groups		Total
	Zydis selegiline	Placebo	
1	0	0	0
2	3	0	3
4	4	2	6
6	7	5	12
8	9	4	13
10	13	3	16
12	7	2	9

<sup>a</sup>Patients who had pre-baseline visits outside the window are not shown in this table because the protocol permitted flexibility in the timing of these visits.  
Data is extracted from Reference Data Listing 2.3

### Prohibited Concomitant Medications

Although the protocol did not specifically prohibit the use of opioids, tricyclic antidepressants and selective serotonin reuptake inhibitor (SSRI) drugs during treatment in the study, use of these drugs within 6 weeks of Visit 1 (first visit) was prohibited and was an exclusion criterion. Use of these drug classes with selegiline is generally not recommended.

One patient (X91-placebo) violated an exclusion criterion by having used an opioid containing drug within 6 weeks prior to Visit 1.

One patient (Z18-ZS) had used an opioid drug within proscribed period before enrollment and also used another opioid containing medication for 3 days during the study. This patient participated in the study through week 4 and was included in the ITT analysis.

One patient (X70) used a SSRI for 2 days during treatment in the study. This patient completed the study and was included in the Per Protocol (PP) population analysis.

### Demographic Characterizations

There were no statistically significant differences ( $p \geq 0.154$ ) between the ZS treatment group and the placebo group with regard to age, gender, race, height, or duration (i.e. years) of Parkinson's disease. Table 31 derived from the sponsor's Table 6-1). Although the mean demographic difference (6.3 years for ZS and 7.5 years for placebo) seemed most notable for duration of Parkinson's disease, neither was this difference statistically significant ( $p = 0.167$ ).

Appears This Way  
On Original

**BEST POSSIBLE COPY**

# CLINICAL REVIEW

## Clinical Review Section

**Table 31 Summary of Demographic Characteristics of ITT Population**

Characteristic	Treatment	
	Zydis selegiline N = 94	Placebo N = 46
<b>Age (yrs)</b>		
Mean (SD)	66.4 (9.3)	63.9 (11.1)
Min, Max	42.0, 85.0	38.0, 84.0
<b>Gender</b>		
Male	59 (62.8%)	30 (65.2%)
Female	35 (37.2%)	16 (34.8%)
<b>Race</b>		
Black	1 (1.1%)	0 (0.0%)
Caucasian	86 (91.5%)	43 (93.5%)
Oriental	2 (2.1%)	0 (0.0%)
Other	5 (5.3%)	3 (6.5%)
<b>Height (cm)</b>		
N	93	46
Mean (SD)	170.0 (11.9)	170.7 (10.3)
Min, Max	142.0, 193.0	142.0, 185.0
<b>Weight (kg)</b>		
N	93	46
Mean (SD)	75.3 (17.7)	78.1 (17.1)
Min, Max	40.9, 120.0	45.0, 127.7
<b>Duration of Parkinson's disease (yrs)</b>		
Mean (SD)	6.3 (4.5)	7.5 (5.1)
Min, Max	0.5, 21.6	0.3, 19.0

Reference: End-of-Text Table 2c

### Efficacy Results

#### Sponsor's Primary Efficacy Endpoint

Analysis of the observed case (OC)/"visit-wise" dataset of the ITT population showed a statistically significant difference ( $p < 0.001$ ) in favor of the ZS group over the placebo group for the primary efficacy endpoint (i.e. the percentage reduction in average daily "OFF" time during waking hours at the end of the study-weeks 10 and 12) in Table 32 (derived from the sponsor's Table 6-2) (see Table 32). More specifically, the change from baseline for the ZS group was -13.1 % for the ZS group (2.5 mg/d) compared to -3.9 % for the placebo group at the "end" of the study (i.e. average of diary data collected at weeks 10 and 12). The mean percentage reduction difference between ZS and placebo group was 9.2 % in favor of ZS and was statistically significant ( $p < 0.001$ ).

The percentage reduction of average daily "OFF" time during waking hours from baseline was also statistically significant ( $p = 0.003$ ) for the ZS group (1.25 mg/d) compared to placebo group by analyzing mean data of diary efficacy parameters collected toward the middle of the study at

## CLINICAL REVIEW

### Clinical Review Section

the week 4 and 6 Visits (Table 32). More specifically, the change from baseline for the ZS group (1.25 mg/d) was -9.9 % compared to -3.2 % for the placebo group. The mean percentage reduction difference between ZS and placebo group was 6.7 % in favor of ZS. **Although the sponsor notes that these data support “the use of a starting dose of 1.25 mg/day” of ZS, this analysis was not for a primary efficacy endpoint that had been prospectively identified.** Such data suggest “early” efficacy of the lower ZS dose but do not provide any support for prolonged efficacy of this lower dose because this lower dose group was not studied toward the end of the study (based upon the average of data collected immediately preceding the week 10 and 12 Visits).

The magnitude of the difference of the reduction in percentage "OFF" during waking hours between ZS and placebo was greater (9.2 %) for high dose (2.5 mg/d) ZS at 10 and 12 weeks than that (6.7 %) for low dose (1.25 mg/d) ZS at 4 and 6 weeks. However, the sponsor did not specify any post-hoc analysis to assess whether this difference was statistically significant.

Table 33 (derived from the sponsor's Table 6-3) shows the percentage change from baseline for in average daily "OFF" time during waking hours over the whole study period. ZS was statistically superior ( $p < 0.05$ ) to placebo at each timepoint except at week 6 where the p value was "borderline" (i.e.  $p = 0.066$ ) for statistical significance. The onset of efficacy as reflected by statistically significant differences between ZS and placebo groups first occurred at week 1 for low dose ZS (1.25 mg/d) for this endpoint. This efficacy persisted over the next few weeks up to week 4.

The magnitude of the mean differences in percentage "OFF" reduction from baseline between ZS and placebo treatment groups appeared to be greater between weeks 8 and 12 for high dose ZS than that at an earlier period between weeks 2-6 for low dose ZS. The sponsor did not conduct an analysis to determine if these data were statistically different. Regardless, it is not clear whether the apparent magnitude of the differences might be related to the higher dose of ZS or to the longer exposure to ZS.

Similar results were observed when data from the LOCF ITT and PP populations were analyzed as had been observed during analysis of data from the OC ITT population. Table 34 (derived from sponsor's Table 6-4) shows these results of the PP population.

#### Secondary Efficacy Endpoints

The secondary efficacy endpoints were based on the actual reduction in hours "OFF", the Unified Parkinson's Disease Rating Scale (UPDRS) (Motor sub-score for "OFF" and "ON", Activities of Daily Living [ADL] sub-score), the Clinical Global Impression Scale (CGI) and the patient's Global Impression Scale (PGI).

The change from baseline (i.e. reduction) for average daily "OFF" hours is shown in Table 35 (derived from sponsor's Table 6-5) for the average of weeks 4 and 6 and for weeks 10 and 12 for placebo groups and for low and high dose ZS. The reduction in "OFF" hours was in fact an efficacy variable identified in the protocol but it was not specified as a secondary efficacy

## CLINICAL REVIEW

### Clinical Review Section

endpoint. Collecting "OFF" time data during waking hours was crucial for calculating the primary efficacy variable (i.e. the on-treatment reduction in percentage of "OFF" time from baseline during waking hours). ZS was statistically greater than placebo for the average of weeks 4 and 6 ( $p = 0.003$  for low dose ZS) and also for the average of weeks 10 and 12 ( $p < 0.001$  for high dose ZS) indicating a favorable effect of ZS for reducing "OFF" time. The magnitude of the difference between ZS and placebo groups was greater for high dose ZS (mean -1.6 hours) later in the study than that for low dose ZS (mean -0.9 hours) earlier in the study but these data were not subjected to post-hoc statistical analyses.

Table 36 shows the change from baseline for average daily "OFF" hours between weeks 1 and 12 for both treatment groups for the OC ITT population. A statistically significant difference (i.e.  $p < 0.05$ ) in favor of ZS (over placebo) occurred initially at week 1 and persisted throughout the study except for data collected at week 6 ( $p = 0.078$ ). Results from analyzing the LOCF ITT and PP populations were similar to those of the OC ITT population. This pattern of statistically significant efficacy over time for ZS for this secondary efficacy variable was similar to the pattern of statistically significant efficacy over time for ZS for the efficacy variable reduction in percentage "OFF" from baseline during waking hours (Table 33).

Table 37 (derived from the sponsor's Table 6-7) shows the mean severity scores for the physician-rated CGI-S (for the OC OTT population) that was used to measure a change in **global severity** of the patient's parkinsonian symptoms throughout the study. A lower score for this measure indicates improvement in the condition. The only statistically significant differences between ZS and placebo groups were observed toward the end of the study at weeks 10 and 12 for high dose ZS. Results from the LOCF ITT population were similar and also showed a statistical difference at week 8 ( $p = 0.025$ ). Results from the PP population showed statistically significant differences at weeks 4 ( $p = 0.042$ ), 6 ( $p = 0.039$ ), 10 ( $p = 0.002$ ), and 12 ( $p = 0.011$ ).

Table 38 (derived from sponsor's Table 6-8) shows the mean physician-rated CGI-Improvement scores for the OC OTT population. A score of 4 indicates no change and a score of 3 indicates minimal improvement. The CGI-I was used as a measure of a change in **global improvement** in condition from visit to visit. There was no statistical differences (i.e.  $p \geq 0.338$ ) between ZS and placebo groups over the whole study period except for week 10 ( $p = 0.042$ ). Analyses of the LOCF ITT and PP populations showed similar but not identical results suggesting no improvement related to ZS as did results from the OC ITT population.

Table 39 (derived from the sponsor's Table 6-9) summarizes the mean improvement scores reported in the patient-rated PGI scale for the OC ITT population. As noted for the CGI-I, a score of 4 indicates no change and a score of 3 indicates minimal improvement. Statistically significant differences between ZS and placebo groups occurred only at week 4 ( $p = 0.028$ ) for low dose ZS and at all timepoints (e.g. weeks 8, 10, and 12;  $p \leq 0.034$ ) for high dose ZS. Whereas the mean score for ZS was 3.06 derived from averaging mean data at weeks 8, 10, and 12, the mean score for placebo was 3.57 derived from averaging mean data at weeks 8, 10, and 12. Analyses of the LOCF ITT population showed that statistically significant superiority for ZS first occurred at week 4 and was maintained through week 12. Analyses of the PP population showed that statistical superiority for ZS occurred at week 1 and persisted throughout the study.

# CLINICAL REVIEW

## Clinical Review Section

Table 40 (derived from the sponsor's Table 6-10) summarizes mean scores at weeks 6 and 12 for UPDRS motor and ADL subscales for "OFF" and "ON" states for both treatment groups in the OC ITT populations. There were no statistically significant differences between ZS and placebo for ADL either at "OFF" or "ON" states at 6 and 12 week timepoints. In contrast, a statistically significant difference ( $p = 0.010$ ) in favor of ZS (1.25 mg/d) occurred for motor "OFF" scores at 6 weeks and a borderline statistically significant difference ( $p = 0.050$ ) was observed for motor "ON" scores at 6 weeks. High dose ZS (2.5 mg/d) showed statistical superiority ( $p = 0.018$ ) over placebo only for motor "OFF" scores at 12 weeks.

Appears This Way  
On Original

**Table 32 Percent Change in Values for Average Daily "OFF" Time During Waking Hours from Baseline to Efficacy Endpoints (ITT Population)**

Timepoint	Treatment		p-value <sup>c</sup>
	Zydis selegiline <sup>b</sup> N = 94	Placebo N = 46	
<b>Baseline, Percentage "OFF" Time<sup>a</sup></b>			
N	94	46	
Mean (SD)	41.5 (11.6)	42.1 (12.5)	
Min, Max	18.0, 68.8	20.7, 70.2	
<b>Average of Weeks 4-6 (%) (Dose = 1.25 mg/day)</b>			
N	91	45	
Mean (SD)	-9.9 (13.3)	-3.2 (10.7)	
95% Confidence Interval <sup>d</sup>	(-11.0, -2.3)		0.003
<b>Average of Weeks 10-12 (%) (Dose = 2.5 mg/day)</b>			
N	87	44	
Mean (SD)	-13.1 (14.7)	-3.9 (10.5)	
95% Confidence Interval <sup>d</sup>	(-14.2, -4.7)		<0.001

<sup>a</sup>Percent "OFF" time of total waking hours for ITT population defined as an average of reported "OFF" time for Weeks -2 and -1.

<sup>b</sup>Weeks 1-6 prescribed dose = 1.25 mg/d, Weeks 7-12 prescribed dose = 2.5 mg/d.

<sup>c</sup>Comparison of treatment groups using ANOVA (with treatment, baseline, and center effects).

<sup>d</sup>Computed for difference between changes in Zydis selegiline and placebo values

Reference: Table 7.1.2a

Appears This Way  
On Original

**BEST POSSIBLE COPY**

# CLINICAL REVIEW

## Clinical Review Section

**Table 33 Percent Change From Baseline Values for Average Daily "OFF" Time During Waking Hours (ITT Population)**

Timepoint	Treatment		p-value <sup>c</sup>
	Zydis selegiline <sup>b</sup> N = 94	Placebo N = 46	
Baseline, Percentage "OFF" Time <sup>a</sup>			
N	94	46	
Mean (SD)	41.5 (11.6)	42.1 (12.5)	
Min, Max	18.0, 68.8	20.7, 70.2	
Week 1, Change from Baseline (%)			
N	94	44	
Mean (SD)	-9.4 (12.8)	-4.4 (12.1)	0.025
95% Confidence Interval <sup>d</sup>	(-9.5, -0.7)		
Week 2, Change from Baseline (%)			
N	93	45	
Mean (SD)	-9.8 (16.9)	-4.1 (12.4)	0.042
95% Confidence Interval <sup>d</sup>	(-10.8, -0.2)		
Week 4, Change from Baseline (%)			
N	91	45	
Mean (SD)	-10.1 (12.7)	-1.9 (11.5)	<0.001
95% Confidence Interval <sup>d</sup>	(-12.6, -4.0)		
Week 6, Change from Baseline (%)			
N	88	45	
Mean (SD)	-10.0 (16.3)	-4.6 (14.7)	0.066
95% Confidence Interval <sup>d</sup>	(-10.5, 0.3)		
Week 8, Change from Baseline (%)			
N	87	42	
Mean (SD)	-12.2 (16.1)	-4.5 (12.6)	0.005
95% Confidence Interval <sup>d</sup>	(-12.9, -2.4)		
Week 10, Change from Baseline (%)			
N	85	43	
Mean (SD)	-12.3 (16.9)	-2.6 (10.4)	<0.001
95% Confidence Interval <sup>d</sup>	(-15.3, -4.4)		
Week 12, Change from Baseline (%)			
N	81	43	
Mean (SD)	-14.0 (15.3)	-5.0 (14.0)	0.001
95% Confidence Interval <sup>d</sup>	(-14.4, -3.7)		

<sup>a</sup>Percent "OFF" time of total waking hours for ITT population defined as an average of reported "OFF" time for Weeks -2 and -1.

<sup>b</sup>Weeks 1-6 prescribed dose = 1.25 mg/d, Weeks 7-12 prescribed dose = 2.5 mg/d.

<sup>c</sup>Comparison of treatment groups using ANCOVA (with treatment, baseline, and center effects).

<sup>d</sup>Computed for difference between changes in Zydis selegiline and placebo values

Reference: Table 7.1a

Appears This Way  
On Original

# CLINICAL REVIEW

## Clinical Review Section

**Table 34 Percent Change From Baseline Values for Average Daily "OFF" Time During Waking Hours (Per Protocol Population)**

Timepoint	Treatment		p-value <sup>c</sup>
	Zydis selegiline <sup>b</sup> N = 87	Placebo N = 44	
Baseline, Percentage "OFF" Time <sup>a</sup>			
N	87	44	
Mean (SD)	41.6 (11.7)	42.3 (12.8)	
Min, Max	18.0, 68.8	20.7, 70.2	
Week 1, Change from Baseline (%)			
N	87	42	
Mean (SD)	-9.7 (12.5)	-4.8 (11.8)	
95% Confidence Interval <sup>d</sup>	(-9.2, -0.4)		0.033
Week 2, Change from Baseline (%)			
N	87	44	
Mean (SD)	-9.9 (16.7)	-4.3 (12.5)	
95% Confidence Interval <sup>d</sup>	(-10.6, -0.1)		0.048
Week 4, Change from Baseline (%)			
N	87	44	
Mean (SD)	-10.1 (12.9)	-1.4 (11.2)	
95% Confidence Interval <sup>d</sup>	(-12.9, -4.1)		<0.001
Week 6, Change from Baseline (%)			
N	86	44	
Mean (SD)	-10.0 (16.5)	-4.2 (14.7)	
95% Confidence Interval <sup>d</sup>	(-11.1, -0.1)		0.048
Week 8, Change from Baseline (%)			
N	78	40	
Mean (SD)	-12.8 (16.5)	-4.9 (12.7)	
95% Confidence Interval <sup>d</sup>	(-12.9, -1.8)		0.010
Week 10, Change from Baseline (%)			
N	77	41	
Mean (SD)	-12.7 (17.4)	-2.1 (10.2)	
95% Confidence Interval <sup>d</sup>	(-16.0, -4.6)		0.001
Week 12, Change from Baseline (%)			
N	75	41	
Mean (SD)	-14.7 (15.3)	-4.6 (14.2)	
95% Confidence Interval <sup>d</sup>	(-15.6, -4.4)		0.001
Average of Weeks 10-12 (%)			
N	79	42	
Mean (SD)	-13.7 (15.0)	-3.5 (10.4)	
95% Confidence Interval <sup>d</sup>	(-15.1, -5.3)		<0.001

<sup>a</sup>Percent "OFF" time of total waking hours for per protocol population defined as an average of reported "OFF" time for Weeks -2 and -1.

<sup>b</sup>Weeks 1-6 prescribed dose = 1.25 mg/d, Weeks 7-12 prescribed dose = 2.5 mg/d.

<sup>c</sup>Comparison of treatment groups using ANOVA (with treatment, baseline, and center effects).

<sup>d</sup>Computed for difference between changes in Zydis selegiline and placebo values  
Reference: Table 7.1c

Appears This Way  
On Original

**CLINICAL REVIEW**

Clinical Review Section

**Table 35 Change From Baseline Values to Endpoints for Average Number of Daily "OFF" Hours**

Timepoint	Treatment		p-value <sup>b</sup>
	Zydis selegiline <sup>a</sup> N = 94	Placebo N = 46	
Baseline, Average "OFF" Time (Hrs)			
N	94	46	
Mean <sup>c</sup> (SD)	6.9 (2.0)	7.0 (2.2)	
Min, Max	2.8, 11.5	3.4, 13.0	
Average of Weeks 4-6 Change from Baseline (Hrs) (Dose = 1.25 mg/day)			
N	91	45	
Mean <sup>c</sup> (SD)	-1.6 (2.3)	-0.5 (1.7)	
95% Confidence Interval <sup>d</sup>	(-1.9, -0.4)		0.003
Average of Weeks 10-12 Change from Baseline (Hrs) (Dose = 2.5 mg/day)			
N	87	44	
Mean <sup>c</sup> (SD)	-2.2 (2.5)	-0.6 (1.6)	
95% Confidence Interval <sup>d</sup>	(-2.4, -0.8)		<0.001

<sup>a</sup>Weeks 1-6 prescribed dose = 1.25 mg/d, Weeks 7-12 prescribed dose = 2.5 mg/d.  
<sup>b</sup>Comparison of treatment groups using ANCOVA (with treatment, baseline, and center effects).  
<sup>c</sup>Mean expressed in Hours  
<sup>d</sup>Computed for difference between changes in Zydis selegiline and placebo values.  
Reference: End-of-Text Table 7.2 2a

Appears This Way  
On Original

**BEST POSSIBLE COPY**

# CLINICAL REVIEW

## Clinical Review Section

**Table 36 Change From Baseline Values for Number of Daily "OFF" Time During Waking Hours**

Timepoint	Treatment		p-value <sup>b</sup>
	Zydis selegiline <sup>a</sup> N = 94	Placebo N = 46	
Baseline, Average "OFF" Time (Hrs)			
N	94	46	
Mean <sup>c</sup> (SD)	6.9 (2.0)	7.0 (2.2)	
Min, Max	2.8, 11.5	3.4, 13.0	
Week 1, Change from Baseline (Hrs)			
N	94	44	
Mean <sup>c</sup> (SD)	-1.5 (2.2)	-0.7 (2.0)	0.024
95% Confidence Interval <sup>d</sup>	(-1.6, -0.1)		
Week 2, Change from Baseline (Hrs)			
N	93	45	
Mean <sup>c</sup> (SD)	-1.7 (2.8)	-0.7 (1.9)	0.026
95% Confidence Interval <sup>d</sup>	(-1.8, -0.1)		
Week 4, Change from Baseline (Hrs)			
N	91	45	
Mean <sup>c</sup> (SD)	-1.6 (2.2)	-0.2 (2.0)	<0.001
95% Confidence Interval <sup>d</sup>	(-2.2, -0.7)		
Week 6, Change from Baseline (Hrs)			
N	88	45	
Mean <sup>c</sup> (SD)	-1.6 (2.8)	-0.7 (2.4)	0.078
95% Confidence Interval <sup>d</sup>	(-1.8, 0.1)		
Week 8, Change from Baseline (Hrs)			
N	87	42	
Mean <sup>c</sup> (SD)	-2.0 (2.7)	-0.7 (2.2)	0.007
95% Confidence Interval <sup>d</sup>	(-2.2, -0.3)		
Week 10, Change from Baseline (Hrs)			
N	85	43	
Mean (SD)	-2.0 (2.8)	-0.5 (1.7)	<0.001
95% Confidence Interval <sup>d</sup>	(-2.5, -0.7)		
Week 12, Change from Baseline (Hrs)			
N	81	43	
Mean <sup>c</sup> (SD)	-2.3 (2.6)	-0.7 (2.2)	0.001
95% Confidence Interval <sup>d</sup>	(-2.5, -0.6)		
Average of Weeks 10-12 (Hrs)			
N	87	44	
Mean <sup>c</sup> (SD)	-2.2 (2.5)	-0.6 (1.6)	<0.001
95% Confidence Interval <sup>d</sup>	(-2.4, -0.8)		

<sup>a</sup>Weeks 1-6 prescribed dose = 1.25 mg/d, Weeks 7-12 prescribed dose = 2.5 mg/d

<sup>b</sup>Comparison of treatment groups using ANCOVA (with treatment, baseline, and center effects).

<sup>c</sup>Mean expressed in Hours

<sup>d</sup>Computed for difference between changes in Zydis selegiline and placebo values.

Reference: End-of-Text Table 7.2a

Appears This Way  
On Original

# CLINICAL REVIEW

## Clinical Review Section

**Table 37 Mean Severity Scores for Physician-rated CGI-S**

Treatment	Baseline	Week #						
		1	2	4	6	8	10	12
<b>Zydis selegiline<sup>a</sup></b>								
N <sup>b</sup>	94	93	93	91	88	87	83	82
Mean	3.70	3.52	3.34	3.32	3.38	3.32	3.22	3.18
SD	0.75	0.88	0.81	0.85	0.93	0.90	0.95	0.92
<b>Placebo</b>								
N	46	46	45	44	45	42	43	43
Mean	3.93	3.72	3.58	3.57	3.64	3.55	3.60	3.53
SD	0.80	0.86	1.01	0.90	1.00	0.74	0.79	0.91
p-value <sup>c</sup>	0.094	0.132	0.174	0.090	0.087	0.088	0.004	0.026

CGI Scores: 1 = Normal 2 = Borderline ill 3 = Mildly ill 4 = Moderately ill 5 = Markedly ill 6 = Severely ill 7 = Extremely ill

<sup>a</sup>Weeks 1-6 prescribed dose = 1.25 mg/day, Weeks 7-12 prescribed dose = 2.5 mg/d

<sup>b</sup>ITT population

<sup>c</sup>Van Elteren Test (based on the underlying contingency table shown in End-of-Text Table 8.2.1a)  
Reference: End-of-Text Table 8.1.1a

**Table 38 Mean Improvement Scores for Physician-rated CGI-I**

Treatment	Baseline	Week #						
		1	2	4	6	8	10	12
<b>Zydis selegiline<sup>a</sup></b>								
N <sup>b</sup>	93	93	93	91	88	87	83	82
Mean	3.97	3.76	3.59	3.60	3.68	3.61	3.48	3.50
SD	0.50	0.67	0.76	0.74	0.78	0.75	0.83	0.79
<b>Placebo</b>								
N	46	46	45	44	45	42	43	43
Mean	4.09	3.74	3.62	3.61	3.71	3.62	3.74	3.63
SD	0.81	0.57	0.61	0.78	0.69	0.73	0.76	0.87
p-value <sup>c</sup>	0.338	0.989	0.868	0.796	0.739	0.942	0.042	0.362

CGI Scores: 1 = Very much improved 2 = Much improved 3 = Minimally improved 4 = No change 5 = Minimally worse 6 = Much worse 7 = Very much worse

<sup>a</sup>Weeks 1-6 prescribed dose = 1.25 mg/day, Weeks 7-12 prescribed dose = 2.5 mg/d

<sup>b</sup>ITT population

<sup>c</sup>Van Elteren Test (based on the underlying contingency table shown in End-of-Text Table 8.2.1a)  
Reference: End-of-Text Table 8.1.2a

Appears This Way  
On Original

**BEST POSSIBLE COPY**

# CLINICAL REVIEW

## Clinical Review Section

**Table 39 Mean Improvement Scores for Patient-rated PGI -I**

Treatment	Week #						
	1	2	4	6	8	10	12
<b>Zydis selegiline<sup>a</sup></b>							
N <sup>b</sup>	94	93	91	87	87	84	82
Mean	3.29	3.12	3.21	3.20	3.14	3.02	3.01
SD	0.93	0.88	1.06	1.03	1.10	1.11	1.07
<b>Placebo</b>							
N	46	45	45	45	43	43	43
Mean	3.50	3.49	3.62	3.53	3.58	3.65	3.47
SD	0.81	0.92	1.07	1.08	1.05	1.11	1.14
p - value <sup>c</sup>	0.052	0.057	0.028	0.054	0.034	0.003	0.029

PGI Scores: 1 = Very much improved 2 = Much improved 3 = Minimally improved 4 = No change  
5 = Minimally worse 6 = Much worse 7 = Very much worse

<sup>a</sup>Weeks 1-6 prescribed dose = 1.25 mg/day, Weeks 7-12 prescribed dose = 2.5 mg/d

<sup>b</sup>ITT population

<sup>c</sup>Van Elteren Test (based on the underlying contingency table shown in End-of-Text Table 8.4a)  
Reference: End-of-Text Table 8.3a

**Table 40 Mean UPDRS Subscale Scores at Weeks 6 and 12**

UPDRS Subscale and Condition	Week 6 (1.25 mg/day)		Week 12 (2.5 mg/day)	
	Treatment		Treatment	
	Zydis selegiline	Placebo	Zydis selegiline	Placebo
<b>ADL "ON"</b>				
N	87	45	81	43
Mean (SD)	5.7 (5.6)	6.7 (5.7)	6.0 (5.3)	6.9 (6.1)
95% CI <sup>a</sup>	(-1.8, 0.5)		(-2.1, 0.6)	
p-value <sup>b</sup>	0.251		0.282	
<b>ADL "OFF"</b>				
N	87	45	81	43
Mean (SD)	14.7 (7.5)	16.8 (8.7)	14.6 (7.7)	16.2 (7.7)
95% CI <sup>a</sup>	(-1.8, 1.3)		(-1.3, 2.0)	
p-value <sup>b</sup>	0.748		0.668	
<b>Motor "ON"</b>				
N	87	45	81	43
Mean (SD)	15.7 (9.7)	18.6 (12.6)	14.6 (8.3)	16.8 (10.8)
95% CI <sup>a</sup>	(-5.1, 0.0)		(-3.9, 0.8)	
p-value <sup>b</sup>	0.050		0.201	
<b>Motor "OFF"</b>				
N	84	43	81	42
Mean (SD)	29.1 (13.0)	33.8 (14.8)	27.3 (12.4)	31.4 (12.5)
95% CI <sup>a</sup>	(-7.6, -1.1)		(-6.4, -0.7)	
p-value <sup>b</sup>	0.010		0.018	

<sup>a</sup>Confidence interval for Zydis selegiline versus placebo based on ANCOVA model

<sup>b</sup>ANCOVA

Reference: End-of-Text Tables 9a and 9b

## CLINICAL REVIEW

### Clinical Review Section

The sponsor's primary efficacy endpoint (i.e. percentage reduction in off time at weeks 10 and 12 from baseline) was computed from diaries in which patients specified 1 of 4 categorical states (e.g. "OFF", "ON", "ON" with dyskinesia, or asleep) at each time. However, the sponsor only presented information for the "OFF" state. Because I had a concern that changes in percentage "OFF" time could occur and potentially be associated with poorer outcomes of these other states, I asked the sponsor to present analyses of all 4 states recorded in diaries. Analyses (for each pivotal trial and combined analysis of both pivotal trials) were conducted to show : 1) change from baseline percent mean of each categorical state; 2) mean categorical state; and 3) change from baseline mean of each categorical state over time (e.g. baseline through week 12) and according to study treatment.

Figure 10 shows results from Z/SEL/97/026 for the primary efficacy endpoint for mean % change from baseline in "OFF" time. These results indicate that "OFF" time appeared to be improved statistically over essentially the whole 12 week period. Figure 11, Figure 12, and Figure 13 shows corresponding responses for "ON" time, asleep time, and "ON" time with dyskinesia, respectively. When "OFF" time is decreased, "ON" time appears to be increased also over essentially the whole treatment period (Figure 11) as a good complimentary outcome to the decrease in "OFF" time. Figure 12 shows that there was no apparent change in asleep time throughout the study. Figure 13 also shows that there was no apparent change in "ON" time with dyskinesia. All 3 presentations/analyses show similar outcomes for all categorical diary states. **Thus, these analyses reinforce the conclusion that ZS-related clinical improvement occurring with reduced "OFF" time is associated with increased "ON" time and is not associated with poor outcome of other measures such sleeping time or "ON" time with dyskinesia.**

Similar analyses of studies Z/SEL/97/025 and Z/SEL/97/026 combined show overall qualitatively similar results as those in study Z/SEL/97/026. Results of study Z/SEL/97/026 were most robust. Results of study Z/SEL/97/025 showed that ZS responses were similar as those in study Z/SEL/97/026 but the large placebo response generally prevented statistical differences. Results of the combined study analyses were essentially intermediate between those of results of study Z/SEL/97/026 and study Z/SEL/97/025. Results from these other analyses will not be presented because they do not add any additional information beyond that learned from reviewing results in study Z/SEL/97/026.

Appears This Way  
On Original

**BEST POSSIBLE COPY**

# CLINICAL REVIEW

## Clinical Review Section

**Figure 10: Change From Baseline Reduction In Percent Mean Daily OFF Time**

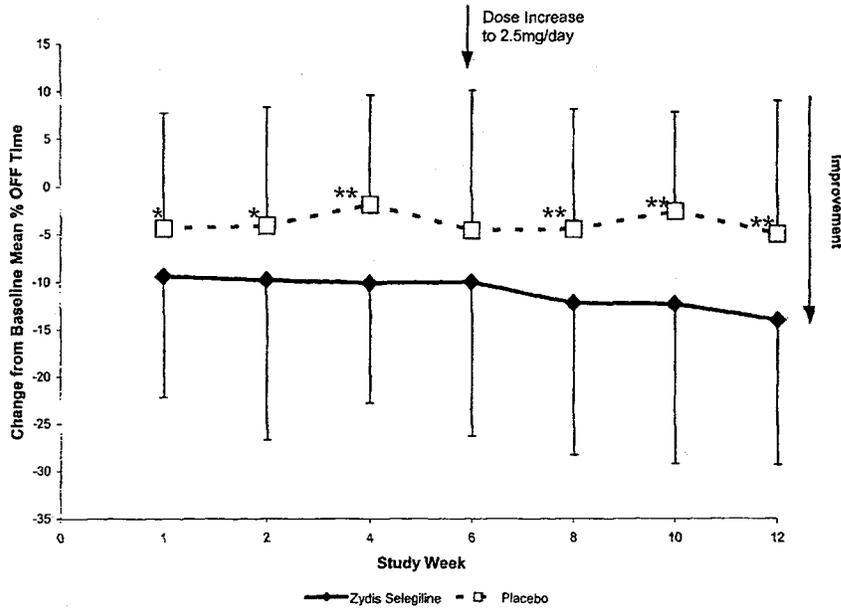


Figure 1. Change From Baseline Mean Percent Daily OFF Time per Visit – Study 97/026. Note that decreased values indicate improvement on this graph. \* indicates  $p \leq 0.05$ , while \*\* indicates  $P \leq 0.01$ . Data Source: Table 7.1a, Study 97/026, Previously Submitted Data.

**Figure 11: Change From Baseline Percent Mean Daily ON Time**

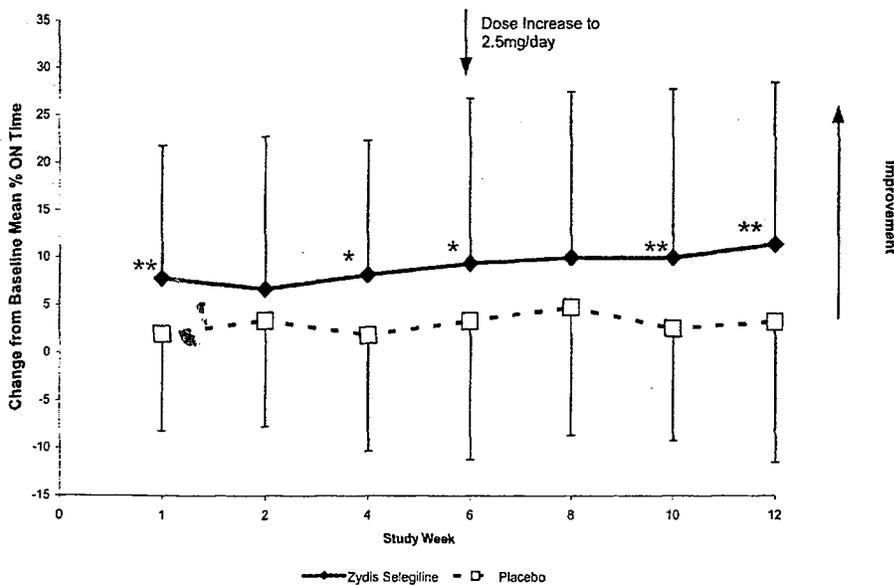


Figure 4. Change From Baseline Mean Percent Daily ON Time per Visit – Study 97/026. \* indicates  $p \leq 0.05$ , while \*\* indicates  $P \leq 0.01$ . Data Source: Table 7.3a, Study 97/026, New Analyses.

# CLINICAL REVIEW

## Clinical Review Section

**Figure 12** Change From Baseline Percent Mean Daily Asleep Time

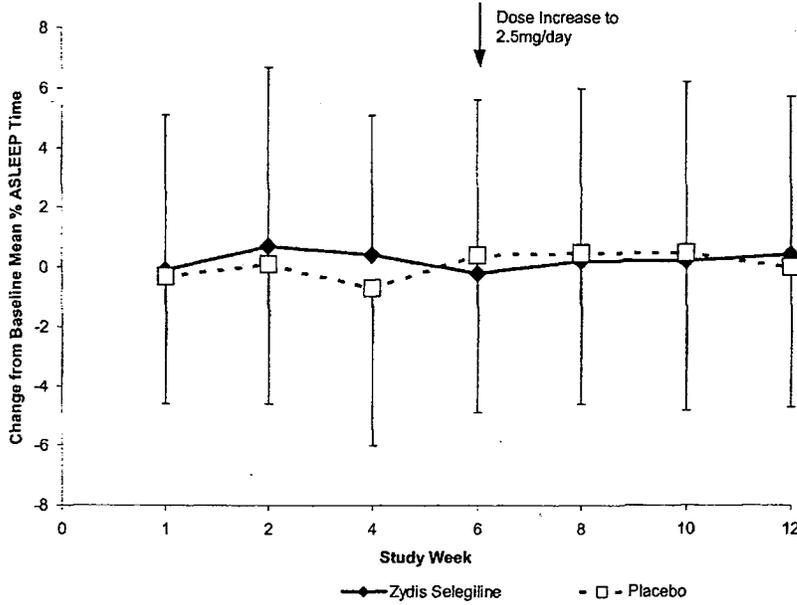


Figure 7. Change From Baseline Mean Percent Asleep Time – Study 97/026. Data Source: Table 7.5a, Study 97/026, New Analyses.

**Figure 13** Change From Baseline Daily Percent Mean ON Time With Dyskinesias

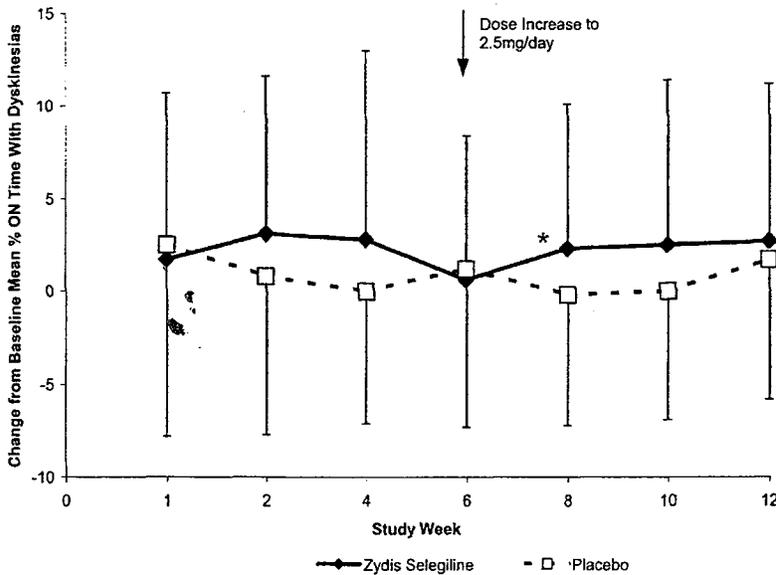


Figure 10. Change From Baseline Mean Percent ON Time With Dyskinesia – Study 97/026. \* indicates  $p \leq 0.05$ , while \*\* indicates  $P \leq 0.01$ . Data Source: Table 7.7a, Study 97/026, New Analyses.

### 13.3.3. Primary Efficacy Endpoint and Statistical Analyses

The primary efficacy endpoint was the percentage reduction in total daily "OFF" time over 12 weeks on treatments during waking hours reported from patient/caregiver completed diary cards. The primary efficacy analysis was the percentage change (i.e. reduction) from baseline for daily "OFF" during waking hours determined from the average of weeks 10 and 12 on treatment for the Intent-to-treat (ITT) population. The ITT population was defined as patients who were randomized to a treatment, received at least 1 dose of study medication, had baseline percent "OFF" time data collected, and had at least one set of "OFF" time data collected during treatment.

During the review of this NDA, questions were raised as to whether the sponsor has conducted the primary efficacy analysis as pre-specified and in accordance with expectations and recommendations by DNDP. One of the overall problems in considering statistical analyses of the ITT population is that this population consists of several datasets. These datasets include the last observation carried forward (LOCF) dataset (when efficacy data are missing), observed case (OC) dataset (when actual data collected are analyzed), per protocol (PP) dataset (when data collected have not significantly deviated from the protocol and as specified in the statistical analysis plan), and completer dataset (when data collection has been collected up through a specified timepoint). **However, the sponsor has not always clearly identified in this NDA or in the Statistical Analysis Plan (SAP) which of these specific datasets (that comprise the whole ITT population) was analyzed or was planned to be analyzed.**

The following is a summary of the chronology of events that provide insight into the problem of the sponsor not conducting the appropriate analysis of the primary efficacy endpoint.

- The sponsor's original protocols for phase 3, pivotal trials (studies Z/SEL/97/026 and Z/SEL/97/025) noted that the primary efficacy analysis would be conducted on the ITT patient population using the LOCF convention, thus the ITT-LOCF dataset.
- Protocol amendment # 2 (2/4/98) noted that the primary efficacy analysis was changed to analyze the ITT population instead of the ITT LOCF dataset. However, this amendment did not specify which dataset of the ITT population would be analyzed. This amendment further noted that a detailed plan of analysis would be prepared before the randomization code is broken and the analysis of the trial results begins.
- DNDP faxed (10/15/99) comments to the sponsor regarding the sponsor's statistical analysis plan for studies Z/SEL/97/026 and Z/SEL/97/025. DNDP pointed out that the ITT population should be included in the primary efficacy analysis and analyses of secondary efficacy variables. The fax further noted that "We recommend that the LOCF method be used for missing data when applicable."
- On 12/10/99 the sponsor (Elan) submitted a revised statistical analysis plan along with

## CLINICAL REVIEW

### Clinical Review Section

responses to DNDP comments communicated to the sponsor on 10/15/99. The sponsor provided the following response to DNDP's recommendation (i.e. that the primary efficacy analysis and efficacy analyses of secondary variables utilize the ITT-LOCF dataset).

"The ITT population will be changed to include all patients who have been randomized and have received at least one dose of study drug. Please note that this will result on a combined analysis of patients receiving 1.25 and 2.5 mg doses. Such an analysis was previously planned to be secondary in nature. This change has been incorporated into Section 3.1 on page 12."

- Section 3.1 of the statistical analysis plan describes analysis populations and the analysis strategy. "The **primary efficacy analysis** is that performed on the primary efficacy parameter and considering an 'Intent-to-Treat' population (see LOCF-ITT population definition below) consisting of patients who were randomized, received at least one dose of study medication and completed a subsequent evaluation visit. Other efficacy analyses are described following definitions for the various patients populations considered."

The LOCF ITT population is described in section 3.1 as follows. "The term '**LOCF ITT Population**' will be used to refer to the ITT population in which the LOCF principal (sic) has been used in handling missing data. (LOCF is applied when data are missing from a post baseline time interval but exist in a preceding on-study-medication time interval. LOCF will be applied to time slotted data)."

Toward the end of section 3.1 there is further mention of the LOCF ITT population and various efficacy analyses. "**Additional efficacy analyses** are performed on the primary efficacy parameter considering the ITT completers population (with no imputation of missing data so that analyses are on the ITT completer only), the LOCF ITT population, and the PP population. All secondary efficacy analysis parameters are analyzed on the ITT completers population, the LOCF ITT population, and the PP population."

- According to the final study report (for study Z/SEL/97/026, the only "positive" pivotal trial) contained within the NDA, efficacy analyses were performed on the observed case (OC) data at each timepoint for all efficacy parameters and analysis of this dataset appeared to be the primary efficacy analysis. Although neither the protocol nor statistical analysis plan specified that the OC ITT would be part of the primary efficacy analysis, the protocol did note that one of the datasets to be analyzed would be the "visit-wise" dataset in which valid observations at each visit would be analyzed. I subsequently learned that the OC dataset is the same as the "visit-wise" dataset. **Furthermore, the statistical analysis plan did not mention nor describe an observed case or visit-wise dataset to be analyzed.** The final study report notes that the ITT LOCF dataset was also similarly statistically significant as the observed case dataset for the primary efficacy endpoint. However, tables are not presented showing specific efficacy responses for the ITT LOCF dataset.
- On 7/29/02 and 11/06/02 there were teleconferences (DNDP and sponsor and sponsor's consultants) discussing the statistical analysis of the primary efficacy endpoint. It became

# CLINICAL REVIEW

## Clinical Review Section

clear that the sponsor had conducted the primary efficacy analysis using the ITT OC dataset. When data were missing at week 10 or 12, the observed data from week 10 or 12 was considered as the average of weeks 10 and 12. DNDP statisticians informed the sponsor that DNDP considered that the ITT LOCF dataset was the population that was supposed to be the used for the primary analysis of the primary efficacy endpoint. DNDP also noted that this is a normal expectation of DNDP. **DNDP told the participants that the sponsor needed to : 1) conduct and submit a primary separate analysis for study Z/SEL/97/026 and study Z/SEL/97/025 of the primary efficacy endpoint using the ITT LOCF dataset; 2) submit the SAS codes and data to DNDP so that DNDP could conduct its own analyses of the sponsor's data; 3) conduct efficacy analyses of the primary and secondary endpoints for the completer datasets as had been specified in the protocols and SAP; and 4) submit a presentation and interpretation/discussion of these new analyses.** DNDP also told the sponsor how to implement the LOCF imputation method. Diary results from the last two different weeks of data collection should be used to obtain on treatment average for the primary efficacy endpoint when data are missing from week 10, week 12 or both weeks.

### 13.3.4. Statistical Reviewer's Analysis of Primary Efficacy Results (ITT LOCF Dataset)

The statistical reviewer (Dr. F. Kong) replicated the sponsor's analyses according to the protocol. The results of this review are depicted in the following table.

**Table 41      Percent Change in Values for Average Daily "OFF" Time During Waking Hours from Baseline to Endpoint ---ITT Population**

Primary Efficacy Parameters	Zydis selegiline (N=94)	Placebo (N=46)	P-value <sup>b</sup>
Baseline, Percentage "OFF" Time <sup>a</sup>			
Mean (SD)	41.5 (11.6)	42.1 (12.5)	
Min, Max	18.0, 68.8	20.7, 70.2	
Average of Weeks 10-12 (%), (Dose=2.5 mg/day)			
N	92	45	
Mean (SD)	-13.9 (15.2)	-5.1 (13.7)	0.0007
95% Confidence Interval <sup>c</sup>	(-14.1, -3.5)		

<sup>a</sup> Percent "OFF" time of total waking hours for ITT population defined as an average of reported "OFF" time for Weeks -2 and -1. <sup>b</sup> Comparison of treatment groups using ANOVA (with treatment, baseline, and center effects). <sup>c</sup> Computed for difference between changes in Zydis selegiline and placebo values.

# CLINICAL REVIEW

## Clinical Review Section

The Shapiro-Wilks test indicates that the normality assumption holds for the primary endpoint of the change of the percentage "OFF" time from baseline. Therefore the significant results in Table 41 are reliable. To assess the robustness of results, DNDP's statistical reviewer performed the Wilcoxon nonparametric test on the change from baseline of the percentage "OFF" time as well as the percentage change from baseline of the same variable, i.e., the change of percentage "OFF" time from baseline divided by baseline. These tests show respective p values equal to 0.0007 and 0.0009. The result of the Wilcoxon test indicates the robustness of results.

The information of each investigator is presented in Table 42 to assess whether the significant result is mainly contributed by one investigator. In Table 42, Nselegiline and NPlacebo are the number of patients in Zydis selegiline and Placebo groups, respectively. T is TTEST statistic performed on the difference of the mean changes from baseline for unequal variances between two treatment groups.

**Table 42 T Statistic by Investigator**

Obs	Invest	NSelegiline	NPlacebo	t-Value
01	104	12	7	-1.43
02	105	8	4	-1.09
03	108	10	5	-3.68
04	112	9	5	-0.75
05	115	8	3	-2.99
06	116	12	6	-0.58
07	118	9	4	0.75
08	G61	6	3	-0.37
09	G62	6	3	-3.33
10	G63	12	5	-0.16

Most of the clinic centers show that the ZS reduces the daily "OFF" time compared to the placebo. Center 108 seems to show a high level of statistical significance. After removing this center, the Wilcoxon test shows a p value = 0.009 and the t-test shows a p value = 0.013 for the statistical significance of the treatment effect of ZS. Thus, the treatment effect appears to be quite stable.

Table 43 shows the treatment difference by sex. DIFF is the mean change from baseline to week 10-12 on the percentage of "OFF" time. ZYDISDIFF is the difference between DIFF of ZS and Placebo for each sex.

Appears This Way  
On Original

**BEST POSSIBLE COPY**

# CLINICAL REVIEW

## Clinical Review Section

**Table 43 Treatment Effect by Sex**

Sex	Therapy	Patient	DIFF	ZYDISDIFF	t-Value
Male	Zydis selegiline	58	-15.4	-10.8	-3.87
	Placebo	29	-4.7		
Female	Zydis selegiline	34	-11.3	-5.5	-1.02
	Placebo	16	-5.8		

Table 43 shows that ZS appears to have a treatment effect in both male and female groups but this effect is statistically significant only in the male group.

### 13.3.5. Discussion of Study Results

The sponsor did not conduct the primary efficacy analysis on the appropriate population/dataset as was expected according to the Statistical Analysis Plan (SAP). There were several datasets of different populations to be analyzed and the sponsor did not consistently nor clearly identify the population/dataset that was supposed to comprise the primary efficacy analysis. Although the study report notes that the ITT population was to comprise the primary analysis, the protocol did not specify that the observed case (OC)/ "visit-wise" dataset (derived from valid observations at each visit) of the ITT population would be analyzed as part of the primary analysis.

Dr. Kong, DNDP statistical reviewer, has recently completed his own analysis of the LOCF ITT dataset for the primary efficacy endpoint. His analysis (provided in this review) shows similar results of efficacy of ZS (2.5 mg daily) at the end of the study (e.g. weeks 10 and 12) as those conducted by the sponsor for the primary efficacy endpoint for the LOCF and PP datasets. However, the LOCF ITT analysis conducted by the sponsor was a supportive analysis and only carried forward a single result for a missing result at week 10 or 12. DNDP informed the sponsor that the LOCF algorithm should analyze the last 2 diary weeks collected as the average at the end of treatment. Thus, the sponsor's original analysis of the LOCF ITT dataset would not be directly comparable to the analysis of Dr. Kong. Dr. Kong's analyses also showed a robust effect, efficacy across different investigators/sites, and a treatment effect in both males and females. Although the treatment effect of ZS was only statistically significant in males, I do not have any significant reservations about efficacy in females because the absolute number of females was relatively low (34 ZS, 16 placebo) and much lower than the number of males ((58 ZS, 20 placebo).

I have reviewed the sequence of events whereby the DNDP has questioned the propriety and validity of the sponsor's primary efficacy analysis of the primary efficacy endpoint in the pivotal trials for several months. As a result, the DNDP (primary statistical reviewer-Dr. Kong, statistical team leader-Dr. Jin, and I) informed (11/6/02 teleconference) the sponsor that it had not conducted the appropriate primary efficacy analysis according to the SAP and normal expectations of DNDP and that it must redo and submit several analyses and SAS codes. As of 1/3/03, the sponsor had not yet submitted analyses/presentations/information requested by DNDP in the 11/6/02 teleconference. This request consists of the separate primary efficacy analysis using the LOCF ITT datasets for both pivotal trials (using the "averaging" LOCF

## CLINICAL REVIEW

### Clinical Review Section

algorithm outlined by the DNDP), the SAS codes for Dr. Kong to perform an analysis as did, the analysis of secondary endpoints using the revised LOCF ITT datasets, the analysis of all efficacy endpoints for the completer dataset, and a presentation/discussion of result.

The number of patients included in the primary analysis of the OC ITT population does not seem correct when one examines Table 32 for the primary efficacy endpoint in each study relative to the Table 33 showing the responses at each visit. The primary efficacy analysis was supposed to be comprised of ITT patients in whom actual data were collected at weeks 10 and 12 in each study and averaged for comparison to baseline. By selecting the lowest number of patients studied at week 10 or 12 for each treatment group, it would appear that the appropriate number of patients to be analyzed for study Z/SEL/97/026 should be 81 (ZS) and 43 (placebo). In contrast, Table 32 shows that 87 and 44 patients comprised the primary analysis, suggesting 6 extra patients and 1 extra patient in each respective group. When this discrepancy was pointed out to the sponsor, the sponsor noted that it did not always have data at both weeks 10 and 12 for each patient included in the analysis but used the available data from 1 week as the average when data were missing from 1 week. Because the analysis of the OC ITT dataset should include data from both weeks 10 and 12, DNDP (statisticians and I) concluded that the sponsor's primary analysis of the primary efficacy endpoint was not done correctly.

The sponsor did not present results of the effects of ZS and placebo treatment on all the categorical entries for the diary cards (e.g. "OFF", "ON", "ON with dyskinesia", "asleep"). Results were presented only for changes in "OFF" hours. It is not clear if the sponsor analyzed these various categories. However, such analyses would be important to ensure that ZS did not have a detrimental effect on other categories such as increasing the average number of hours of "ON with dyskinesias" or "asleep." In theory, it is conceivable that a drug could reduce the percentage of average "OFF" time during waking hours by minimally decreasing the number of "OFF" hours while substantially increasing the number of hours "asleep" and thereby decreasing the number of waking hours. The sponsor should present and analyze results of study medication treatment on all categories of diary entries including total number of hours awake and asleep.

**In general**, analyses of results from the different populations and their respective datasets appeared to show similar (but not identical) results with respect to statistically significant p values (e.g.  $< 0.05$ ), p values trending toward statistical significance (e.g.  $> 0.05$  but  $< 0.25$ ), and p values not approaching statistical significance (e.g.  $> 0.25$ ). This general consistency of results tends to confirm the validity of the protocol defined primary efficacy analysis of the primary population and dataset with regard to different outcome measures.

Initially, I had concerns because the protocol did not require that patients taking LD must also be taking a peripheral DDCI such as carbidopa (CD). However, this appears to be an academic, theoretical issue of no concern because it appears that all patients who enrolled in this trial were always taking both LD and CD as a form of Sinemet. Results from this study could have been problematic if a significant number of patients were not also taking CD because it might not be possible to conclude that ZS was equally effective in LD-treated patient who were also taking CD and LD-treated patient who were not taking CD. This potential concern could have been related to differential effects of ZS (especially different doses) on metabolism of dopamine in the

## CLINICAL REVIEW

### Clinical Review Section

presence and absence of a DDCL.

Results (Table 32, Table 33, Table 34, Table 35, Table 36, Table 39, and Table 40) of low dose ZS (1.25 mg/d) frequently showed a statistically significant benefit on various efficacy outcome measures at various (e.g. one or more) times between 1 and 6 weeks of treatment. These efficacy measures included percentage change of average daily "OFF" time during waking hours from baseline, change of average daily "OFF" time from baseline, PGI-I, and motor subscale of UPDRS for both "OFF" and "ON" states. However, it is not possible to state whether this low dose of ZS is effective after 12 weeks of treatment as can be said for high dose ZS (2.5 mg) because this dose was studied relative to the primary outcome measure at weeks 10 and 12. It would be speculative to say whether ZS is effective after 12 weeks of treatment. Unfortunately, the design utilized (e.g. taking ZS 1.25 mg/d for 6 weeks and then taking ZS 2.5 mg/d for the next 6 weeks) does not permit one to say whether 1.25 mg/d of ZS is an effective dose following prolonged (e.g.  $\geq 12$  weeks) treatment. It is a general requirement of the DNDP for drug approval to demonstrate effective treatment of chronic neurological condition after a minimal treatment period of at least 12 weeks. To make an efficacy claim for low dose ZS, it would have been necessary to have a three arm parallel group trial consisting of 12 weeks of treatment randomized to placebo, or 1.25 mg/d or 2.5 mg/d of ZS. Although the sponsor notes in proposed labeling that efficacy with 1.25 mg/d of ZS was demonstrated, the sponsor does not conclude at the end of the study report that low dose ZS is an effective dose for treating advanced Parkinson's disease patients exhibiting deterioration of the response to LD. It is not possible to determine whether the efficacy shown by high dose ZS in the second half of the study and especially toward the end of the study is related to the dose of ZS or extent of exposure to ZS. I think that these results are more likely related to the higher dose considering the PK/PD relationships of ZS, the pharmacological mechanism of action of selegiline, the generally greater magnitude of the effect of high dose ZS, and the more extensive efficacy of high dose ZS for more outcome measures. Furthermore, there would be no reason to expect that prolonged exposure would be necessary for a statistically significant benefit, especially considering the relatively rapid onset of efficacy observed as early as 1 week after treatment with low dose ZS.

Whereas some secondary efficacy outcome measures reflected beneficial effects of ZS, some showed less benefit and others did not show any benefit. For example, physician rated global impressions of improvement and severity (e.g. CGI-I and CGI-S) were generally insensitive measures of efficacy of low and high dose ZS with the exception of high dose ZS for CGI-S at 10 and 12 weeks and for CGI-I at 10 weeks. Similarly, the ADL subscales of the UPDRS for both "OFF" and "ON" states were not affected by either low or high dose ZS. In contrast, patient-rated global impression of improvement (PGI-I) was generally marginally statistically significant for low dose ZS and always statistically significant for high dose ZS. Motor "OFF" subscales of the UPDRS were statistically improved after low and high dose ZS at 6 and 12 weeks respectively. However, only the motor subscale for "ON" was statistically improved after treatment with low dose ZS.

There are some apparent deficiencies in the sponsor's final study report with respect to certain issues : 1) description of pharmacokinetic and pharmacodynamic relationships impacting on

## CLINICAL REVIEW

### Clinical Review Section

efficacy; and 2) a description of subgroup analyses of efficacy data based upon age, gender, and race.

Results from this pivotal study appear to be robust for supporting efficacy of ZS (2.5 mg/d) by virtue of: 1) the magnitude of the statistical difference from placebo and the respective p value; 2) the supportive nature of results of several secondary efficacy outcome measures; 3) the combined results and analyses of the two identically designed pivotal trials (studies Z/SEL/97/025 and Z/SEL/97/026); and 4) the post-hoc analysis of statistical robustness of efficacy described at the end of the protocol amendments section.

#### 13.3.6. Conclusions

##### Sponsor's Conclusions

The sponsor concludes that ZS at 2.5 mg/d over a period of 12 weeks is an effective adjunctive treatment with LD in patients exhibiting deterioration of their response to LD/CD because of the statistically significant reduction in motor "OFF" time.

##### Reviewer's Conclusions

This reviewer agrees with the sponsor's conclusion that ZS 2.5 mg/d is an effective adjunctive treatment with LD in patients exhibiting deterioration of their response to LD (i.e. advanced Parkinson's disease patients) because of the statistically significant reduction in percentage of motor "OFF" time during waking hours. These results showed statistically significant superiority of ZS (2.5 mg/d) over placebo. However, this study did not show that ZS at 1.25 mg/d is similarly an effective treatment adjunctive treatment with LD in patients at 10 and 12 weeks because this dose was not studied at that those timepoints. Neither did the sponsor characterize and establish dose-response information for efficacy and safety of ZS by randomizing patients to a range of fixed doses in parallel groups. I view this as a significant shortcoming in the development of this product. It is desirable that the dose response curve for both efficacy and safety be characterized to determine the optimal therapeutic doses associated with minimal toxicity. This is best accomplished by randomizing patients to fixed parallel dose groups across a wide range of doses and comparing these groups with a placebo group in a double-blinded trial.

Finally, my conclusions are based upon the assumption that the data and analyses presented and summarized are valid. It will be desirable to see the sponsor's results of the requested analyses and Dr. Kong's analyses after the sponsor has provided him with the SAS codes to conduct his own analyses and compare them with those of the sponsor.

## CLINICAL REVIEW

### Clinical Review Section

#### 13.4. Study Z/SEL/97/025\_(Study Supporting Efficacy)

Study initiation date : 12/11/97

Study completion date : 11/24/99

##### 13.4.1. Description of Protocol Z/SEL/97/025 (Study Supporting Efficacy)

This protocol is identical to study Z/SEL/97/026 (see description).

Protocol amendments are also identical to those described for Study Z/SEL/97/026 (see description).

Planned statistical analyses were similar to those described in study Z/SEL/97/026 (see description).

DNDP had advised the sponsor (Scherer Pharmaceuticals) to conduct a single large study instead of two identical, smaller studies. When Elan Pharmaceuticals took over ownership of ZS and the ongoing pivotal studies from Scherer, Elan decided to continue the studies as they had begun as smaller, identical studies.

##### 13.4.2. Results of Study Z/SEL/97/025\_(Study Supporting Efficacy)

###### Patient Disposition

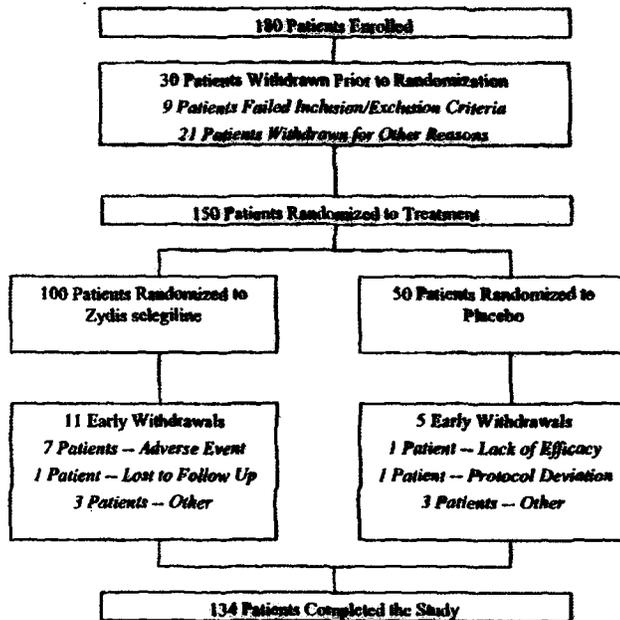
A total of 180 patients enrolled and 150 patients were randomized to one of two treatments in 15 North American medical centers (14 U.S., 1 Canadian). Of these patients, 100 received ZS and 50 received placebo. The number of patients completing the study was 134. Eleven patients in the ZS and five patients in the placebo groups discontinued from the study prematurely for various reasons (i.e. adverse event, lack of efficacy, protocol deviation, lost to follow-up, "other"). The disposition of all patients is shown in Figure 14 (derived from sponsor's Figure 5-1).

Appears This Way  
On Original

# CLINICAL REVIEW

## Clinical Review Section

**Figure 14 Patient Disposition**



Reference: End-of-Text Table 1.2

### Protocol Violations, Deviations, and Prohibited Concomitant Medications

The sponsor did not define what constituted a protocol violation and protocol deviation but appeared to use these terms interchangeably. One patient (A46) in the ZS group, who did not receive the higher dose (2.5 mg/d), exhibited a protocol deviation. Patient B07 used a prohibited medication (e.g. COMT inhibitor), thereby deviating from the protocol, and was excluded from the ITT analysis. Patient C32 (ZS group) was also excluded from the ITT analysis because the patient did not return for any post-treatment efficacy assessments. Patient A53 was discontinued from the study because of a protocol violation related to dosing compliance. Patient C44, who had been taking St. John's wort at baseline was excluded from the PP analysis but was included in the ITT analysis. Other patients were excluded from the PP population because of early study withdrawal.

The protocol specified that scheduled visits were to occur within a 7-day window (e.g. visit day  $\pm$  3 days). There were several instances in which the scheduled visit occurred outside of the 7-day window. Table 44 (derived from sponsor's Table 5-1) shows the number of visits outside this window for each treatment group.

# CLINICAL REVIEW

## Clinical Review Section

Table 44 Visit Outside Treatment Window

Week <sup>a</sup>	Treatment Groups		Total
	Zydis selegiline	Placebo	
1	0	0	0
2	3	0	3
4	4	3	7
6	10	6	16
8	7	6	13
10	6	3	9
12	16	7	23

<sup>a</sup> Patients who had pre-baseline visits outside the window are not shown in this table because the protocol permitted flexibility in the timing of these visits.  
Reference Listing 2.3

### Prohibited Concomitant Medications

Although the protocol did not specifically prohibit the use of opioids, tricyclic antidepressants and selective serotonin reuptake inhibitor (SSRI) drugs during treatment in the study, use of these drugs within 6 weeks of Visit 1 (first visit) was prohibited and was an exclusion criterion. Use of these drug classes with selegiline is generally not recommended.

One patient (A20), assigned to ZS, was taking an antidepressant (i.e. Pamelor) at baseline and during the study. This patient, who violated a study entrance criterion, was included in the PP analysis.

Two patients (B36, C39), assigned to ZS, and one patient (B82) assigned to placebo, used a prohibited opioid medication (i.e. Ultram). Although this use appeared to be a violation of an entrance criterion, these patients were still included in the PP analysis.

Patient B87, randomized to ZS, may have used a prohibited opioid analgesic (i.e. Darvocet) along with ZS during the study, and thus was excluded from the PP analysis.

Patient C38, randomized to placebo, used a prohibited opioid medication (e.g. Darvocet and Vicoden) but was still included in the PP analysis.

### **Demographic Characterizations**

There were no statistically significant differences ( $p \geq 0.2105$ ) between the ZS treatment group and the placebo group with regard to age, gender, race, height, or duration (i.e. years) of Parkinson's disease (Table 45 derived from the sponsor's Table 6-1). Although the mean

# CLINICAL REVIEW

## Clinical Review Section

demographic difference (7.2 years for ZS and 6.2 years for placebo) seemed most notable for duration of Parkinson's disease, neither was this difference statistically significant ( $p = 0.268$ ).

**Table 45 Summary of Demographic Characteristics of ITT Population**

Characteristic	Treatment	
	Zydis selegiline N = 98	Placebo N = 50
<b>Age (yrs)</b>		
N	98	50
Mean (SD)	68.4 (9.0)	66.3 (10.6)
Min, Max	41.0, 93.0	39.0, 85.0
<b>Gender</b>		
Male	68 (69.4%)	36 (72.0%)
Female	30 (30.6%)	14 (28.0%)
<b>Race</b>		
Black	3 (3.1%)	0 (0.0%)
Caucasian	93 (94.9%)	49 (98.0%)
Other	2 (2.0%)	1 (2.0%)
<b>Height (cm)</b>		
N	98	50
Mean (SD)	170.8 (8.9)	170.8 (19.9)
Min, Max	149.0, 188.0	60.0 <sup>a</sup> , 201.0
<b>Weight (kg)</b>		
N	97	49
Mean (SD)	77.6 (18.2)	79.4 (18.5)
Min, Max	43.6, 158.9	50.0, 129.4
<b>Duration of Parkinson's disease (yrs)</b>		
N	98	50
Mean (SD)	7.2 (5.5)	6.2 (4.5)
Min, Max	0.3, 32.7	0.4, 20.4

<sup>a</sup> This value is incorrect. It was determined after database lock that this patient is actually 60 inches tall, not 60 cm as shown. The actual minimum height was 151cm.

Reference: End-of-Text Table 2c

## Sponsor's Efficacy Results

### Primary Efficacy Endpoint

Analysis of the OC ITT population did not show a statistically significant difference ( $p < 0.05$ ) in favor of the ZS group over the placebo group for the primary efficacy endpoint (i.e. the percentage reduction in average daily "OFF" time during waking hours) in Table 46 (derived from the sponsor's Table 6-2). More specifically, the change from baseline for the ZS group was  $-11.6\%$  for the ZS group (2.5 mg/d) compared to  $-9.8\%$  for the placebo group at the "end" of the study (i.e. average of diary data collected at weeks 10 and 12). Although the mean percentage reduction difference between ZS and placebo group was  $1.8\%$  in favor of ZS, this difference was not statistically significant ( $p = 0.467$ ).

## CLINICAL REVIEW

### Clinical Review Section

Neither was the percentage reduction of average daily "OFF" time during waking hours from baseline statistically significant ( $p = 0.449$ ) for the ZS group (1.25 mg/d) compared to placebo group by analyzing mean data of diary efficacy parameters collected toward the middle of the study at the week 4 and 6 Visits (Table 46). More specifically, the change from baseline for the ZS group (1.25 mg/d) was  $-10.5\%$  compared to  $-9.0\%$  for the placebo group. The mean percentage reduction difference between ZS and placebo group was  $1.5\%$  in favor of ZS but this difference was statistically insignificant.

The magnitude of the difference of the reduction in percentage "OFF" during waking hours (Table 47) between ZS and placebo was similar ( $1.8\%$ ) for high dose (2.5 mg/d) ZS at 10 and 12 weeks as that ( $1.5\%$ ) for low dose (1.25 mg/d) ZS at 4 and 6 weeks.

Table 47 (derived from the sponsor's Table 6-3) shows the percentage change from baseline for average daily "OFF" time during waking hours over the whole study period for the observed case dataset. ZS was statistically similar (i.e.  $p > 0.05$ ) to placebo at each timepoint. Differences with respect to p values showed a general trend toward lower values in the second half of the study than in the first half. Although most of the p values for these treatment differences were relatively high (i.e.  $p > 0.1$ ), the lowest p value (0.083) occurred at the end of the study for the week 12 data. In contrast to results from Study Z/SEL/97/026, these results did not suggest a treatment benefit (for ZS) based upon statistically significant differences because of the much larger changes observed in the placebo-treated patients.

Although the 12 week percentage change from baseline for average daily "OFF" time during waking hours was greater for the ZS group ( $-11.6 \pm 17.7\%$ ) than that of the placebo group ( $-7.5 \pm 17.7\%$ ) for the LOCF ITT dataset, this difference was not statistically significant. A similar pattern was observed for the PP dataset with the ZS group ( $-12.9 \pm 17.8\%$ ) showing a greater change from baseline (but statistically insignificant) than the placebo group ( $-7.1 \pm 18.4\%$ ).

A similar pattern of results, that was not statistically significant, was also observed when the average of 10 and 12 week percentage change from baseline for average daily "OFF" time during waking hours was compared for the ZS and placebo groups for the LOCF ITT dataset ( $p = .793$ ) and for the PP dataset ( $p = .506$ ).

### Secondary Efficacy Parameters

The change from baseline (i.e. reduction) for average daily "OFF" hours is shown in Table 48 (derived from sponsor's Table 6-4) for the average of weeks 4 and 6 and for weeks 10 and 12 for placebo groups and for low and high dose ZS. The reduction in "OFF" hours was in fact an efficacy variable identified in the protocol but it was not specified as a secondary efficacy endpoint. Collecting "OFF" time data during waking hours was crucial for calculating the primary efficacy variable (i.e. the on-treatment reduction in percentage of "OFF" time from baseline during waking hours). The ZS group ( $-1.7$  hours) showed a slightly greater reduction in "OFF" hours than placebo group ( $-1.5$  hours) for the average of weeks 4 and 6 but this difference was not statistically significant ( $p = 0.553$ ). For the average of weeks 10 and 12, the ZS group (-

## CLINICAL REVIEW

### Clinical Review Section

1.8 hours) also showed a slightly greater reduction in "OFF" hours than the placebo group (-1.6 hours) but this small difference was not statistically significant ( $p = 0.588$ ).

Table 49 shows the change from baseline for average daily "OFF" hours between weeks 1 and 12 for both treatment groups for the OC ITT population. There were no statistically significant differences (i.e.  $p \geq 0.108$ ) over the whole study. The lowest  $p$  value (i.e.  $p = 0.108$ ) for any of the comparisons occurred at the end of the study at week 12 when the ZS group exhibited a mean reduction (from baseline) in "OFF" hours of 2.1 and the placebo group showed a corresponding mean reduction of 1.3. Neither were there statistically significant differences when the LOCF ITT (i.e.  $p \geq 0.218$ ) and PP datasets (i.e.  $p \geq 0.111$ ) were analyzed.

Table 50 (derived from the sponsor's Table 6-6) shows the mean severity scores for the physician-rated CGI-S (for the OC OTT population) that was used to measure a change in **global severity** of the patient's parkinsonian symptoms throughout the study. A lower score for this measure indicates improvement in the condition. Mean values for both treatment groups were similar as reflected by the fact that there were no statistically significant differences (i.e.  $p \geq 0.463$ ) over the whole study. Analyses of the LOCF ITT and PP datasets showed similar results (i.e. no treatment effect of ZS) as observed for the OC ITT dataset.

Table 51 (derived from sponsor's Table 6-7) shows the mean physician-rated CGI-Improvement scores for the OC OTT population. A score of 4 indicates no change and a score of 3 indicates minimal improvement. The CGI-I was used as a measure of **global improvement** in condition from visit to visit. Although mean scores in the ZS group were always lower than those of the placebo group, these numerical differences were small (e.g.  $\leq 11\%$ ) and statistically significant only at two early timepoints ( week 2,  $p = 0.048$ ; week 4,  $p = 0.004$ ). In addition, the  $p$  value ( $p = 0.068$ ) for the difference at the end of the study (i.e. week 12) approached statistical significance, the  $p$  values at other timepoints (i.e. weeks 1, 6, 8, 10) were  $\geq 0.105$ .

Analyses of the LOCF ITT and PP populations for CGI-I showed similar but not identical results in that statistically significant differences favoring ZS were observed at isolated timepoints. A statistically significant difference (i.e.  $< 0.05$ ) occurred at week 4 ( $p = 0.005$ ) and a borderline statistically significant difference (i.e.  $p = 0.05$ ) occurred at week 12 for the LOCF ITT population. The PP population exhibited statistically significant differences at week 4 ( $p = 0.003$ ) and week 12 ( $p = 0.044$ ).

Table 52 (derived from the sponsor's Table 6-8) summarizes the mean improvement scores reported in the patient-rated PGI scale for the OC ITT population. As noted for the CGI-I, a score of 4 indicates no change and a score of 3 indicates minimal improvement. Statistically significant differences between ZS and placebo groups occurred only at week 4 ( $p = 0.042$ ) for low dose ZS and only at the end of the study (i.e. week 12,  $p = 0.020$ ) for high dose ZS. There were no statistically significant differences ( $p \geq 0.093$  at all the other visits (e.g. weeks 1, 2, 6, 8, and 10). Analysis of the LOCF ITT population was similar to that for the OC ITT analysis and ZS was statistically superior ( $p = 0.027$ ) to placebo only at week 12. Statistically significant differences in favor of ZS were also observed at weeks 4 ( $p = 0.040$ ) and 12 ( $p = 0.019$ ) for the PP population analysis.

# CLINICAL REVIEW

## Clinical Review Section

Table 53 (derived from the sponsor's Table 6-9) summarizes mean scores at weeks 6 and 12 for UPDRS motor and ADL subscales for "OFF" and "ON" states for both treatment groups. There were no statistically significant differences ( $p \geq 0.115$ ) between ZS and placebo for ADL for "OFF" or "ON" states nor for motor UPDRS scores for "OFF" and "ON" states at 6 and 12 week timepoints. Most p values (7 of 8) were relatively high (i.e.  $p \geq 0.306$ ) and did not even suggest a trend toward statistical significance.

**Table 46 Percent Change in Values for Average Daily "OFF" Time During Waking Hours from Baseline to Efficacy Endpoints (ITT Population)**

Timepoint	Treatment		p-value <sup>c</sup>
	Zydis selegiline <sup>b</sup> N = 98	Placebo N = 50	
<b>Baseline, Percentage "OFF" Time<sup>a</sup></b>			
N	98	50	
Mean (SD)	41.8 (14.1)	41.7 (12.9)	
Min, Max	18.6, 100.0	20.0, 72.4	
<b>Average of Weeks 4-6 (%) (Dose = 1.25 mg/day)</b>			
N	95	50	
Mean (SD)	-10.5 (15.0)	-9.0 (12.1)	
95% Confidence Interval <sup>d</sup>	(-6.5, 3.2)		0.499
<b>Average of Weeks 10-12 (%) (Dose = 2.5 mg/day)</b>			
N	89	46	
Mean (SD)	-11.6 (17.5)	-9.8 (14.9)	
95% Confidence Interval <sup>d</sup>	(-8.0, 3.7)		0.467

<sup>a</sup>Percent "OFF" time of total waking hours for ITT population defined as an average of reported "OFF" time for Weeks -2 and -1.

<sup>b</sup>Weeks 1-6 prescribed dose = 1.25 mg/d, Weeks 7-12 prescribed dose = 2.5 mg/d.

<sup>c</sup>Comparison of treatment groups using ANCOVA (with treatment, baseline, and center effects).

<sup>d</sup>Computed for difference between changes in Zydis selegiline and placebo values

Reference: Table 7.1 2a

Appears This Way  
On Original

# CLINICAL REVIEW

## Clinical Review Section

**Table 47** Percent Change From Baseline Values for Average Daily "OFF" Time During Waking Hours (ITT Population)

Timepoint	Treatment		p-value <sup>c</sup>
	Zydis selegiline <sup>b</sup> N = 98	Placebo N = 50	
<b>Baseline, Percentage "OFF" Time<sup>a</sup></b>			
N	98	50	
Mean (SD)	41.8 (14.1)	41.7 (12.9)	
Min, Max	18.6, 100.0	20.0, 72.4	NA
<b>Week 1, Change from Baseline (%)</b>			
N	96	50	
Mean (SD)	-5.7 (14.5)	-4.1 (11.8)	
95% Confidence Interval <sup>d</sup>	(-6.5, 3.0)		0.468
<b>Week 2, Change from Baseline (%)</b>			
N	93	50	
Mean (SD)	-8.1 (16.2)	-7.3 (13.4)	
95% Confidence Interval <sup>d</sup>	(-6.3, 4.2)		0.696
<b>Week 4, Change from Baseline (%)</b>			
N	93	49	
Mean (SD)	-8.9 (14.9)	-9.3 (15.7)	
95% Confidence Interval <sup>d</sup>	(-5.1, 5.5)		0.940
<b>Week 6, Change from Baseline (%)</b>			
N	91	48	
Mean (SD)	-12.2 (16.9)	-8.2 (16.3)	
95% Confidence Interval <sup>d</sup>	(-10.0, 1.8)		0.175
<b>Week 8, Change from Baseline (%)</b>			
N	92	46	
Mean (SD)	-9.5 (18.1)	-4.6 (19.3)	
95% Confidence Interval <sup>d</sup>	(-11.8, 1.2)		0.108
<b>Week 10, Change from Baseline (%)</b>			
N	87	44	
Mean (SD)	-10.3 (19.1)	-12.1 (15.6)	
95% Confidence Interval <sup>d</sup>	(-5.0, 7.7)		0.680
<b>Week 12, Change from Baseline (%)</b>			
N	84	45	
Mean (SD)	-12.9 (17.7)	-7.4 (18.3)	
95% Confidence Interval <sup>d</sup>	(-12.2, 0.8)		0.083
<b>Average of Weeks 10-12 (%)</b>			
N	89	46	
Mean (SD)	-11.6 (17.5)	-9.8 (14.9)	
95% Confidence Interval <sup>d</sup>	(-8.0, 3.7)		0.467

<sup>a</sup> Percent "OFF" time of total waking hours for ITT population defined as an average of reported "OFF" time for Weeks -2 and -1.

<sup>b</sup> Weeks 1-6 prescribed dose = 1.25 mg/d, Weeks 7-12 prescribed dose = 2.5 mg/d.

<sup>c</sup> Comparison of treatment groups using ANCOVA (with treatment, baseline, and center effects).

<sup>d</sup> Computed for difference between changes in Zydis selegiline and placebo values

Reference: Table 7.1a

Appears This Way  
On Original

# CLINICAL REVIEW

## Clinical Review Section

**Table 48** Change From Baseline Values to Endpoints for Average Number of Daily "OFF" Hours

Timepoint	Treatment		p-value <sup>b</sup>
	Zydis selegiline <sup>a</sup> N = 98	Placebo N = 50	
<b>Baseline, Average "OFF" Time (Hrs)</b>			
N	98	50	
Mean <sup>c</sup> (SD)	6.7 (2.3)	6.8 (2.2)	
Min, Max	3.1, 15.6	3.1, 12.0	
<b>Average of Weeks 4-6 Change from Baseline (Hrs) (Dose = 1.25 mg/day)</b>			
N	95	50	
Mean <sup>c</sup> (SD)	-1.7 (2.5)	-1.5 (2.1)	
95% Confidence Interval <sup>d</sup>	(-1.0, 0.6)		0.553
<b>Average of Weeks 10-12 Change from Baseline (Hrs) (Dose = 2.5 mg/day)</b>			
N	89	46	
Mean <sup>c</sup> (SD)	-1.9 (2.7)	-1.6 (2.3)	
95% Confidence Interval <sup>d</sup>	(-1.2, 0.7)		0.588

<sup>a</sup>Weeks 1-6 prescribed dose = 1.25 mg/d, Weeks 7-12 prescribed dose = 2.5 mg/d.  
<sup>b</sup>Comparison of treatment groups using ANCOVA (with treatment, baseline, and center effects).  
<sup>c</sup>Mean expressed in Hours  
<sup>d</sup>Computed for difference between changes in Zydis selegiline and placebo values.  
Reference: End-of-Text Table 7.2 2a

Appears This Way  
On Original

# CLINICAL REVIEW

## Clinical Review Section

**Table 49**      **Change From Baseline Values for Number of Daily “OFF” Time During Waking Hours**

Timepoint	Treatment		p-value <sup>b</sup>
	Zydis selegiline <sup>a</sup> N = 98	Placebo N = 50	
<b>Baseline, Average “OFF” Time (Hrs)</b>			
N	98	50	
Mean <sup>c</sup> (SD)	6.7 (2.3)	6.8 (2.2)	
Min, Max	3.1, 15.6	3.1, 12.0	NA
<b>Week 1, Change from Baseline (Hrs)</b>			
N	96	50	
Mean <sup>c</sup> (SD)	-0.8 (2.4)	-0.6 (2.0)	
95% Confidence Interval <sup>d</sup>	(-1.0, 0.6)		0.588
<b>Week 2, Change from Baseline (Hrs)</b>			
N	93	50	
Mean <sup>c</sup> (SD)	-1.3 (2.5)	-1.2 (2.2)	
95% Confidence Interval <sup>d</sup>	(-1.0, 0.7)		0.754
<b>Week 4, Change from Baseline (Hrs)</b>			
N	93	49	
Mean <sup>c</sup> (SD)	-1.4 (2.5)	-1.5 (2.7)	
95% Confidence Interval <sup>d</sup>	(-0.9, 0.9)		0.964
<b>Week 6, Change from Baseline (Hrs)</b>			
N	91	48	
Mean <sup>c</sup> (SD)	-2.0 (2.7)	-1.4 (2.7)	
95% Confidence Interval <sup>d</sup>	(-1.6, 0.4)		0.220
<b>Week 8, Change from Baseline (Hrs)</b>			
N	92	46	
Mean <sup>c</sup> (SD)	-1.6 (2.8)	-0.9 (2.7)	
95% Confidence Interval <sup>d</sup>	(-1.7, 0.2)		0.135
<b>Week 10, Change from Baseline (Hrs)</b>			
N	87	44	
Mean <sup>c</sup> (SD)	-1.6 (3.0)	-2.0 (2.4)	
95% Confidence Interval <sup>d</sup>	(-0.7, 1.4)		0.492
<b>Week 12, Change from Baseline (Hrs)</b>			
N	84	45	
Mean <sup>c</sup> (SD)	-2.1 (2.8)	-1.3 (2.8)	
95% Confidence Interval <sup>d</sup>	(-1.9, 0.2)		0.108
<b>Average of Weeks 10-12 (Hrs)</b>			
N	89	46	
Mean <sup>c</sup> (SD)	-1.9 (2.7)	-1.6 (2.3)	
95% Confidence Interval <sup>d</sup>	(-1.2, 0.7)		0.588

<sup>a</sup> Weeks 1-6 prescribed dose = 1.25 mg/d, Weeks 7-12 prescribed dose = 2.5 mg/d.

<sup>b</sup> Comparison of treatment groups using ANCOVA (with treatment, baseline, and center effects).

<sup>c</sup> Mean expressed in Hours

<sup>d</sup> Computed for difference between changes in Zydis selegiline and placebo values.

Reference: End-of-Text Table 7.2a

# CLINICAL REVIEW

## Clinical Review Section

**Table 50 Mean Severity Scores for Physician-rated CGI-S**

Treatment	Baseline	Week #						
		1	2	4	6	8	10	12
<b>Zydis selegiline<sup>a</sup></b>								
N <sup>b</sup>	98	95	91	92	90	90	85	83
Mean	3.79	3.28	3.24	3.24	3.33	3.29	3.24	3.24
SD	0.89	0.97	1.05	1.05	0.99	1.00	1.13	1.07
<b>Placebo</b>								
N <sup>b</sup>	49	49	49	49	47	46	42	45
Mean	3.57	3.18	3.31	3.37	3.30	3.17	3.21	3.27
SD	0.82	0.93	0.89	0.97	0.95	0.97	1.12	1.01
p - value <sup>c</sup>	0.075	0.580	0.673	0.463	0.731	0.879	0.682	0.880

CGI Scores: 1 = Normal 2 = Borderline ill 3 = Mildly ill 4 = Moderately ill 5 = Markedly ill  
6 = Severely ill 7 = Extremely ill

<sup>a</sup> Weeks 1-6 prescribed dose = 1.25 mg/day, Weeks 7-12 prescribed dose = 2.5 mg/d

<sup>b</sup> ITT population

<sup>c</sup> Van Elteren Test (based on the underlying contingency table shown in End-of-Text Table 8.2.1a)

Reference: End-of-Text Table 8.1.1a

**Table 51 Mean Improvement Scores for Physician-rated CGI-I**

Treatment	Baseline	Week #						
		1	2	4	6	8	10	12
<b>Zydis selegiline<sup>a</sup></b>								
N <sup>b</sup>	97	94	91	91	90	90	85	82
Mean	4.05	3.50	3.45	3.44	3.56	3.50	3.46	3.43
SD	0.70	0.81	0.89	0.85	0.86	0.91	0.99	0.83
<b>Placebo</b>								
N <sup>b</sup>	48	48	48	48	46	45	42	44
Mean	4.08	3.63	3.75	3.85	3.74	3.60	3.62	3.70
SD	0.65	0.82	0.79	0.74	0.74	0.75	0.91	0.79
p - value <sup>c</sup>	0.541	0.105	0.048	0.004	0.123	0.310	0.343	0.064

CGI Scores: 1 = Very much improved 2 = Much improved 3 = Minimally improved 4 = No change 5 = Minimally worse 6 = Much worse 7 = Very much worse

<sup>a</sup> Weeks 1-6 prescribed dose = 1.25 mg/day, Weeks 7-12 prescribed dose = 2.5 mg/d

<sup>b</sup> ITT population

<sup>c</sup> Van Elteren Test (based on the underlying contingency table shown in End-of-Text Table 8.2.1a)

Reference: End-of-Text Table 8.1.2a

# CLINICAL REVIEW

## Clinical Review Section

**Table 52 Mean Improvement Scores for Patient-rated PGI -I**

Treatment	Week #						
	1	2	4	6	8	10	12
<b>Zydis selegiline<sup>a</sup></b>							
N <sup>b</sup>	96	92	92	91	91	87	84
Mean	3.25	3.16	3.14	3.14	3.25	3.09	3.06
SD	1.10	1.15	1.14	0.98	1.13	1.11	1.23
<b>Placebo</b>							
N <sup>b</sup>	49	49	49	46	47	43	45
Mean	3.41	3.35	3.53	3.46	3.40	3.26	3.49
SD	0.89	0.97	1.08	1.09	1.08	1.09	1.25
p - value <sup>c</sup>	0.215	0.233	0.042	0.093	0.428	0.649	0.020

PGI Scores: 1 = Very much improved 2 = Much improved 3 = Minimally improved 4 = No change 5 = Minimally worse 6 = Much worse 7 = Very much worse  
<sup>a</sup> Weeks 1-6 prescribed dose = 1.25 mg/day, Weeks 7-12 prescribed dose = 2.5 mg/d  
<sup>b</sup> ITT population  
<sup>c</sup> Van Elteren Test (based on the underlying contingency table shown in End-of-Text Table 8.4a)  
Reference: End-of-Text Table 8.3a

**Table 53 Mean UPDRS Subscale Scores at Weeks 6 and 12**

UPDRS Subscale and Condition	Week 6 (1.25 mg/day)		Week 12 (2.5 mg/day)	
	Zydis selegiline	Placebo	Zydis selegiline	Placebo
<b>ADL "ON"</b>				
N	89	48	82	45
Mean (SD)	6.2 (5.4)	6.0 (4.5)	7.0 (6.2)	5.7 (5.0)
95% Ci <sup>a</sup>	(-1.3, -1.0)		(-1.3, -1.5)	
p-value <sup>b</sup>	0.843		0.869	
<b>ADL "OFF"</b>				
N	88	47	80	45
Mean (SD)	13.5 (6.3)	12.5 (5.2)	14.0 (7.3)	12.3 (5.7)
95% Ci <sup>a</sup>	(-0.9, -2.1)		(-1.3, -2.1)	
p-value <sup>b</sup>	0.431		0.635	
<b>Motor "ON"</b>				
N	88	46	82	45
Mean (SD)	13.9 (9.9)	14.5 (10.0)	15.5 (10.4)	13.5 (10.3)
95% Ci <sup>a</sup>	(-3.4, -1.8)		(-1.2, -3.9)	
p-value <sup>b</sup>	0.551		0.306	
<b>Motor "OFF"</b>				
N	86	45	77	44
Mean (SD)	27.9 (13.0)	24.0 (11.4)	27.4 (14.5)	25.0 (15.5)
95% Ci <sup>a</sup>	(-0.6, -6.1)		(-3.6, -3.2)	
p-value <sup>b</sup>	0.115		0.892	

<sup>a</sup> Confidence interval for Zydis selegiline versus placebo based on ANCOVA model  
<sup>b</sup> ANCOVA  
Reference: End-of-Text Table 9a

# CLINICAL REVIEW

## Clinical Review Section

### 13.4.3. Statistical Reviewer's Analysis of Primary Efficacy Results (ITT LOCF Dataset)

The statistical reviewer (Dr. F. Kong) replicated the sponsor's analyses according to the protocol. The results of this review are depicted in Table 54.

**Table 54**      **Percent Change in Values for Average Daily "OFF" Time During Waking Hours from Baseline to Endpoint ---ITT Population**

Primary Efficacy Parameters	Zydis selegiline (N=98)	Placebo (N=50)	P-value <sup>b</sup>
Baseline, Percentage "OFF" Time <sup>a</sup>			
Mean (SD)	41.8 (14.1)	41.7 (12.9)	0.98
Min, Max	18.6, 100.0	20.0, 72.4	
Average of Weeks 10-12 (%), (Dose=2.5 mg/day)			
N	93	48	0.127
Mean (SD)	-12.1 (17.8)	-7.4 (18.1)	
95% Confidence Interval <sup>c</sup>	(-11.0, 1.5)		

<sup>a</sup> Percent "OFF" time of total waking hours for ITT population defined as an average of reported "OFF" time for Weeks -2 and -1. <sup>b</sup> Comparison of treatment groups using ANOVA (with treatment, baseline, and center effects). <sup>c</sup> Computed for difference between changes in Zydis selegiline and placebo values.

The Shapiro-Wilks test indicates that the normality assumption holds for the primary endpoint of the reduction in percent "OFF" time from baseline. Therefore, the significant results in Table 54 are reliable. To assess the robustness of results, the statistical reviewer performed the Wilcoxon nonparametric test on the reduction from baseline of the percent "OFF". This test shows a p value = 0.2062. The result of the Wilcoxon test indicates the robustness.

The ANCOVA indicates that there is no center effect. Table 55 presents the reduction in percent "OFF" time made by each investigator. In the following table, Nselegiline and NPlacebo are the numbers of patients in ZS and Placebo groups, respectively. T is TTEST statistic performed on the difference of the mean reduction from baseline for unequal variances between two treatment groups.

Appears This Way  
On Original

# CLINICAL REVIEW

## Clinical Review Section

**Table 55 T Statistic by Investigator**

Obs	Invest	Nselegiline	NPlacebo	DIFF	t-Value
01	002	24	12	3.7	0.51
02	011	22	10	-0.3	-0.04
03	018	8	6	-22.2	-2.78
04	019	8	5	-18.8	-1.54
05	G51	5	3	-6.3	-0.73
06	G52	7	3	-6.7	-0.68
07	G53	7	3	0.53	0.06
08	G54	12	6	-5.3	-0.54

Most of the clinic centers show that the ZS reduces the daily "OFF" time compared to the placebo. Center 018 especially seems to have a high reduction that is statistically significant. However, because of the high variance, the overall reduction lacks statistical significance.

Table 56 shows the treatment difference by sex. DIFF is the mean change from baseline to week 10-12 on the percentage of "OFF" time. ZYDISDIFF is the difference between DIFF of ZS and Placebo.

**Table 56 Treatment Effect by Sex**

Sex	Therapy	Patient	DIFF	ZYDISDIFF	t-Value
Male	Zydis selegiline	64	-10.4	-2.14	-0.62
	Placebo	34	-8.3		
Female	Zydis selegiline	29	-15.9	-10.72	-1.56
	Placebo	14	-5.1		

Table 56 shows that ZS has a treatment effect in both male and female groups but it has a higher effect in the female group. However, none of the groups is statistically significant.

### Discussion of Study Results

The sponsor did not conduct the appropriate primary analysis of the primary efficacy endpoint in study Z/SEL/97/025 as it had not in study Z/SEL/97/026 (see Discussion of Study Results for study Z/SEL/97/026). The statistical analysis conducted by Dr. Kong, DNDP primary statistical reviewer, also did not find a statistically significant effect as was the case for the sponsor's multiple analyses. In contrast to study Z/SEL/97/026, Dr. Kong found a greater treatment effect in females in this study but results were not statistically significant for either sex.

Although studies Z/SEL/97/026 and Z/SEL/97/025 were planned as two pivotal trials identical in design, study Z/SEL/97/025 was not successful in showing a statistically significant difference for ZS over placebo for the primary efficacy endpoint in the primary population dataset (i.e. OC ITT) as did study Z/SEL/97/026. In study Z/SEL/97/025, the mean reduction in percentage "OFF" during waking hours for this primary efficacy endpoint (change of mean data from weeks

## CLINICAL REVIEW

### Clinical Review Section

10 and 12 vs baseline) was less (11.6 %) for the ZS group (2.5 mg/d) than that of the same group (13.1 %) in study Z/SEL/97/026. In addition, the mean reduction in percentage "OFF" during waking hours for the placebo group was greater (9.8 %) than that group (3.9 %) in study Z/SEL/97/026. These results translated to a much greater mean difference favoring ZS in study Z/SEL/97/026 (-9.2 %) than that difference (-1.8 %) observed in study Z/SEL/97/025. Although the responses of the ZS groups in both studies were quantitatively similar, the much greater response of the placebo group in study Z/SEL/97/025 (than that in study Z/SEL/97/026) was likely responsible for the lack of statistical difference for ZS showing efficacy as adjunctive therapy.

Whereas the co-efficient of variation ( $CV = SD/mean$ ) for the primary efficacy endpoint for ZS was less (112%) in study Z/SEL/97/026 than that (151 %) in Z/SEL/97/025, the CV for placebo was greater (269 %) for placebo in study Z/SEL/97/026 than that (152 %) in Z/SEL/97/025. Similar quantitative results for ZS and placebo treatment groups were also observed in study Z/SEL/97/025 near the middle of the whole study period (i.e. mean of weeks 4 and 6, toward the end of the treatment with low dose ZS-1.25 mg/d) as had been observed at the end of this study with 2.5 mg/d of ZS. The mean difference between the treatment groups was - 1.5 % (for mean change of weeks 4 and 6 vs baseline) in favor of ZS and this difference was similar in magnitude to that (-1.8 %) occurring at the end of the study with 2.5 mg/d of ZS.

The number of patients included in the ITT analysis of the primary prospectively designated population (i.e. OC) does not seem correct when one examines the Table 46 for the primary efficacy endpoint in each study relative to the Table 47 showing the responses at each visit. The primary efficacy analysis was supposed to be comprised of ITT patients in whom actual data were collected at weeks 10 and 12 in each study and averaged for comparison to baseline. By selecting the lowest number of patients studied at week 10 or 12 for each treatment group, it would appear that the appropriate number of patients to be analyzed for study Z/SEL/97/025 should be 84 (ZS) and 44 (placebo). In contrast, Table 15 shows that 89 and 46 patients comprised the primary analysis, suggesting 5 and 2 extra patients in each respective group. This discrepancy, with which the statistical reviewer concurs, has been pointed out to the sponsor and remains to be addressed.

It is not apparent why results from study Z/SEL/97/025 were negative for efficacy of ZS while results from study Z/SEL/97/026 were positive. There did not appear to be demographic differences between studies. Although there may be an increased risk of placebo effect by taking two pills after 6 weeks, this risk should be similar in both studies. The sponsor noted that the analysis by treatment center did not supposedly show any significant differences between these 2 studies that could explain a larger placebo response in study Z/SEL/97/025 and this was confirmed by Dr. Kong's analyses. However, it is interesting to note that study Z/SEL/97/026 involved a higher percentage of university medical school centers (e.g.  $8/16 = 50\%$ ) compared to study Z/SEL/97/025 ( $4/15 = 27\%$ ). Although the significance of this observation is unknown, conceivably a subgroup analysis of efficacy data derived from university medical school centers might be revealing, perhaps because of more rigorous data collection. Nevertheless, even if such a subgroup analysis did show greater efficacy in study Z/SEL/97/026 and statistically significant results in study 25, a clear or plausible explanation for the greater placebo response observed in

## CLINICAL REVIEW

### Clinical Review Section

study Z/SEL/97/025 would not be apparent.

In general, the magnitude of the treatment effect of ZS on the primary endpoint and some secondary endpoints was similar to that observed in study Z/SEL/97/026. However, the relatively large "response" in patients in the placebo groups is a plausible explanation for the lack of a statistically significant effect on the primary efficacy endpoint. Of interest, the p value for the analysis of the primary efficacy endpoint for the LOCF ITT dataset conducted by Dr. Kong was much lower ( $p = 0.127$ ) than that ( $p = 0.467$ ) obtained by the sponsor's analysis of the OC ITT dataset.

#### 13.4.4. Conclusions

##### Sponsor's Conclusions

The sponsor concludes that ZS at 2.5 mg/d over a period of 12 weeks did not produce a statistically significant treatment effect as adjunctive treatment with LD in patients exhibiting deterioration of their response to LD/CD because of the large placebo effect.

##### Reviewer's Conclusions

I believe that the sponsor's conclusion is reasonable. I further believe that given the robust results of study Z/SEL/97/026, the changes in the ZS group in study Z/SEL/97/025, and the apparent effects on multiple efficacy outcome measures in both pivotal trials, that one can view the results of this trial as supportive of the claim of substantial evidence of efficacy of ZS based primarily upon the robust results observed in study Z/SEL/97/026.

#### **13.5. Combined Efficacy Results and Analyses of Studies Z/SEL/97/026 and Z/SEL/97/025**

The sponsor has submitted a combined analysis of all efficacy endpoints for both pivotal studies Z/SEL/97/026 and Z/SEL/97/025 that were identical in design. This plan was a desire of the sponsor and was not requested by DNDP. DNDP had recommended that a large pivotal study be conducted instead of 2 separate, smaller with identical design but this was not done. In general, ZS group responses for efficacy endpoints in Z/SEL/97/025 study were similar to those of study Z/SEL/97/026. The main difference between results of these studies was that there appeared to be a much greater response of the placebo group for many efficacy parameters in study Z/SEL/97/025 compared to that of study Z/SEL/97/026. When data from both studies are combined, ZS was superior to placebo group for many of the efficacy endpoints as had been observed when study Z/SEL/97/026 had been analyzed separately. However, I have not reviewed the combined efficacy analyses in any significant detail. Because DNDP considers that the efficacy of this product (i.e. ZS) must be based upon the results of study Z/SEL/97/026, I will not present nor discuss the combined efficacy analyses in any greater detail.

## CLINICAL REVIEW

### Clinical Review Section

The combined analysis was not conducted by the sponsor using the ITT LOCF datasets as had been recommended and required by DNDP for the primary efficacy analysis.

Appears This Way  
On Original

**14. INTEGRATED SUMMARY OF SAFETY (ISS)****14.1. Summary of Process for Handling/Coding Adverse Events (AEs)**

I was unable to find a description in the ISS of how the sponsor approached treatment-emergent adverse events (TEAEs) and coded and compiled them starting from the initial recording of an AE by an investigator to compilation within a final study report and integration eventually into the ISS. No description had been provided in the NDA describing how adverse events (AEs) were handled/coded. The following information is based upon the sponsor's response to my inquiries of how were AEs handled/processed/coded.

AE data were initially handled like all other case report form (CRF) data (i.e. verbatim terms and associated information were entered into a database using double key entry procedures). The data management Clinical Research Organization (CRO) performed validation checks on the data, then AE verbatim terms were processed into COSTART terms using an autoencoder. Once the database was cleaned and all queries resolved, the database was locked and the blind was broken (in blinded studies). The "cleaned," locked database was then made available to the Biometrics division of the CRO for programming and generation of tables and listings as needed.

Studies Z/SEL/95/008, Z/SEL/95/008E, Z/SEL/96/014 and AN17933-101 initially used a MedDRA dictionary for coding AEs in the study reports. However, subsequently all AEs in these studies were recorded to COSTART terms and these COSTART terms were used for all the ISS tables and listings.

**There was no systematic collapsing of COSTART Preferred Terms during the generation of the AE tables or listings for the Study Reports or the ISS.** All "grouping" of terms was done in the text discussion of the ISS (e.g. pulling out and discussing all AE preferred terms related to oral AEs, or all terms related to blood pressure regulation, etc.).

AEs/SAEs should be reanalyzed using a systematic collapsing of similar preferred terms. Because there was no systematic collapsing of COSTART preferred terms during the generation of the AE/SAE tables or listings for the ISS, it is not possible to know if a certain AEs/SAEs (e.g. lightheadedness related to orthostatic hypotension) may have occurred more frequently than is apparent based upon the present analyses. These analyses did not consist of a systematic collapsing of various verbatim terms describing an event that may have been mapped to different preferred terms (e.g. syncope, near syncope, dizziness, light-headedness, postural dizziness or light-headedness, etc.). In addition, frequency tables illustrating the incidence of preferred terms for AEs/SAEs should always also specify preferred terms for the AEs/SAE rather than **only** indicating an organ system (e.g. special senses, skin and appendages, metabolic and nutritional) to which the preferred terms for the specific AEs/SAEs are related.

**14.2. Classification of Treatment Emergent Adverse Events (TEAEs)**

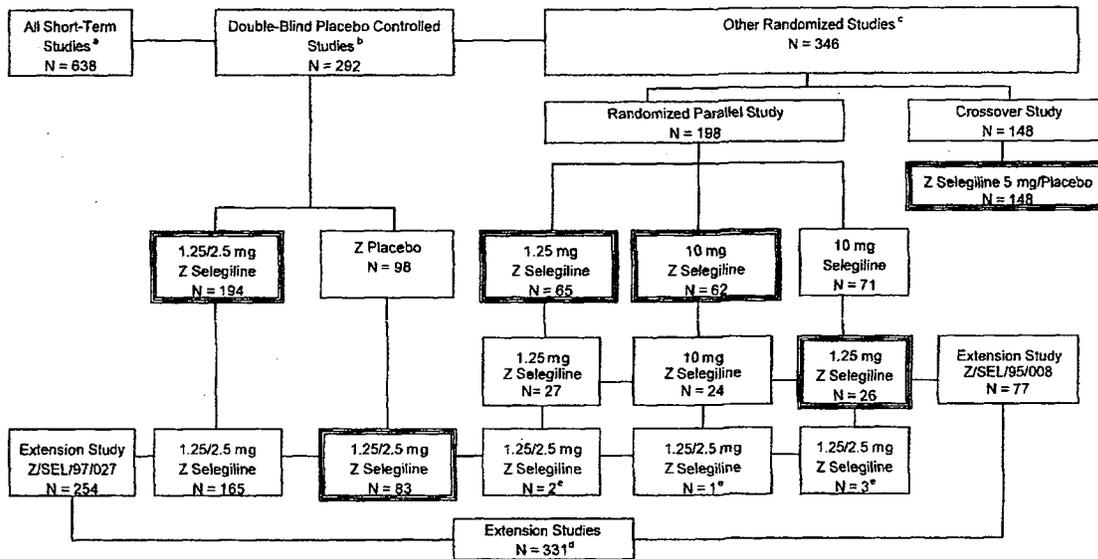
The clinical section (#8) contains final study reports for all clinical trials except study

# CLINICAL REVIEW

## Clinical Review Section

Z/SEL/94/026, the taste preference one day crossover study. Figure 15 shows the patient flow chart across all clinical studies.

**Figure 15 Patient Flow Chart Across Studies and Treatments**



Note: Triple-border boxes represent Zydys-naïve patients first exposure to Zydys selegiline.  
 a. All Short-Term Studies included Protocols Z/SEL/97/025, Z/SEL/97/026, Z/SEL/95/008, and Z/SEL/94/026.  
 b. The Double-Blind Placebo Controlled Studies included Protocols Z/SEL/97/025 and Z/SEL/97/026.  
 c. The Other Randomized Studies were Protocol Z/SEL/95/008 (Randomized Parallel Study) and Z/SEL/94/Z/SEL/97/026 (Crossover Study).  
 d. The Extension Studies included Protocols Z/SEL/97/027 and Z/SEL/95/008 Extension. Protocol Z/SEL/97/027 was an extension of the Double-Blind Placebo Controlled Studies and Protocol Z/SEL/95/008 Extension was an extension of Protocol Z/SEL/95/008.  
 e. Six patients in Protocol Z/SEL/95/008 Extension were enrolled into Protocol Z/SEL/97/027. Exposure to Zydys selegiline was not continuous for these 6 patients. The time period without exposure to Zydys selegiline ranged from 189 to 388 day for these 6 patients. Due to the large time period without exposure to Zydys selegiline between Protocols Z/SEL/95/008 Extension and Z/SEL/97/027, these 6 patients were counted twice in the denominator for the Extension Studies; once for their exposure in Protocol Z/SEL/95/008 and once for their exposure in Protocol Z/SEL/97/027.

In the ISS, the sponsor defined treatment-emergent adverse events (TEAEs) "as those adverse events that occurred between the first dose date and two days after the last dose date in the short-term, randomized studies and as an event occurring between the first dose date and 30 days after the last dose date in the extension Studies." A representative of the sponsor also confirmed that TEAEs would also include an AE that was present before treatment and that got worse during the treatment window presented.

A 2 day windowing convention for classifying AEs as TEAEs was applied to the short term studies (Z/SEL/97/025, Z/SEL/97/026, Z/SEL/95/008, and Z/SEL/94/026) and a 30 day windowing convention for classifying AEs as TEAEs was applied to extension studies (Z/SEL/95/008E, Z/SEL/97/027). The windowing convention for considering AEs as TEAEs in the ISS was the same as the windowing convention using for analyzing data in each study with the exception of studies Z/SEL/95/008E and Z/SEL/94/026. In study Z/SEL/95/008E a 2 day post-dose windowing convention was used. In study Z/SEL/94/026, a windowing convention period was not specified. Data collected in these studies were classified or reclassified as TEAEs according to the convention described above for analyzing TEAEs in the ISS.

## CLINICAL REVIEW

### Clinical Review Section

It is important and relevant to know about the follow-up conducted at the completion of each trial when trying to understand how comprehensively TEAE data may have been captured. Protocol reviews revealed that studies Z/SEL/97/025, Z/SEL/97/026, Z/SEL/95/008, and Z/SEL/95/008E provided for a formal follow-up visit approximately 2 weeks after completing the trial or withdrawing from the trial except when a patient entered an extension trial. There did not appear to be a specified follow-up time for collecting adverse events after the last treatment or discontinued dose in the extension trial (Z/SEL/97/027).

The present sponsor seemed to argue that the 2 day and 30 day cut-offs were the windowing conventions used for analyzing TEAEs because this was the policy practiced by each respective company (i.e. Scherer and Elan) for considering an AE as treatment-emergent. However, these specified cut-off periods were not identified within the protocols and both companies conducted studies Z/SEL/97/025, Z/SEL/97/026, and Z/SEL/97/027. Considering these observations, it appears that AEs occurring outside the protocol specified follow-up period were not captured systematically and would not be expected to provide a comprehensive picture of AEs occurring after that timepoint. For example, because there was no protocol specified follow-up after completion of extension study Z/SEL/97/027, it is difficult to understand the significance of AEs occurring within the 30 days cut-off period. Similarly, because the last follow-up visit in extension study Z/SEL/95/008E occurred approximately 14 days after the last dose, it is difficult to understand the significance of AEs that were considered TEAEs and occurred between 14 and 30 days after the last dose of study treatment. Finally, it may be of interest to note that most patients who completed a controlled trial entered an extension trial and would have had AE data collected in the extension phase. Thus, the proportion of subjects who did not enter an extension trial was relatively limited.

### 14.3. Deaths

Eight deaths occurred in the original NDA database out of a total number of 578 unique patients who had received at least 1 dose of Zydys selegiline (ZS). Eight deaths occurred in all studies up to the time of the data cut-off (6/30/01) and the database lock (10/17/01) and are found in the primary database. Regarding data accumulated prior to database lock, three deaths occurred in the randomized, open-label study (Z/SEL/95/008), and five deaths occurred in extension studies (1 in Z/SEL/95/008E and 4 in Z/SEL/97/027). There were no deaths in subjects who received ZS in pharmacokinetic (PK) studies. AEs and serious adverse events (SAEs) experienced in subjects who participated in PK studies are presented separately in the PK section of the NDA and are not contained nor integrated into the ISS. There was no analysis of mortality rates by the sponsor.

The sponsor's attributed cause of death consisted of various causes (e.g. cardiovascular, cancer, natural). No death was considered related to study drug. The sponsor considered all deaths as expected in an older population of patients (all > 65 years old).

The sponsor reported deaths in eight subjects in all the ZS trials in the primary database in the ISS up to the time of the data cutoff. Seven deaths occurred in patients treated with ZS and one

# CLINICAL REVIEW

## Clinical Review Section

occurred in a patient treated with conventional selegiline. All deaths were considered not to be related to any study drug. I reviewed the narrative summaries and CRTs for these deaths and have summarized these deaths in my own narratives. The patient's identification (ID) is designated by the patient's site (i.e. either last name of Principal Investigator at the site or site #) and the patient's number. Table 57 and Table 58 (created by sponsor) summarize some information about the 8 deaths.

### 14.3.1. Tabular Listing of Deaths

**Table 57 List of Deaths : Randomized Parallel Study**

Patient ID (Dose)	Age (Sex)	Verbatim (Preferred)	Onset (Days <sup>a</sup> )	End (Duration <sup>b</sup> )	Intensity	Related
Khanna-048 (Z SEL 10 mg)	73 (M)	Coronary Artery Thrombosis (Coronary Artery Disease)	8-25-96 (38)	<del>8-25-96</del> (0)	Severe	No
Selzer-217 (Z SEL 10 mg)	77 (M)	Myocardial Infarct (Myocardial Infarct)	9-9-97 (83)	<del>9-9-97</del> (4)	Severe	No
Park-053 (SEL 10 mg)	77 (M)	Ruptured Aneurysm, Abdominal Aorta (Vascular Disorder)	<del>9-9-97</del> (0)	<del>9-9-97</del> (0)	Severe	No

b(6)

b(6)

Protocol Z/SEL/95/008

Data Source: End-of-Text Listing 4

<sup>a</sup> Number of days from date of first dose dispensed to date of onset.

<sup>b</sup> Number of day from onset to end

**Table 58 List of Deaths : Extension Studies**

Protocol Patient ID (Dose)	Age (Sex)	Verbatim (Preferred)	Onset (Days <sup>a</sup> )	End (Duration <sup>b</sup> )	Intensity	Related
Z/SEL/95/008 ext Sergay-191 (Z SEL 10 mg)	83 (M)	Left Subacute Subdural Hematoma (Subdural Hematoma)	10-2-98 (457)	<del>10-2-98</del> (12)	Severe	No
		Right Anteromedial Frontal Subdural Hematoma (Subdural Hematoma)	10-2-98 (457)	<del>10-2-98</del> (12)	Moderate	No
Z/SEL/97/027 002-A64 (Z SEL 1.25/2.5 mg)	85 (M)	Death Due to Natural Causes (Death)	8-9-00 (398)	<del>8-9-00</del> (0)	Severe	No
Z/SEL/97/027 011-A50 (Z SEL 1.25/2.5 mg)	79 (F)	Cardiorespiratory Arrest (Heart Arrest)	9-29-98 (35)	<del>9-29-98</del> (5)	Severe	No
Z/SEL/97/027 108-Y24 (Z SEL 1.25/2.5 mg)	84 (F)	Sigmoid Volvulus (Gastrointestinal Disorder)	10-4-98 (101)	<del>10-4-98</del> ( $<1$ )	Severe	No
		Cardiac Arrest (Heart Arrest)	10-5-98 (102)	<del>10-5-98</del> ( $<1$ )		
Z/SEL/97/027 115-Z45 (Z SEL 1.25/2.5 mg)	65 (M)	Lung Cancer (Carcinoma of Lung)	12-9-99 (343)	<del>12-9-99</del> (425)	Severe	No

b(6)

b(6)

b(6)

b(6)

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

Data Source: End-of-Text Listing 4

<sup>a</sup> Number of days from date of first dose dispensed in Extension Study to date of onset.

<sup>b</sup> Number of day from onset to end

## CLINICAL REVIEW

### Clinical Review Section

#### 14.3.2. Narrative Description of Deaths

**Patient : Khanna/048 (Initials \_\_\_\_\_) in Study Z/SEL/95/008**

This 73 year-old male, who was enrolled in an open-label, active control study, "developed a coronary artery thrombosis and died in his sleep." This patient also had a significant medical history including myocardial infarction ('82) and asthma ('94). He had taken ZS (10 mg/d) for 38 days up to the time of death. This patient had experienced an SAE consisting of a hospitalization for an asthma attack 7 days after starting ZS. The attack resolved after increased asthmatic medical therapy. This SAE was considered unrelated to study drug. Eleven days later, the patient began experiencing "mild episodes of syncope" that resolved by the next day without any specific treatment. Death occurred eleven days later after resolution of syncope and was considered unrelated to study drug according to the investigator. Medications at the time of death included, Sinemet LS and CR, tabulation, prednisolone, Pulmicort, Frumil, and aspirin. There was no mention of an autopsy in the narrative summary and no documentation for a coronary artery thrombosis as opposed to categorizing this as a case of sudden death.

b(6)

**Patient : Selzer/217 (Initials \_\_\_\_\_) in Study Z/SEL/95/008**

This 77 year-old male, who was enrolled in an open-label, active control study, was hospitalized for a severe myocardial infarction that resulted in death. This patient also had a significant medical history that included hypertension, hypercholesterolemia, and diverticulosis. After 52 days of ZS, the patient had developed hypertension. He had been taking ZS (10 mg/d) for 70 days until he developed an AE, moderate insomnia, that prompted him to stop taking ZS and to withdraw from the study (8 days later). Thirteen days after discontinuing ZS the patient developed chest, abdominal, and arm pain, was admitted to a hospital, and diagnosed with a myocardial infarction. Four days later the patient experienced a second myocardial infarction that was fatal. Medications at the time of death included aspirin, heparin, captopril, metoprolol, atenolol, Zestril, nitroglycerine paste, Sinemet 250 CR, and Sinemet 125. There was no mention of an autopsy in the narrative summary. This SAE with a fatal outcome was considered by the investigator to be unrelated to study drug.

b(6)

**Patient : Park/053 (Initials \_\_\_\_\_) in Study Z/SEL/95/008**

This 77 year-old male/female, who was enrolled in an open-label, controlled study, "died in his sleep." No significant medical history was mentioned in the narrative summary. Fifteen days after taking conventional selegiline, the patient "experienced a fatal ruptured abdominal aortic aneurysm." The narrative summary did not specify the basis of diagnosing a ruptured aortic aneurysm as the cause of death and did not mention an autopsy. Medications at the time of death included Sinemet LS, praxilene, Zestril, and diazepam. This SAE with a fatal outcome was considered by the investigator to be unrelated to study drug.

b(6)

**Patient : Sergay/191 (Initials \_\_\_\_\_) in Study Z/SEL/95/008E**

This 83 year-old male, who was enrolled in an open-label extension study, died during hospitalization for bilateral subdural hematomas. This patient also had a significant medical

b(6)

## CLINICAL REVIEW

### Clinical Review Section

history including prostate cancer. Prior to entering the open-label study, the patient had received ZS in a placebo-controlled study. Approximately 3 weeks after receiving ZS (10 mg/d) in the open-label trial the patient developed a sideroblastic anemia and 9 months later the patient was diagnosed with chronic myelocytic leukemia and received unspecified treatment. Approximately 2.5 months after the diagnosis of leukemia, the patient exhibited decreased ambulatory skills, hesitant speech pattern and right lower leg tremors. The patient's ZS was stopped and 3 days later the patient was diagnosed as having SAEs consisting of bilateral subdural hematomas. Following a craniotomy and evacuation and drainage of the left hematoma the patient showed marked neurological improvement. However, 12 days alter surgery the patient died (no other clinical information prior to death was provided). These SAEs with a fatal outcome were considered by the investigator to be unrelated to study drug. This patient had taken ZS for a total of 15 months and died 14 days after the last does of ZS (10 mg/d). Possible medications at the time of death included vitamin C, vitamin B6, folic acid, Sinemet CR 250, l-thyroxine, Centrum A-Z, hydroxyurea, and Procrit. There was no specification of end dates for the possible medications at death and there was no mention of an autopsy in the narrative summary.

#### **Patient : 002/A64 (Initials : ) in Study Z/SEL/97/027**

This 85 year-old male, who was enrolled in an open-label extension study, "died due to natural causes" one day after admission to a nursing home. This patient also had a significant medical history including hypertension, carotid stenosis, S/P carotid endarterectomy, enlarged prostate, ulcers, diabetes, and macular degeneration. He had taken ZS (most recent dose 2.5 mg/d) for 13 months up to the time of death. Possible medications at the time of death included aspirin, Capoten, glyburide, Immodium, cimetidine, Sinemet, and pergolide. There was no specification of end dates for the possible medications at death and there was no mention of an autopsy in the narrative summary. This death was considered by the investigator to be unrelated to study drug.

#### **Patient : 011/A50 (Initials : ) in Study Z/SEL/97/027**

This 79 year-old female, who was enrolled in an open-label extension study, experienced a cardio-respiratory arrest and died 5 days later. No additional information was provided regarding the patient's course following the arrest and up to the time of death. This patient also had a significant medical history including atrial fibrillation, dyspnea, and fatigue. She had taken ZS (2.5 mg/d) for 34 days up to the time of the cardio-respiratory arrest at which time ZS was discontinued. Possible medications at the time of death included potassium phosphate, norepinephrine, lidocaine, digoxin, Sinemet and Sinemet CR, meclizine, lorabid, triamterene/HCTZ, lorazepam Coumadin, Cortisporin OTIC. There was no mention of an autopsy in the narrative summary. This SAE with a fatal outcome was considered by the investigator to be unrelated to study drug.

#### **Patient : 108/Y24(Initials : ) in Study Z/SEL/97/027**

This 84 year-old female, who was enrolled in an open-label extension study, was hospitalized for sigmoid volvulus that had a fatal outcome 1 day later after a cardiac arrest. This patient also had a significant medical history including hypertension, arrhythmia, hysterectomy, and hypothyroidism. She had taken ZS (2.5 mg/d most recent dose) for 3.5 months up until 2 days prior to the hospitalization for sigmoid volvulus. The reason ZS was withdrawn was not

## CLINICAL REVIEW

### Clinical Review Section

specified. It appeared that all other medications including Sinemet CR, amantadine, digoxin, "thyroid", and captopril were discontinued 3 days prior to death. There was no mention of an autopsy in the narrative summary. This SAE with a fatal outcome was considered by the investigator to be unrelated to study drug.

#### **Patient : 115/Z45(Initials . — ) in Study Z/SEL/97/027**

This 66 year-old male, who was enrolled in an open-label extension study, developed dyspnea prompting a hospitalization during which the patient was found to have a pleural effusion and pneumothorax and was diagnosed with lung cancer and metastatic adenocarcinoma. the patient was treated with a chest tube and chemotherapy including Gemzar and Carboplatin. Approximately 2 months after the diagnosis of lung cancer, the patient died as a result of this cancer. This patient also had a significant medical history including irregular heart rhythm and back pain. He had taken ZS (2.5 mg/d most recent dose) for approximately 13 months up to the time of death. Possible medications at the time of death included Sinemet, Sinemet CR, amantadine, ropinirole, diphenhydramine, Flexeril, aspirin, and Percocet. There was no specification of end dates for the possible medications at death and there was no mention of an autopsy in the narrative summary. This SAE with a fatal outcome was considered by the investigator to be unrelated to study drug.

b(6)

### 14.4. Serious Adverse Events (SAEs)

#### 14.4.1. Definition and Approach to Serious Adverse Events (SAEs)

The ISS did not specify a definition for serious adverse event (SAE). However, a definition for SAE derived from a Scherer protocol and an Elan protocol is provided here.

**Scherer definition** : *"A Serious Adverse Event is defined as any event which is fatal, life-threatening, disabling or incapacitating or results in hospitalisation, prolongation of a hospital stay or is associated with congenital abnormality, carcinoma or overdose."*

**Elan definition** : *"A serious adverse event is defined as any event which is fatal, immediately life-threatening, permanently disabling or incapacitating or results in hospitalization, prolongation of a hospital stay or is associated with congenital abnormality. A new diagnosis of cancer or a significant change in the baseline cancer status should be reported as an adverse event."*

The definitions by different sponsors were similar but not identical. For practical purposes, it seems that the definition for SAE was sufficiently similar to provide a useful compilation and analysis of SAEs in the ISS. Neither does it appear the either sponsor used the expanded definition for SAE described in U.S. CFR §312.32 for serious adverse drug experience :

*"Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon*

## CLINICAL REVIEW

### Clinical Review Section

*appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse."*

Consequently, any important medical event (i.e. AE) as described above would not necessarily be expected to be recorded as an SAE in this NDA.

The sponsor presented a narrative summary for each patient experiencing an SAE and interspersed treatment-emergent (TE) SAEs with SAEs that were not TE within a narrative summary and amongst narrative summaries. TE SAEs and non-TE SAEs were also mixed in data listings and designated by a symbol as TE or not TE. Generally, the quality of the narrative summary was poor and did not contain desired details to help a reader make an intelligent, reasonable assessment of what actually happened to a patient in real time.

The generally, poor quality of the narrative summary also made it difficult for me to make a reasonable causal assessment of whether the SAE was related to study drug. CRTs typically did not provide additional detail about SAEs/AEs to help compliment the narrative summary. In many instances, it appeared that information provided in the narrative summary was not contained in the NDA to allow a reviewer an opportunity to confirm the accuracy of information presented in the sponsor's narrative summary. In addition, study investigators frequently did not seem to take a conservative approach and consider SAEs as potentially "related" when I would have considered the SAEs as possibly related considering a conservative perspective. Categories for causal assessment of an SAE provided to investigators included : probably unrelated, unrelated, probably related, and related. The sponsor analyzed SAEs/AEs as "related" when was an investigator's assessment was "probably related" or "related" and as "unrelated" when an investigator's assessment was "probably unrelated" or "unrelated." Protocol guidelines for assessing relatedness of SAEs/AEs are presented here.

*"In assessing the likelihood of a causal relationship between study drug and adverse event, the investigator should take into account the nature of the disease for which the subject is being treated, any disease present and any concomitant drug treatment. The degree of certainty with which the relationship of an adverse event is linked to drug treatment will be determined by how well the event can be understood in terms of the known pharmacology of the drug, reactions of a similar nature being seen previously, the event having often been reported in the literature as drug related, e.g. skin rashes, blood abnormality, or the event being related by time to drug ingestion or reproduced on re-challenge."*

Such guidelines to investigators do not seem conservative and oriented to toward considering unexpected SAEs as potentially related to study drug. Instead, they seem biased toward assessing an SAE as "unrelated" when there was not a strong rationale supporting a "related" assessment. This approach seems to beg the question and make it more difficult to consider unexpected SAEs as potentially related to study drug.

## CLINICAL REVIEW

### Clinical Review Section

In the double-blind, placebo controlled trials, 9 ZS (1.25 or 2.5 mg/d) treated patients experienced 13 TE-SAEs and two placebo treated patients experienced 2 TE SAEs (Table 59 created by sponsor in ISS). Body as a whole was the most common category for ZS patients. The most frequent SAEs occurring in this category were accidental injury and chest pain, and none of these SAEs occurred in placebo treated patients. There did not appear to be an increased frequency of any SAEs according to dose of ZS.

In the randomized, parallel group active control trial, no specific TE-SAE appeared to stand out with respect to any treatment group (Table 60 created by sponsor in ISS).

TE-SAEs in the extension trials are illustrated in Table 61 (created by sponsor in ISS). Sixty patients treated with ZS (1.25 or 2.5 mg/d) experienced 99 TE-SAEs. The most frequent categories for TE-SAEs was body as a whole and cardiovascular system. The most common specific SAEs occurring on 4 or more occasions were backpain, accidental injury, chest pain, postural hypotension, and pneumonia. The much smaller number of patients exposed to high dose ZS (10 mg/d) makes it difficult to assess a dose response in SAEs.

The sponsor provided narrative summaries for all SAEs (TE and non-TE). I reviewed all of the sponsor's narrative summaries. In addition, I also reviewed CRTs, tables, and listings when warranted to help construct my own narrative summaries of selected SAEs of interest that warrant further description. Potentially pertinent past medical history was included in my narrative summaries.

Appears This Way  
On Original

**BEST POSSIBLE COPY**

# CLINICAL REVIEW

## Clinical Review Section

**Table 59 Treatment Emergent Serious Adverse Events : Double Blind Placebo Controlled Studies**

	Z SEL 1.25 mg	Z SEL 2.5 mg	Z SEL 1.25/2.5 mg	Z Placebo
Number Of Patients	194	178	194	98
Number of Patients With At Least One SAE	5 (2.6%)	4 (2.2%)	9 (4.6%)	2 (2.0%)
Number Of SAEs	9	4	13	2
Body as a Whole	3 (1.5%)	1 (0.6%)	4 (2.1%)	1 (1.0%)
Accidental Injury	1 (0.5%)	1 (0.6%)	2 (1.0%)	0 (0.0%)
Chest Pain	2 (1.0%)	0 (0.0%)	2 (1.0%)	0 (0.0%)
Cellulitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
Cardiovascular	1 (0.5%)	1 (0.6%)	2 (1.0%)	1 (1.0%)
Congestive Heart Failure	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)
Syncope	0 (0.0%)	1 (0.6%)	1 (0.5%)	0 (0.0%)
Atrial Flutter	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
Digestive	1 (0.5%)	1 (0.6%)	2 (1.0%)	0 (0.0%)
Colitis	1 (0.5%)	1 (0.6%)	2 (1.0%)	0 (0.0%)
Metabolic & Nutritional	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)
Edema	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)
Musculoskeletal	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)
Myasthenia	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)
Nervous	0 (0.0%)	1 (0.6%)	1 (0.5%)	0 (0.0%)
Depression	0 (0.0%)	1 (0.6%)	1 (0.5%)	0 (0.0%)
Urogenital	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)
Urination Impaired	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)

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

Data Source: Table 4.4.2a

Note: At each level of summarization, a patient was counted once if he /she reported one or more adverse events at that level.

Appears This Way  
On Original

# CLINICAL REVIEW

## Clinical Review Section

**Table 60 Treatment Emergent Serious Adverse Events : Other Randomized Studies**

	Randomized Parallel Studies			Crossover Study
	Z SEL 1.25 mg	Z SEL 10 mg	SEL 10 mg	Z SEL 5mg /Placebo
Number Of Patients	65	62	71	148
Number of Patients With At Least One SAE	4 (6.2%)	6 (9.7%)	5 (7.0%)	2 (1.4%)
Number Of SAE	5	7	5	2
Cardiovascular	1 (1.5%)	2 (3.2%)	2 (2.8%)	1 (0.7%)
Cardiomyopathy	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Coronary Artery Disease	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Myocardial Infarct	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cerebral Ischemia	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Syncope	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Vascular Disorder	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Body as a Whole	2 (3.1%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Hernia	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Accidental Injury	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Back Pain	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Urogenital	2 (3.1%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Prostatic Disorder	1 (1.5%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Urinary Tract Infection	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Digestive	0 (0.0%)	2 (3.2%)	0 (0.0%)	0 (0.0%)
Dyspepsia	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Gastrointestinal Disorder	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Hemic and Lymphatic	0 (0.0%)	1 (1.6%)	1 (1.4%)	0 (0.0%)
Anemia	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Lymphoma Like Reaction	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Respiratory	0 (0.0%)	2 (3.2%)	0 (0.0%)	0 (0.0%)
Asthma	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Pneumonia	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Skin and Appendages	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Skin Carcinoma	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)

Protocols Z/SEL/95/008 Extension and Z/SEL/94/026

Data Source: End-of-Text Table 4.4.2b

Note: At each level of summarization, a patient was counted once if he /she reported one or more adverse events at that level.

Appears This Way  
On Original

## CLINICAL REVIEW

### Clinical Review Section

**Table 61 Treatment-Emergent Serious Adverse Events Reported by >1 Patient in Either the Zydis Selegiline 1.25/2.5 mg or 10 mg Treatment Group : Extension Studies**

	Z SEL 1.25/2.5 mg <sup>a</sup>	ZSEL 10mg	Overall
Number Of Patients	307	24	331
Number of Patients With At Least One SAE	60 (19.5%)	8 (33.3%)	68 (20.5%)
Number Of SAE	99	13	112
Body as a Whole	21 (6.8%)	2 (8.3%)	23 (6.9%)
Back Pain	7 (2.3%)	0 (0.0%)	7 (2.1%)
Accidental Injury	5 (1.6%)	1 (4.2%)	6 (1.8%)
Chest Pain	5 (1.6%)	0 (0.0%)	5 (1.5%)
Aggravation Reaction	2 (0.7%)	0 (0.0%)	2 (0.6%)
Cardiovascular System	17 (5.5%)	1 (4.2%)	18 (5.4%)
Postural Hypotension	4 (1.3%)	0 (0.0%)	4 (1.2%)
Coronary Artery Disorder	2 (0.7%)	0 (0.0%)	2 (0.6%)
Heart Arrest	2 (0.7%)	0 (0.0%)	2 (0.6%)
Congestive Heart Failure	2 (0.7%)	0 (0.0%)	2 (0.6%)
Cerebral Ischemia	2 (0.7%)	0 (0.0%)	2 (0.6%)
Digestive System	10 (3.3%)	1 (4.2%)	11 (3.3%)
Cholelithiasis	3 (1.0%)	0 (0.0%)	3 (0.9%)
Respiratory System	11 (3.6%)	0 (0.0%)	11 (3.3%)
Pneumonia	6 (2.0%)	0 (0.0%)	6 (1.8%)
Dyspnea	2 (0.7%)	0 (0.0%)	2 (0.6%)
Nervous System	8 (2.6%)	2 (8.3%)	10 (3.0%)
Anxiety	3 (1.0%)	0 (0.0%)	3 (0.9%)
Dyskinesia <sup>a</sup>	3 (1.0%)	0 (0.0%)	3 (0.9%)

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

Data Source: End-of-Text Table 4.4.3

Note: At each level of summarization, a patient was counted once if he /she reported one or more adverse events at that level.

<sup>a</sup> The initial dose of Zydis selegiline in the Extension Studies was 1.25 mg for 53 patients and 2.5 mg for 254 patients.

Appears This Way  
On Original

**BEST POSSIBLE COPY**

## CLINICAL REVIEW

### Clinical Review Section

#### 14.4.2. Reviewer's Selected Treatment-Emergent SAE Narrative Summaries

##### SAEs Related to Accidental Injury, Trauma, Falls

**Patient Z/SEL/97/025 (015/C09)**, a 74 year old male with a history of vertigo, unilateral hearing loss, and hypertension, sustained mild lacerations and multiple bruises from a car accident and was admitted to a hospital. Lacerations and bruises were recorded as 2 separate SAEs.

This accident occurred 24 days after receiving ZS (1.25 mg/d). There was no specification about how the accident occurred and if the patient was driving the car. Approximately 1 week after the accident the lacerations and bruises resolved with treatment and the patient was discharged from the hospital. Both SAEs were assessed by the investigator as probably unrelated to study drug.

**Patient Z/SEL/97/025 (020/B66)**, a 76 year old male with a history of arthritis and back surgery, sustained a hip fracture after an accidental fall 65 days after starting ZS (2.5 mg/d most recent dose). No additional details were provided surrounding the occurrence of the hip fracture. The patient was hospitalized, underwent hip replacement surgery. Study drug was discontinued and the patient was withdrawn from the study. This SAE was assessed by the investigator as unrelated to study drug.

**Patient Z/SEL/95/008 (Mondal/058)**, a 72 year old male, sustained a severe accidental fall at home and was admitted to a hospital for observation. the patient had been taking conventional selegiline (10 mg/d) for two months. Physical therapy was initiated and the patient was discharged. This SAE was assessed by the investigator as unrelated to study drug.

**Patient Z/SEL/95/008E (Sergay/211)**, an 81 year-old male, fell in the shower and sustained a left fractured rib associated with a pleural effusion. The patient was diagnosed with a tension pneumothorax and admitted to the hospital. The patient had been taking ZS (1.25 mg/d as most recent dose) for approximately 8 months. The tension pneumothorax was noted to be resolved three days later and the patient was discharged. This SAE was assessed by the investigator as unrelated to study drug.

**Patient Z/SEL/95/008E (Siemers/136)**, a 76 year-old male with atrial fibrillation, hypokalemia, back, leg, and shoulder joint pain, fell on the ice and fractured his left ankle. The patient was diagnosed with a severe fracture dislocation of the left ankle and admitted to a hospital where he underwent surgical repair consisting of a plate and pins. He had been taking ZS (10 mg/d as most recent dose) for approximately 11 months. Study drug was temporarily interrupted but then restarted and the patient was discharged. This SAE was assessed by the investigator as unrelated to study drug.

**Patient Z/SEL/97/027 (002/A25)**, a 75 year-old male with a history of hip replacement and lower back disc herniation, experienced ataxia at home and fell. Three days later he was diagnosed with a fractured pelvis and hospitalized. Although surgery was not advised, physical therapy was initiated and the patient improved and was discharged. The patient had been taking

## CLINICAL REVIEW

### Clinical Review Section

ZS (2.5 mg/d as most recent dose) for approximately 7 months. This SAE was assessed by the investigator as unrelated to study drug.

**Patient Z/SEL/97/027 (008/B15)**, a 72 year old female with a history of hypotension and S/P cataract surgery, fell and experienced back pain. Approximately 1 month later, the patient sustained a left arm fracture from a fall associated with ataxic gait and the patient was admitted to a nursing home for rehabilitation on the next day. The patient had been taking ZS (2.5 mg/d as most recent dose) for approximately 3.5 months. The fracture was repaired by unspecified treatment. This SAE was assessed by the investigator as unrelated to study drug.

**Patient Z/SEL/97/027 (008/B15)**, a 67 year-old male with a history of tinnitus, severed his left thumb at the metacarpophalangeal joint while using a table saw. He had been taking ZS (unable to find/document most recent dose) for approximately 22.5 months but ZS had been discontinued (for unspecified reason) 18 days prior to severing the thumb. The patient was admitted to a hospital, underwent surgical repair and was discharged. This SAE was assessed by the investigator as unrelated to study drug.

**Patient Z/SEL/97/027 (102/X35)**, a 59 year-old female with history of diplopia and visual focusing, S/P right cataract surgery, back pain, sciatica, depression, and hypothyroidism, sustained a right arm fracture after tripping and falling into a door. She was diagnosed with a "splint bone" but admitted to a hospital for pain management. Subsequently, further evaluation revealed a spiral fracture of the humerus that was casted. She had been taking ZS (2.5 mg/d as most recent dose) for approximately 13 months. The patient was discharged from the hospital and transferred to a rehabilitation facility. Nineteen days after sustaining the fracture she re-fractured her right arm (details not provided) and arm immobilization was re-applied. This SAE was assessed by the investigator as probably unrelated to study drug.

**Patient Z/SEL/97/027 (104/Y92)**, a 54 year-old male with a history of intermittent orthostatic hypotension and anxiety, experienced frequent falling episodes that were associated with choreic movements, freezing episodes, and anxiety. He was admitted to a hospital for the falling episodes and re-titration of Parkinson's disease's medications. He had been taking ZS (2.5 mg/d as most recent dose) for nearly 2 months. The patient was subsequently discharged without any change in study drug and the frequent falling episodes continued. Approximately 5 weeks after admission a CRF for a visit on 1/5/00 shows moderate orthostatic hypotension for systolic BP and borderline orthostatic hypotension for diastolic BP (i.e. supine 142/88, sitting 112/86, standing 114/78) without a significant rise in pulse after sitting or standing. It is not specified whether any symptoms were associated with these changes. This SAE was assessed by the investigator as probably unrelated to study drug and possibly due to anxiety-related exacerbation of Parkinson's disease. The patient subsequently developed moderate depression, ZS was discontinued, and the patient withdrew from the study 6 days after developing depression. Of interest, the narrative notes that the patient "developed mild orthostatic hypotension that resolved the same day and was reported as probably unrelated to study drug." An AE for orthostatic hypotension (without VS recordings) on the study withdrawal date can be found in the CRTs and the CRF notes that there was no action taken with regard to study drug. However, there is no completed CRF for the study withdrawal.

## CLINICAL REVIEW

### Clinical Review Section

**Patient Z/SEL/97/027 (104/Y94)**, a 74 year-old male with a history of mild asymptomatic orthostatic hypotension, pernicious anemia, anxiety, depression, and angina, "developed intermittent severe lightheadedness and intermittent, mild vasovagal episodes" on the day of enrolling in an open label extension trial after having received ZS in a double-blinded, placebo-controlled trial. One month later the severe lightheadedness and vasovagal episodes resolved, but the patient experienced a near-syncopal episode that resolved with unspecified treatment two months later. After approximately 6 months, the patient developed lightheadedness, pallor, diaphoresis after taking both morning and afternoon doses of Sinemet, quetiapine, and ropinirole. In the clinic the patient was drowsy, exhibited severe orthostatic hypotension (BPs supine 120/70, sitting 80/50, standing 50 /unobtainable), and was admitted to a hospital for severe symptomatic (lightheadedness, pallor, diaphoresis, drowsiness) orthostatic hypotension. He had been taking ZS (2.5 mg/d as most recent dose) for 12 months. ZS was discontinued on the day of admission and the patient withdrew from the study because of severe orthostatic hypotension. Five days later the orthostatic hypotension resolved without treatment. This SAE was assessed by the investigator as unrelated to study drug and "possibly related to the subject taking morning and afternoon doses of Parkinson's disease medications on \_\_\_\_\_ simultaneously."

u(6)

b(6)

#### SAEs Related to Chest Pain/Discomfort, Myocardial Ischemia/Infarction

**Patient Z/SEL/97/025 (018/C29)**, a 61 year old male, with a history of diabetes, and possible left atrial enlargement with minimal ST elevation in inferior ECG leads, experienced acute onset of mild chest pressure upon awakening and was admitted to a hospital. He had received ZS (1.25 mg/d) for 42 days. Laboratory tests and ECG did not indicate a cardiac event. The chest pressure resolved with IV Ativan treatment and the patient was discharged from the hospital on the same day. This SAE was assessed by the investigator as probably unrelated to study drug.

**Patient Z/SEL/97/026 (105/X66)**, with a history of coronary artery disease, myocardial infarction, S/P angioplasty, hypertension and exertional dyspnea, and nitroglycerine use, experienced severe chest pain in the recovery room immediately after undergoing a transurethral resection of the prostate. The patient had been treated with ZS (1.25 mg/d) for 14 days. ECG and serial enzymes ruled out a myocardial infarction. After failing a stress test, the patient underwent an angiogram that showed a 90 % occlusion of the right coronary artery and underwent stent placement. The patient's chest pain resolved and the patient was discharged from the hospital. Study drug that had been interrupted was resumed. This SAE was assessed by the investigator as unrelated to study drug.

**Patient Z/SEL/95/008 (Koller/181)**, a 69 year-old male with a history of left ventricular hypertrophy and hypercholesterolemia, was hospitalized for a severe myocardial infarction that had developed after 17 days of ZS (1.25 mg/d). Cardiac catheterization showed total occlusion of the right distal artery. A stent was placed after angioplasty, medical therapy was initiated, and the patient was discharged from the hospital. This SAE was assessed by the investigator as probably unrelated to study drug.

## CLINICAL REVIEW

### Clinical Review Section

**Patient Z/SEL/95/008 (Selzer/217)**, a 77 year-old male with a history of hypertension and hypercholesterolemia, was hospitalized for a severe myocardial infarction that resulted in death. After 52 days of ZS, the patient had developed hypertension. He had been taking ZS (10 mg/d) for 70 days until he developed an AE, moderate insomnia, that prompted him to stop taking ZS and to withdraw from the study (8 days later). Thirteen days after discontinuing ZS the patient developed chest, abdominal, and arm pain, was admitted to a hospital, and diagnosed with a myocardial infarction. Four days later the patient experienced a second myocardial infarction that was fatal. Medications at the time of death included aspirin, heparin, captopril, metoprolol, atenolol, Zestril, nitroglycerine paste, Sinemet 250 CR, and Sinemet 125. There was no mention of an autopsy in the narrative summary. This SAE with a fatal outcome was considered by the investigator to be unrelated to study drug.

**Patient Z/SEL/95/008E (Kelly/102)**, a 67 year old male with a history of coronary artery disease, hypertension, diabetes mellitus, hypercholesterolemia, and medically treated hypothyroidism, developed exertional chest pain and dyspnea, diaphoresis, and left arm numbness prompting hospitalization. ECG revealed "repolarization abnormalities" and a diagnosis of unstable angina was made. The patient had been treated for approximately 6 months with ZS (1.25 mg/d as most recent dose). Angioplasty was performed after an angiogram and the unstable angina resolved. This SAE was considered by the investigator as probably unrelated to study drug.

**Patient Z/SEL/95/008E (Tanner/288)**, a 77 year old male who was S/P coronary artery graft surgery, mitral valve replacement, and pacemaker placement and had previously developed chest pain, hypertension and hypercholesterolemia, experienced severe chest pain prompting hospitalization. He underwent coronary artery bypass surgery, the chest pain resolved, and the patient was discharged. The patient had been treated for approximately 6 months with ZS (1.25 mg/d as most recent dose). These SAEs (# 1 chest pain, # 2 graft surgery) were considered by the investigator as unrelated to study drug.

**Patient Z/SEL/97/027 (011/A58)**, a 74 year-old male with a history of myocardial infarction (x 2), S/P coronary artery bypass graft, S/P angioplasty, paroxysmal atrial fibrillation, and peripheral atherosclerosis, was awakened by severe chest pain associated with diaphoresis, left arm pain, and "racing heart." He was diagnosed as having atrial fibrillation with a rapid ventricular response and admitted to a cardiac ICU. The chest pain abated and a normal sinus rhythm resumed after medical therapy. The patient had been treated for approximately 10 months with ZS (2.5 mg/d as most recent dose). During this hospitalization, hypercholesterolemia was diagnosed and a myocardial infarction was excluded. He was discharged from the hospital. This patient's experience was considered by the investigator as probably unrelated to study drug.

**Patient Z/SEL/97/027 (01/B72)**, a 48 year-old male with a history of cardiomyopathy, hypertension, and multiple PVCs, experienced vague non-radiating chest discomfort, moderate dyspnea, and bilateral ankle swelling. Four days later the patient presented to an emergency room with increased dyspnea and ankle swelling, was diagnosed with congestive heart failure with pulmonary edema, and was admitted to the hospital and treated for congestive heart failure

## CLINICAL REVIEW

### Clinical Review Section

and pulmonary edema. The patient had been treated for approximately 13 months with ZS (2.5 mg/d as most recent dose). Cardiac testing revealed single vessel coronary disease. The congestive heart failure resolved with treatment and the patient was discharged. This SAE was considered by the investigator as unrelated to study drug.

**Patient Z/SEL/97/027 (019/C15)**, a 64 year-old male with a history of angina, hypertension, and possible stroke, was admitted to a hospital for evaluation of chest pain. The patient had developed bilateral lower extremity pain and two weeks later was treated with manipulation of the chest and back areas and dexamethasone. Nearly one month later the patient experienced the chest pain prompting hospitalization. He had been taking ZS (2.5 mg/d as the most recent dose) for approximately 7 months. An ECG did not reveal anything clinically significant, the chest pain resolved with unspecified treatment, and the patient was discharged. This SAE was considered by the investigator as unrelated to study drug.

**Patient Z/SEL/97/027 (111/Y44)**, a 55 year-old male with a history of hypertension, developed chest pain associated with dyspepsia and was admitted to a hospital for evaluation. He had been taking ZS (2.5 mg/d as the most recent dose) for approximately 3.5 months. A cardiac evaluation was negative, the chest pain resolved with unspecified treatment, and the patient was discharged without a change in ZS. This SAE was considered by the investigator as unrelated to study drug.

**Patient Z/SEL/97/027 (112/Y75)**, a 63 year-old female with a history of angina and hypertension developed chest pain that because severe prompting hospitalization for cardiac evaluation. A stress test and angiogram did not reveal any abnormalities. Treatment with nifedipine XL, isosorbide, and aspirin was initiated, the patient's chest pain resolved, and the patient was discharged. There was no action taken with study drug. This SAE was considered by the investigator as unrelated to study drug.

**Patient Z/SEL/97/027 (118/Z67)**, a 55 year-old male with a history of hypertension, hypercholesterolemia, developed chest pain one hour after taking ZS and other medications. The patient presented at an emergency room with hypotension (BP 80/50 mm Hg) and was admitted for evaluation and treatment. He had been taking ZS (2.5 mg/d as the most recent dose) for approximately 10 months. ECG showed normal sinus rhythm with occasional PVCs. The chest pain, that resolved after unspecified treatment, was thought to be stress-induced. The patient was discharged without any action taken for study drug. This SAE was considered by the investigator as unrelated to study drug.

#### SAEs Related to Syncope, Near Syncope, Vertigo/Dizziness or Orthostatic Hypotension

**Patient Z/SEL/94/026 (McKeraan/183)**, a 76 year-old male, 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 conventional Eldepryl (i.e. 5 mg BID) and ZS 5 mg on the same day. More specifically, he experienced nausea in the middle of the night (2 am), got up to go to the bathroom, felt faint and passed out and

## CLINICAL REVIEW

### Clinical Review Section

regained consciousness after 10 minutes. The patient was examined by physician and recovered within 3-4 hours without treatment. The patient was participating in a study to assess tolerability of ZS vs selegiline and was supposed to omit his routine second dose of oral selegiline (5 mg) at noon after having taken his oral selegiline (5 mg) in the am. By mistake the patient forgot to omit the noon oral selegiline and took this in addition to the study drug ZS (5 mg). This overdose was considered an SAE that the investigator assessed as probably related to study drug.

**Patient Z/SEL/97/025 (011/B55)**, a 78 year old male with a history of orthostatic hypotension, Shy-Drager syndrome, bradycardia, coronary artery disease, and S/P coronary artery angioplasty with stent placement, experienced a syncopal episode almost 3 months after receiving ZS (2.5 mg/d most recent dose) and was hospitalized. The patient underwent cardiac catheterization with stent replacement. A few days later, the patient's syncopal episode was noted to have resolved without specific treatment study drug that had been temporarily interrupted was restarted, and the patient was discharged from the hospital. This syncopal event was assessed by the investigator as probably unrelated to study drug.

**Patient Z/SEL/95/008E (Sergay/204)**, a 67 year-old male developed dizziness after taking ZS (1.25 mg/d as most recent dose) for approximately 15 months and was hospitalized. The patient was diagnosed with benign positional vertigo. Four days later the vertigo resolved after unspecified treatment and was discharged. An MRI revealed a benign, hypertrophic choroid plexus. This SAE was assessed by the investigator as unrelated to study drug.

**Patient Z/SEL/97/027 (011/B55)**, a 79 year-old male with a history of Shy-Drager syndrome, orthostatic hypotension, coronary artery disease, and S/P angioplasty and stent placement, was hospitalized for evaluation of severe Shy-Drager syndrome that was associated with depression and visual hallucinations. The patient had been treated for approximately 8 months with ZS (2.5 mg/d as most recent dose). Fluoxetine was given for the depression and the patient was discharged with severe Shy-Drager syndrome that was not treated. This SAE was assessed by the investigator as unrelated to study drug.

**Patient Z/SEL/97/027 (103/X21)**, a 76 year-old female with a history of hypertension, bilateral carotidarterectomy, and anxiety, experienced intermittent episodes of mild postural hypotension, and fell and "passed out" four times. The patient was admitted to a hospital for evaluation of severe orthostatic hypotension. The patient had been treated for approximately 27 months with ZS (2.5 mg/d as most recent dose). Holter monitoring showed 4 episodes of supraventricular beats and non-sustained ventricular tachycardia (longest run = 7 beats). Blood pressure readings showed greater than 50-point drop between supine and standing position readings. Specific BP or pulse readings were not specified (no VS showing orthostatic hypotension found in CRTs). ZS was withdrawn on the day after admission because of the orthostatic hypotension. The patient experienced episodes of labile BP readings and her BP eventually stabilized on oral labetalol for hypertension. The patient was discharged and instructed to keep her mattress in reverse Trendelenberg. The severe orthostatic hypotension had resolved and there was no significant orthostatic hypotension 17 days after discontinuing ZS. This SAE was assessed by the investigator as unrelated to study drug but possibly related to Shy-Drager syndrome. However, it is not clear why this was considered because I was not able to

## CLINICAL REVIEW

### Clinical Review Section

document that the patient had Shy-Drager syndrome in the narrative summary, CRTs, nor in the case report tabulations (CRTs) for past medical history and concurrent conditions.

**Patient Z/SEL/97/027 (104/Y18)**, a 69 year-old male with a history of orthostatic hypotension, hypercholesterolemia, restless leg syndrome, depression, and anxiety, was admitted to a hospital for evaluation of orthostatic hypotension, severe dyspnea and diaphoresis two days after he "developed moderate orthostatic hypotension." He had been treated for approximately 5 months with ZS (2.5 mg/d as most recent dose). In the clinic prior to hospitalization BP readings were 120/70 mm Hg while supine, 110/70 mm Hg while sitting, and 110/70 mm hg after standing. Telemetry was started and an echocardiogram revealed valve insufficiency and mitral valve regurgitation. A myocardial infarction was excluded. Two days after admission BP was 106/68 mm Hg sitting and 74/54 mm Hg standing but the patient was asymptomatic. After treatment with nadolol the patient's severe orthostatic hypotension, dyspnea, and diaphoresis resolved and the patient was discharged. Approximately 2 weeks later the patient developed moderate hypertension (BPs, supine 180/106, standing 180/90), proamitine dose was discontinued, and hypertension resolved. This SAE of orthostatic hypotension was assessed by the investigator as unrelated to study drug but possibly related to the patient's Parkinson's disease.

**Patient Z/SEL/97/027 (104/Y81)**, a 60 year-old female with a history of stress incontinence, experienced a sever near-syncopal episode prompting hospitalization. She had been treated for approximately 6.5 months with ZS (2.5 mg/d as most recent dose). The patient's near syncope resolved on the same day and the patient was subsequently discharged without a change in study drug. This SAE was assessed by the investigator as probably unrelated to study drug.

#### Liver / Hepatic Related SAEs

**Patient Z/SEL/95/008E (Kelly/225)**, a 67 year old female, was hospitalized after presenting with a few day history of abdominal pain, malaise, nausea, vomiting, poor oral intake, and epigastric pain that worsened with coughing, eating, and hiccups. An gallbladder ultrasound revealed cholelithiasis. Upper endoscopy showed 3 linear gastric ulcers in the stomach body and antrum and granular erythematous mucosa. An abdominal CT revealed a renal cyst. Laboratory evaluation showed a mild elevation of serum alkaline phosphatase and serum GGT but no elevation in serum ALT or AST. "The patient was diagnosed with cholelithiasis, severe gastritis, and moderate hepatitis. The patient's cholelithiasis and hepatitis resolved without treatment, and the patient's gastritis resolved with treatment." Study drug was discontinued and the patient was discharged from the hospital. These events were assessed by the investigator as probably unrelated to study drug.

#### Hematological Related SAEs

**Patient Z/SEL/95/008 (Kelly/062)**, a 76 year old female, was diagnosed with moderately severe anemia (hemoglobin - 6.8 g/dL and hematocrit - 22.6%) and hospitalized for treatment and

## CLINICAL REVIEW

### Clinical Review Section

evaluation approximately one month after receiving ZS (10 mg/d). Hemocult results were negative. GI evaluation revealed 2 small polyps that were removed and "numerous bleeding perforations" on upper endoscopy. The patient received packed RBCs as treatment and experienced resolution of the anemia approximately 2 months later "with treatment." This event was assessed by the investigator as probably unrelated to study drug.

**Patient Study Z/SEL/95/008E (Sergay/191)**, an 83 year-old male with a history of prostate cancer developed a sideroblastic anemia and subsequently chronic myelocytic leukemia. Approximately 3 weeks after receiving ZS (10 mg/d) in the open-label trial the patient developed a sideroblastic anemia and 9 months later the patient was diagnosed with chronic myelocytic leukemia and received unspecified treatment. Approximately 2.5 months after the diagnosis of leukemia, the patient exhibited decreased ambulatory skills, hesitant speech pattern and right lower leg tremors. The patient's ZS was stopped and 3 days later the patient was diagnosed as having SAEs consisting of bilateral subdural hematomas. Following a craniotomy and evacuation and drainage of the left hematoma the patient showed marked neurological improvement. However, 12 days after surgery the patient died (no other clinical information prior to death were provided). These SAEs with a fatal outcome were considered by the investigator to be unrelated to study drug. This patient had taken ZS for a total of 15 months and died 14 days after the last does of ZS (10 mg/d). Possible medications at the time of death included vitamin C, vitamin B6, folic acid, Sinemet CR 250, l-thyroxine, Centrum A-Z, hydroxyurea, and Procrit. There was no specification of end dates for the possible medications at death and there was no mention of an autopsy in the narrative summary.

#### Overdose Related SAEs

There were no SAEs in patients related to an overdose of ZS alone. However, one patient experienced an SAE due to an overdose from taking both conventional selegiline and ZS. This patient developed hypotension and a brief episode of syncope in a single-dose cross-over taste preference study (Z/SEL/94/026) after mistakenly receiving both 10 mg of conventional Eldepryl (i.e. 5 mg BID) and ZS 5 mg on the same day. A more detailed narrative summary was presented earlier under another section (e.g. SAEs Related to Syncope, Near Syncope, Vertigo/Dizziness or Orthostatic Hypotension).

#### SAEs Related to Hypertensive Crisis or Serotonin Syndrome

There were no SAEs related to hypertensive crisis or serotonin syndrome with ZS.

#### SAEs Related to Serious Rash or Non-Malignant Dermatological Reactions

There were no SAEs related to serious skin reaction, rash, or non-malignant skin conditions.

Auxiliary SAEs

Some SAEs were received by the sponsor after the data cutoff (6/30/01) and preliminary information on these SAEs are presented in narrative summaries in a section termed "Auxiliary Events." The sponsor plans to present these SAEs/AEs in the 120 day Safety Update to the NDA. These SAEs are not reviewed here at this time but will be reviewed eventually in the Safety Update. A preliminary review of these SAEs does not suggest any additional safety concerns other than those raised by SAEs and deaths in the primary safety database.

**14.5. Dropouts, Study Discontinuations/Withdrawals due to Adverse Events and Overall Disposition of Patients****14.5.1. Disposition of Patients**

The overall disposition of patients in all Parkinson's disease trials can be seen in Table 62, Table 63, and Table 64 taken from the sponsor's ISS. In the double-blind, placebo-controlled trials (Table 62), the percent of patient withdrawals for any reason was similar for both groups with 9.3 % for ZS and 8.2 % for placebo. Whereas adverse event (5.2 %) was the most common reason for withdrawal in the ZS group, the most common reason for withdrawal in the placebo group was "other" (4.1%). In the other randomized studies (Table 63), all withdrawals occurred in Study Z/SEL/95/008. The percent of patient withdrawals was greater with low dose ZS (1.25 mg/d; 20.0 %) and high dose ZS (10 mg/d; 22.6 %) than with oral selegiline (10 mg/d; 12.7 %). Adverse event was the most common reason for withdrawal in the low dose ZS group (10.8 %) and oral selegiline group (5.6 %), but adverse event was the most common reason for withdrawal in the high dose Zs group (11.3 %). In the extension studies (Table 64), the percent of patient withdrawals for any reason was 40.1 % in the low dose ZS group (i.e. 1.25 or 2.5 mg/d) and 20.8 % in the high ZS group (i.e. 10 mg/d). However, the total number of patients in the high dose ZS groups was much smaller (24) than the number (307) in the low dose group. Adverse event was the most common reason for study withdrawal in the low dose ZS group (14.0 %), and "other" was the most common reason for study withdrawal in the high dose ZS group (12.5 %).

Appears This Way  
On Original

## CLINICAL REVIEW

### Clinical Review Section

**Table 62 Disposition of Patients : Double-Blind Placebo Controlled Studies**

	Z Placebo	Z selegiline	Overall
Total <sup>a</sup>	98	194	292
Completed Study	90 (91.8%)	176 (90.7%)	266 (91.1%)
Withdrawn	8 (8.2%)	18 (9.3%)	26 (8.9%)
Reason for withdrawal			
Adverse events	1 (1.0%)	10 (5.2%)	11 (3.8%)
Protocol deviation	2 (2.0%)	2 (1.0%)	4 (1.4%)
Lost to follow-up	0 (0.0%)	2 (1.0%)	2 (0.7%)
Lack of efficacy	1 (1.0%)	1 (0.5%)	2 (0.7%)
Other	4 (4.1%)	3 (1.5%)	7 (2.4%)

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

Data Source: End-of-Text Table 1.2.1a

<sup>a</sup> Total number of patients in the safety population.

**Table 63 Disposition of Patients : Other Randomized Studies**

	Randomized Parallel Study (Z/SEL/95/008)				Crossover Study (Z/SEL/94/026)
	Z SEL 1.25 mg	Z SEL 10 mg	SEL 10 mg	Overall	Z SEL 5 mg/Placebo
Total <sup>a</sup>	65	62	71	198	148
Completed Study	52 (80.0%)	48 (77.4%)	62 (87.3%)	162 (81.8%)	148 (100.0%)
Withdrawn	13 (20.0%)	14 (22.6%)	9 (12.7%)	36 (18.2%)	0 (0.0%)
Reason for withdrawal					
Adverse events	0 (0.0%)	7 (11.3%)	3 (4.2%)	10 (5.1%)	0 (0.0%)
Protocol deviation	4 (6.2%)	2 (3.2%)	2 (2.8%)	8 (4.0%)	0 (0.0%)
Lack of efficacy	2 (3.1%)	0 (0.0%)	0 (0.0%)	2 (1.0%)	0 (0.0%)
Other	7 (10.8%)	5 (8.1%)	4 (5.6%)	16 (8.1%)	0 (0.0%)

Protocols Z/SEL/95/008 and Z/SEL/94/026

Data Source: End-of-Text Table 1.2.1b

<sup>a</sup> Total number of patients in the safety population.

Appears This Way  
On Original

# CLINICAL REVIEW

## Clinical Review Section

**Table 64      Disposition of Patients : Extension Studies**

	Previous Placebo <sup>b</sup>	Extension Studies		Overall
		Z SEL 1.25/2.5 mg	Z SEL 10 mg	
Total <sup>a</sup>	83	307	24	331
Completed Study	3 (3.6%)	52 (16.9%)	19 (79.2%)	71 (21.5%)
Ongoing	37 (44.6%)	132 (43.0%)	0 (0.0%)	132 (39.9%)
Withdrawn	43 (51.8%)	123 (40.1%)	5 (20.8%)	128 (38.7%)
Reason for withdrawal <sup>b</sup>				
Adverse events	20 ( 24.1%)	43 (14.0%)	2 (8.3%)	45 (13.6%)
Protocol deviation	0 ( 0.0%)	6 (2.0%)	0 (0.0%)	6 (1.8%)
Lost to follow-up	1 ( 1.2%)	5 (1.6%)	0 (0.0%)	5 (1.5%)
Lack of efficacy	9 ( 10.8%)	29 (9.4%)	0 (0.0%)	29 (8.8%)
Other	13 ( 15.7%)	40 (13.0%)	3 (12.5%)	43 (13.0%)

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

Data Source: End-of-Text Table 1.2.2

<sup>a</sup> Total number of patients in the safety population.

<sup>b</sup> Of the 331 patients enrolled in the Extension studies, 83 patients had previously been randomized to Zydys placebo in the original studies and started on Zydys selegiline in the Extension studies.

### 14.5.2. Dropouts, Study Discontinuations/Withdrawals due to Adverse Events

This section will focus on patients who withdrew from a study because of one or more adverse event. In the double-blind, placebo controlled studies, eleven patients (1-placebo; 10 ZS, with 7 receiving 1.25 mg/d and 3 receiving 2.5 mg/d) experienced 22 adverse events that led to study withdrawal (Table 65 created by sponsor in ISS). Most commonly they were related to the central nervous system (CNS). Three of these AEs were considered to be SAEs and eleven were considered to be related to study drug. With regard to intensity, 12 were mild, 5 were moderate, and 5 were severe. Mild was the most common (50 %) categorization for AE severity. The single patient who withdrew for an AE in the placebo group experienced dizziness and confusion that were judged to be mild in severity and related to study drug. One additional patient (019/A13) experienced AEs of anxiety, insomnia, and hypertension and discontinued the study drug ZS (1.25 mg/d) but the reason for withdrawal in the CRF that was never completed was coded as other during the data clean-up phase. Although the hypertension was considered mild and related to study drug, the anxiety and insomnia were considered moderate and probably not related to

## CLINICAL REVIEW

### Clinical Review Section

study drug. The patient was recorded as withdrawing from the study approximately 6 weeks after taking the last dose of study drug.

Table 66 (created by sponsor in ISS ) shows various AEs that led to study withdrawal in patients in the randomized, parallel group, active control study. Three patients taking 1.25 mg ZS experienced 7 AEs none of which were considered serious. All were assessed as related to study drug and moderate or severe. Eight patients taking 10 mg ZS experienced 12 AEs, three of which were considered to be SAEs and associated with the CNS. All were moderate or severe and the majority were considered to be related to study drug.

Table 67 (created by sponsor in ISS) shows the various AEs that led to study withdrawal in the extension trials. Forty patients treated with 1.25 or 2.5 mg/d of ZS experienced 61 AEs. The CNS was the most common organ system involved. The most common AEs leading to study withdrawal in this group in descending order were depression, hallucinations, dizziness, dyskinesia, constipation, and postural hypotension. Three patients treated with 10 mg/d of ZS experienced 3 various AEs.

In the ISS the sponsor notes that because study withdrawals due to AEs were not directly collected on the AE CRF pages, that the sponsor discussed all AEs that could be construed as leading to withdrawal if at least one of the following 3 conditions was met.

1. Listed on the adverse event CRF page with an "action taken" as "dose withdrawn." See End-of-Text Tables 4.5.2, 4.5.2a, 4.5.2b, 4.5.2c, and 4.5.3 and Listings 5.1 to 5.4 Note that these tables and listings are actually titled "adverse events leading to discontinuation" even though they present adverse events that led to dose withdrawal;
2. Listed on the Withdrawal/Completion CRF page with a reason for discontinuation as "adverse event" (See End-of-Text Tables 1.2.1 a, 1.2.1 b, and 1.2.1c and Listings 11 to 1.4.); or
3. Listed on the Withdrawal/Completion CRF page with a reason for discontinuation as "other" that included a reference to either general or specific adverse events (See End-of-Text Tables 1.2.1a, 1.2.1b, and 1.2.1c and Listings 1.1 to 1.4.).

Table 68 shows the "unspecified" AEs in 6 patients in the extension studies who were not officially considered to have withdrawn from the study because of an AE but who may have withdrawn in reality from a study because of an AE.

A narrative summary for each patient that the sponsor considered to have led to study withdrawal is presented in Appendix 3 in the NDA. I reviewed each of these narrative summaries in the primary database and have concluded that a further description of individual cases is not warranted.

# CLINICAL REVIEW

## Clinical Review Section

**Table 65 List of Patients Who Had Dose Withdrawal and Withdrew from the Double-Blind Placebo Controlled Studies Due to an Adverse Event**

Patient	Dose	Withdrawal	Last Dose	Adverse Events	Onset	Stop	Severity	Related
002-C01	Z SEL 1.25 mg	1-12-99	12-1-98	Depression*	12-3-98	Continuing	Severe	Yes
				Dizziness	12-3-98	Continuing	Mild	Yes
				Anorexia	12-3-98	Continuing	Mild	Yes
				Insomnia	12-3-98	Continuing	Mild	Yes
008-B11	Z SEL 1.25 mg	11-6-98	10-15-98	Skin Disorder (ie, eosinophilic and lymphocytic dermal infiltrate right leg)	10-15-98	11-13-98	Severe	Yes
011-C45	Z SEL 2.5 mg	3-23-99	3-17-99	Chest Pain	3-16-99	Continuing	Mild	No
018-B59	Z SEL 1.25 mg	2-22-99	1-29-99	Myasthenia	1-29-99	1-31-99	Moderate	Yes
				Tremor			Moderate	Yes
018-C32	Z SEL 1.25 mg	12-03-98	11-26-98	Dizziness	11-26-98	11-26-98	Mild	No
				Dyskinesia			Severe	No
020-B66	Z SEL 2.5 mg	2-17-99	2-17-99	Accidental Injury*	2-5-99	Continuing	Severe	No
020-B78	Z SEL 1.25 mg	7-28-99	7-27-99	Urticaria	6-30-99	Continuing	Moderate	Yes
101-X10	Z SEL 1.25 mg	6-25-99	6-25-99	Pain	6-21-99	Continuing	Mild	No
				Abdominal Pain			Mild	No
				Chest Pain			Mild	No
103-X24	Z SEL 1.25 mg	9-10-98	7-30-98	Dizziness	7-30-98	8-6-98	Moderate	No
104-Y84	Z SEL 1.25 mg	6-25-98	5-25-98	Dehydration	5-25-98	5-26-98	Mild	No
				Hallucinations	5-25-98	5-26-98	Moderate	Yes
				Accidental Injury	5-25-98	5-25-98	Mild	No
				Myasthenia*	5-24-98	5-25-98	Severe	No
109-X47	Placebo	8-20-98	8-20-98	Dizziness	8-20-98	8-20-98	Mild	Yes
			8-20-98	Confusion			8-20-98	Mild

Protocols Z/SEL/97/025 and Z/SEL/97/026  
 Data Source: Listings 1.1, 1.2, 5.1 and 5.2.  
 \*Serious adverse events

Appears This Way  
On Original

# CLINICAL REVIEW

## Clinical Review Section

**Table 66 List of Patients Who Withdrew from the Randomized Parallel Study Due to an Adverse Event**

Patient ID	Dose	Withdrawal	Last Dose	Adverse Events	Onset	Stop	Severity	Related
Bakheit-024 <sup>a</sup>	Z SEL 1.25 mg	5-30-96	5-30-96	Hallucinations	5-UNK-96	Continuing	Moderate	Yes
Schiff-163 <sup>a</sup>	Z SEL 1.25 mg	4-24-97	4-12-97	Abdominal Pain	4-12-97	4-15-97	Moderate	Yes
				Increased Salivation	4-12-97	4-15-97	Severe	Yes
				Dizziness	4-12-97	4-15-97	Moderate	Yes
				Hypertonia (ie, muscle cramps)	4-12-97	4-15-97	Moderate	Yes
				Hypertonia (ie, Rigidity)	4-12-97	4-15-97	Severe	Yes
Sergay-192 <sup>a</sup>	Z SEL 1.25 mg	7-24-97	7-24-97	Aggravation Reaction	7-12-97	7-24-97	Moderate	Yes
Bakheit-020	Z SEL 10 mg	4-18-96	4-10-96	Headache	4-5-96	4-10-96	Moderate	Yes
				Vasodilatation	4-5-96	4-10-96	Moderate	Yes
Crome-028	Z SEL 10 mg	11-29-96	11-29-96	Depression	11-26-96	12-6-96	Moderate	Yes
				Agitation	11-26-96	12-6-96	Moderate	Yes
Grosset-087	Z SEL 10 mg	1-28-97	1-22-97	Paranoid Reaction	1-20-97	1-24-97	Severe	Yes
Khanna-048	Z SEL 10 mg	8-25-96	8-24-96	Coronary Artery Disorder*	8-25-96	8-25-96	Severe	No
Koller-175	Z SEL 10 mg	8-6-97	7-21-97	Dizziness	7-8-97	7-28-97	Moderate	Yes
				Syncope	7-8-97	7-22-97	Moderate	Yes
Selzer-217 <sup>a</sup>	Z SEL 10 mg	9-4-97	8-27-97	Myocardial Infarct*	9-9-97	9-13-97	Severe	No
Selzer-219	Z SEL 10 mg	9-4-97	9-4-97	Somnolence	7-10-97	Continuing	Moderate	Yes
Sergay-200	Z SEL 10 mg	4-4-97	4-3-97	Pneumonia*	4-4-97	4-25-97	Moderate	No
Kotschwar-171	10 mg	11-7-97	11-7-97	Depression	10-20-97	Continuing	Moderate	No
Lieberman-103 <sup>a</sup>	10 mg	10-3-97	10-3-97	Tremor	9-26-97	Continuing	Mild	No
Lieberman-279	10 mg	9-17-97	9-10-97	Delusions	9-UNK-97	Continuing	Moderate	No
				Paranoid Reaction	9-UNK-97		Moderate	No
Park-053	10 mg	6-6-96	6-5-96	Vascular Disorder	6-6-96	6-6-96	Severe	No

Protocol Z/SEL/95/008

Data Source: Listings 1.2, 1.3, 1.4, 5.2, 5.3 and 5.4.

\*Serious

\*Patients did not have adverse event recorded as the reason for withdrawal from the study on the Withdrawal/Completion CRF. The reason for withdrawal was "Protocol Deviation" for Bakheit-024; "Other" reason of relapse for Schiff-163, Sergay-192, and Lieberman-103; and "Other" reason of insomnia for Selzer-217.

Appears This Way  
On Original

## CLINICAL REVIEW

### Clinical Review Section

**Table 67 Treatment-Emergent Adverse Events by Patient Leading to Drug Withdrawal During the Extension Studies Reported by >1 Patient in the Zydys Selegiline 1.25/2.5 mg Group**

	Z SEL 1.25/2.5 mg <sup>a</sup>	Z SEL 10mg	Overall
Number Of Patients	307	24	331
Number of Patients With At Least One AE	40 (13.0%)	3 (12.5%)	43
Number Of AE	61	4	65
Nervous	20 (6.5%)	1 (4.2%)	21 (6.3%)
Depression	5 (1.6%)	0 (0.0%)	5 (1.5%)
Hallucinations	4 (1.3%)	0 (0.0%)	4 (1.2%)
Dizziness	3 (1.0%)	0 (0.0%)	3 (0.9%)
Dyskinesia	3 (1.0%)	0 (0.0%)	3 (0.9%)
Anxiety	2 (0.7%)	0 (0.0%)	2 (0.6%)
Ataxia	2 (0.7%)	0 (0.0%)	2 (0.6%)
Confusion	2 (0.7%)	0 (0.0%)	2 (0.6%)
Insomnia	2 (0.7%)	0 (0.0%)	2 (0.6%)
Digestive	9 (2.9%)	0 (0.0%)	9 (2.7%)
Constipation	3 (1.0%)	0 (0.0%)	3 (0.9%)
Cholelithiasis	2 (0.7%)	0 (0.0%)	2 (0.6%)
Gastrointestinal Disorder	2 (0.7%)	0 (0.0%)	2 (0.6%)
Cardiovascular	6 (2.0%)	0 (0.0%)	6 (1.8%)
Postural Hypotension	3 (1.0%)	0 (0.0%)	3 (0.9%)
Heart Arrest	2 (0.7%)	0 (0.0%)	2 (0.6%)
Body as a Whole	5 (1.6%)	0 (0.0%)	5 (1.5%)
Abdominal pain	2 (0.7%)	0 (0.0%)	2 (0.6%)
Skin and Appendages	3 (1.0%)	1 (4.2%)	4 (1.2%)
Rash	2 (0.7%)	0 (0.0%)	2 (0.6%)
Metabolic and Nutritional	2 (0.7%)	0 (0.0%)	2 (0.6%)
Urogenital	2 (0.7%)	0 (0.0%)	2 (0.6%)
Hemic and Lymphatic	0 (0.0%)	1 (4.2%)	1 (0.3%)
Musculoskeletal	1 (0.3%)	0 (0.0%)	1 (0.3%)
Respiratory	1 (0.3%)	0 (0.0%)	1 (0.3%)

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

Data Source: End-of-Text Table 4.5.3

<sup>a</sup> The initial dose of Zydys selegiline in the Extension Studies was 1.25 mg for 53 patients and 2.5 mg for 254 patients.

Note: At each level of summarization, a patient was counted once if he /she reported one or more adverse events at that level.

# CLINICAL REVIEW

## Clinical Review Section

**Table 68 List of Patients with Unspecified Adverse Events Noted as the Reason for Study Withdrawal**

Patient ID	Dose	Withdrawal	Last Dose	Adverse Events	Onset	Stop	Severity	Related
012-B81	1.25/2.5 mg	2-22-99	2-22-99	Anxiety (ie, Anxiety)	1-UNK-99	Continuing	Moderate	Yes
				Depression	1-UNK-99	Continuing	Moderate	No
				Anxiety (ie, Impatient)	1-UNK-99	Continuing	Moderate	No
				Nervousness	1-UNK-99	Continuing	Moderate	No
				Abnormal Dreams	1-UNK-99	Continuing	Moderate	Yes
018-C71		3-7-00	2-29-00	Cyanosis of Lips	11-15-99	Continuing	Mild	No
				Depression	1-UNK-00	Continuing	Moderate	No
				Flu Syndrome	1-27-00	2-10-00	Mild	No
108-Y33		7-6-99	6-25-99	Dry Mouth	3-18-99	Continuing	Moderate	Yes
				Abnormal Dreams	3-18-99	Continuing	Moderate	Yes
				Gingivitis	6-8-99	Continuing	Mild	No
				Arthritis	6-9-99	6-28-99	Mild	No
				Tongue Disorder	7-6-99	Continuing	Mild	No
				Bone Disorder	7-6-99	Continuing	Mild	No
112-Y73		5-24-99	5-10-99	Dyskinesia (ie, Increased Dyskinesia)	4-30-99	Continuing	Moderate	Yes
				Dyskinesia (ie, Sleep Disorder Secondary to Dyskinesia)	4-30-99	Continuing	Mild	Yes
116-Y09		2-3-00	2-3-00	Tongue Disorder (ie, Mild Focal Reddening Tongue Surface Underside)	7-22-99	Continuing	Mild	No
116-Y64		4-19-00	4-19-00	Abnormal Dreams	8-1-99	Continuing	Mild	Yes
				Insomnia	9-6-99	Continuing	Mild	No
				Vaginal Hemorrhage	12-15-99	Continuing	Mild	No
				Depression	3-19-00	Continuing	Moderate	No

Data Source: Listings 1.2 and 2.2.

## 14.6. Treatment Emergent Adverse Events (TEAEs)

### 14.6.1. Approach to Treatment Emergent Adverse Events (TEAEs) in Patients

The sponsor analyzed and presented data regarding TEAEs in the patient clinical trials according to three categories (i.e. placebo-controlled studies, other randomized studies, extension studies). I will review and present these data in a similar fashion. Data from 9 trials of healthy volunteers were not incorporated in the ISS but were analyzed separately by the sponsor. These data will be presented separately at the end of the presentation of TEAEs for patients in clinical trials.

Incidence of TEAEs was the focus of the ISS and was defined as the number of patients in the exposed population who experienced a TEAE. In general, a patient was counted once among all the patients treated if the patient experienced one or more AEs at that level. Incidence of TEAEs were analyzed and presented according to body system, severity, and relationship to study drug.

Table 69 (derived from sponsor's Table 8-A 1 in the ISS) show the incidence of TEAEs occurring in  $\geq 5\%$  of patients in the double-blind placebo controlled trials according to body system and treatment and regardless of relationship to study drug. All body systems are shown along with a specific AE whenever the AE occurred in  $\geq 5\%$  of patients in at least one treatment group or in a combined group of patients treated with either dose of ZS. Overall, the incidence

## CLINICAL REVIEW

### Clinical Review Section

of patients who experienced at least one AE was less in each ZS dose group (1.25 and 2.5 mg daily) than in the group of placebo-treated patients. The majority of these 10 specific AEs occurred in the digestive and nervous systems and body as whole. The incidence of all specific AEs was greater in the placebo group than in either ZS dose group with the exception of insomnia (placebo – 4.1 %; ZS 1.25 mg – 4.6 %) and dyskinesia (placebo – 5.2 %; ZS 1.25 mg – 3.1 %). A lower incidence of insomnia and dyskinesia in the high dose ZS group showed that there no dose-dependent effect and argued against the AE as being related to ZS.

Table 70 (derived from sponsor's Table 8-D in the ISS) shows the incidence (occurring in  $\geq 2\%$  of ZS treated patients) of specific TEAEs in descending order in the placebo controlled studies by each treatment group separately and also by any dose of ZS treatment. Table 70 could be used as the source of a table to include in labeling by including all TEAEs that numerically exceeded the incidence in the placebo group. The vast majority (e.g.  $\sim 70\%$ ) of these specific AEs would be included because the incidence of most of these AEs in the ZS group as a whole was greater than that of the placebo group.

Table 71 (derived from sponsor's Table 8-B in the ISS) shows the incidence of TEAEs occurring in  $\geq 5\%$  of patients in the other randomized trials according to body system and treatment and regardless of relationship to study drug. This table is similar in format to Table 69. Stomatitis, tongue disorder, accidental injury, pain, tremor, and skin ulcer comprise a list of specific of TEAEs that occurred with ZS treatment and that may be of potential interest. These TEAEs occurring with ZS treatment (1.25 or 10 mg daily) showed a greater incidence in the higher ZS dose group and also a numerically greater incidence than that for Eldepryl (5 mg BID).

Table 72 (derived from sponsor's Table 8-C in the ISS) show the incidence of TEAEs occurring in  $\geq 5\%$  of patients in the extension studies according to body system and treatment and regardless of relationship to study drug. This table is similar in format to Table 69. Specific TEAEs that stimulate interest include accidental injury, pain, infection, stomatitis, mouth ulcer, nausea, constipation, pharyngitis, peripheral edema, and rash because the incidence was higher in the 10 mg vs the 1.25 mg daily dose group.

A variety of significant AEs were rarely reported as ECG abnormalities and rhythm disturbances. These abnormalities and rhythm disturbances included various types of bundle branch block, ventricular premature beats, bradycardia, supraventricular premature beats, supraventricular tachycardia, and atrial arrhythmias. However, the incidence in the double-blind placebo studies did not suggest a significant increased incidence in the ZS group over placebo. Neither did the incidence of these abnormal ECGs in the different treatment groups in the randomized, controlled study suggest a dose-dependent effect of ZS as a cause of these abnormal ECGs. Of potential interest, there were no instances of QTc prolongation in any treatment group.

Appears This Way  
On Original

# CLINICAL REVIEW

## Clinical Review Section

**Table 69 Treatment-Emergent Adverse Events by Patient and Body System Occurring in  $\geq 5\%$  of the Patients in the 1.25/2.5 Zydys Selegiline Group : Double Blind Placebo Controlled Studies**

	Z SEL 1.25mg	Z SEL 2.5mg	Z SEL 1.25/2.5mg	Z Placebo
Number Of Patients	194	178	194	98
Number of Patients With At Least One AE	125 (64.4%)	106 (59.6%)	158 (81.4%)	75 (76.5%)
Number Of AEs	333	249	582	245
Digestive	49 (25.3%)	39 (21.9%)	76 (39.2%)	29 (29.6%)
Nausea	15 (7.7%)	6 (3.4%)	21 (10.8%)	9 (9.2%)
Stomatitis	4 (2.1%)	6 (3.4%)	10 (5.2%)	4 (4.1%)
Body as a Whole	49 (25.3%)	38 (21.3%)	75 (38.7%)	38 (38.8%)
Accidental Injury	12 (6.2%)	8 (4.5%)	18 (9.3%)	12 (12.2%)
Pain	10 (5.2%)	7 (3.9%)	16 (8.2%)	7 (7.1%)
Headache	9 (4.6%)	6 (3.4%)	13 (6.7%)	6 (6.1%)
Back Pain	5 (2.6%)	5 (2.8%)	10 (5.2%)	3 (3.1%)
Nervous	47 (24.2%)	35 (19.7%)	69 (35.6%)	29 (29.6%)
Dizziness	14 (7.2%)	11 (6.2%)	21 (10.8%)	8 (8.2%)
Insomnia	9 (4.6%)	4 (2.2%)	13 (6.7%)	4 (4.1%)
Dyskinesia	10 (5.2%)	3 (1.7%)	12 (6.2%)	3 (3.1%)
Cardiovascular	15 (7.7%)	24 (13.5%)	34 (17.5%)	15 (15.3%)
Respiratory	21 (10.8%)	18 (10.1%)	34 (17.5%)	12 (12.2%)
Rhinitis	11 (5.7%)	5 (2.8%)	13 (6.7%)	6 (6.1%)
Skin And Appendages	14 (7.2%)	15 (8.4%)	27 (13.9%)	1 (7.1%)
Musculoskeletal	14 (7.2%)	5 (2.8%)	19 (9.8%)	7 (7.1%)
Metabolic and Nutritional Disorders	10 (5.2%)	7 (3.9%)	17 (8.8%)	6 (6.1%)
Special Senses	6 (3.1%)	4 (2.2%)	10 (5.2%)	9 (9.2%)
Urogenital	6 (3.1%)	2 (1.1%)	7 (3.6%)	11 (11.2%)
Hemic and Lymphatic	2 (1.0%)	4 (2.2%)	6 (3.1%)	2 (2.0%)

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

Data Source: End-of-Text Table 4.1.3a

Note: At each level of summarization, a patient was counted once if he /she reported one or more adverse events at that level.

Appears This Way  
On Original

**BEST POSSIBLE COPY**

# CLINICAL REVIEW

## Clinical Review Section

**Table 70 Treatment-Emergent Adverse Events By Descending Frequency Occurring in  $\geq 2\%$  of the Patients in the Zydys selegiline 1.25/2.5 mg group : Double Blind Placebo Controlled Studies**

	Z SEL 1.25mg	Z SEL 2.5mg	Z SEL 1.25/2.5mg	Z Placebo
Number Of Patients	194	178	194	98
Number of Patients With At Least One AE	125	106	158	75
Number Of AE	333	249	582	245
Dizziness	14 (7.2%)	11 (6.2%)	21 (10.8%)	8 (8.2%)
Nausea	15 (7.7%)	6 (3.4%)	21 (10.8%)	9 (9.2%)
Accidental Injury	12 (6.2%)	8 (4.5%)	18 (9.3%)	12 (12.2%)
Pain	10 (5.2%)	7 (3.9%)	16 (8.2%)	7 (7.1%)
Headache	9 (4.6%)	6 (3.4%)	13 (6.7%)	6 (6.1%)
Insomnia	9 (4.6%)	4 (2.2%)	13 (6.7%)	4 (4.1%)
Rhinitis	11 (5.7%)	5 (2.8%)	13 (6.7%)	6 (6.1%)
Dyskinesia	10 (5.2%)	3 (1.7%)	12 (6.2%)	3 (3.1%)
Back Pain	5 (2.6%)	5 (2.8%)	10 (5.2%)	3 (3.1%)
Stomatitis	4 (2.1%)	6 (3.4%)	10 (5.2%)	4 (4.1%)
Dyspepsia	7 (3.6%)	2 (1.1%)	9 (4.6%)	3 (3.1%)
Abnormal Dreams	5 (2.6%)	3 (1.7%)	8 (4.1%)	4 (4.1%)
Dry Mouth	5 (2.6%)	3 (1.7%)	8 (4.1%)	2 (2.0%)
Infection	4 (2.1%)	5 (2.8%)	8 (4.1%)	7 (7.1%)
Pharyngitis	2 (1.0%)	6 (3.4%)	8 (4.1%)	2 (2.0%)
Rash	2 (1.0%)	6 (3.4%)	8 (4.1%)	1 (1.0%)
Asthenia	4 (2.1%)	4 (2.2%)	7 (3.6%)	5 (5.1%)
Constipation	6 (3.1%)	1 (0.6%)	7 (3.6%)	0 (0.0%)
Hallucinations	3 (1.5%)	4 (2.2%)	7 (3.6%)	2 (2.0%)
Skin Disorder	4 (2.1%)	3 (1.7%)	7 (3.6%)	1 (1.0%)
Mouth Ulceration	3 (1.5%)	6 (3.4%)	7 (3.6%)	5 (5.1%)
Flu Syndrome	2 (1.0%)	4 (2.2%)	6 (3.1%)	4 (4.1%)
Postural Hypotension	5 (2.6%)	2 (1.1%)	6 (3.1%)	4 (4.1%)
Somnolence	2 (1.0%)	5 (2.8%)	6 (3.1%)	2 (2.0%)
Tremor	4 (2.1%)	2 (1.1%)	6 (3.1%)	1 (1.0%)
Ataxia	3 (1.5%)	2 (1.1%)	5 (2.6%)	1 (1.0%)
Cheilitis	2 (1.0%)	3 (1.7%)	5 (2.6%)	0 (0.0%)
Leg Cramps	2 (1.0%)	3 (1.7%)	5 (2.6%)	1 (1.0%)

Appears This Way  
On Original

	Z SEL 1.25mg	Z SEL 2.5mg	Z SEL 1.25/2.5mg	Z Placebo
Dyspnea	2 (1.0%)	3 (1.7%)	5 (2.6%)	0 (0.0%)
Hypertension	4 (2.1%)	2 (1.1%)	5 (2.6%)	2 (2.0%)
Myalgia	4 (2.1%)	1 (0.6%)	5 (2.6%)	0 (0.0%)
Abdominal Pain	3 (1.5%)	2 (1.1%)	5 (2.6%)	3 (3.1%)
Tongue Disorder	0 (0.0%)	5 (2.8%)	5 (2.6%)	4 (4.1%)
Vomiting	3 (1.5%)	3 (1.7%)	5 (2.6%)	0 (0.0%)
Anxiety	3 (1.5%)	1 (0.6%)	4 (2.1%)	3 (3.1%)
Arthralgia	3 (1.5%)	1 (0.6%)	4 (2.1%)	2 (2.0%)
Cough Increased	4 (2.1%)	0 (0.0%)	4 (2.1%)	4 (4.1%)
Depression	3 (1.5%)	1 (0.6%)	4 (2.1%)	1 (1.0%)
Diarrhea	4 (2.1%)	0 (0.0%)	4 (2.1%)	1 (1.0%)
Dysphagia	1 (0.5%)	3 (1.7%)	4 (2.1%)	1 (1.0%)
Ecchymosis	1 (0.5%)	3 (1.7%)	4 (2.1%)	0 (0.0%)
Peripheral Edema	2 (1.0%)	2 (1.1%)	4 (2.1%)	3 (3.1%)
Flatulence	4 (2.1%)	1 (0.6%)	4 (2.1%)	1 (1.0%)
Gingivitis	3 (1.5%)	1 (0.6%)	4 (2.1%)	2 (2.0%)
Hypokalemia	3 (1.5%)	1 (0.6%)	4 (2.1%)	0 (0.0%)
Chest Pain	3 (1.5%)	1 (0.6%)	4 (2.1%)	0 (0.0%)
Tooth Disorder	2 (1.0%)	2 (1.1%)	4 (2.1%)	1 (1.0%)
Skin Ulcer	3 (1.5%)	1 (0.6%)	4 (2.1%)	1 (1.0%)

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

Data Source: End-of-Text Table 4.1.5

Note: At each level of summarization, a patient was counted once if he/she reported one or more adverse events at that level.

BEST POSSIBLE COPY

# CLINICAL REVIEW

## Clinical Review Section

**Table 71 Treatment-Emergent Adverse Events by Body System Occurring in  $\geq 5\%$  of the Patients in at Least One Zydys Selegiline Group : Other Randomized Studies**

	Randomized Parallel Study			Crossover Study
	Z SEL 1.25 mg	Z SEL 10 mg	SEL 10 mg	Z.SEL 5mg/Placebo
Number Of Patients	65	62	71	148
Number of Patients With At Least One AE	51 (78.5%)	57 (91.9%)	56 (78.9%)	6 (4.1%)
Number Of AEs	179	202	150	10
Digestive	24 (36.9%)	31 (50.0%)	25 (35.2%)	2 (1.4%)
Stomatitis	8 (12.3%)	11 (17.7%)	6 (8.5%)	1 (0.7%)
Tongue Disorder	4 (6.2%)	5 (8.1%)	2 (2.8%)	0 (0.0%)
Constipation	1 (1.5%)	5 (8.1%)	3 (4.2%)	0 (0.0%)
Body as a Whole	25 (38.5%)	21 (33.9%)	27 (38.0%)	1 (0.7%)
Accidental Injury	8 (12.3%)	9 (14.5%)	4 (5.6%)	0 (0.0%)
Pain	6 (9.2%)	6 (9.7%)	2 (2.8%)	0 (0.0%)
Back Pain	5 (7.7%)	1 (1.6%)	4 (5.6%)	0 (0.0%)
Infection	4 (6.2%)	0 (0.0%)	4 (5.6%)	0 (0.0%)
Nervous	21 (32.3%)	27 (43.5%)	20 (28.2%)	2 (1.4%)
Dizziness	3 (4.6%)	6 (9.7%)	5 (7.0%)	2 (1.4%)
Tremor	4 (6.2%)	6 (9.7%)	3 (4.2%)	0 (0.0%)
Respiratory	20 (30.8%)	13 (21.0%)	8 (11.3%)	1 (0.7%)
Pharyngitis	6 (9.2%)	4 (6.5%)	5 (7.0%)	0 (0.0%)
Rhinitis	7 (10.8%)	0 (0.0%)	3 (4.2%)	0 (0.0%)
Cough Increased	1 (1.5%)	4 (6.5%)	1 (1.4%)	0 (0.0%)
Cardiovascular	6 (9.2%)	13 (21.0%)	2 (2.8%)	1 (0.7%)
Syncope	0 (0.0%)	4 (6.5%)	0 (0.0%)	1 (0.7%)
Skin and Appendages	5 (7.7%)	12 (19.4%)	5 (7.0%)	0 (0.0%)
Skin Ulcer	3 (4.6%)	4 (6.5%)	0 (0.0%)	0 (0.0%)
Metabolic and Nutritional	7 (10.8%)	4 (6.5%)	10 (14.1%)	0 (0.0%)
Musculoskeletal	6 (9.2%)	8 (12.9%)	4 (5.6%)	0 (0.0%)
Hemic and Lymphatic	3 (4.6%)	4 (6.5%)	7 (9.9%)	0 (0.0%)
Urogenital System	5 (7.7%)	3 (4.8%)	3 (4.2%)	1 (0.7%)
Special Senses	2 (3.1%)	6 (9.7%)	2 (2.8%)	1 (0.7%)

Protocols Z/SEL/95/008 and Z/SEL/94/026 Data Source: End-of-Text Table 4.1.3b Note: At each level of summarization, a patient was counted once if he /she reported one or more adverse events at that level.

Appears This Way  
On Original

**BEST POSSIBLE COPY**

# CLINICAL REVIEW

## Clinical Review Section

**Table 72 Treatment-Emergent Adverse Events Occurring in >-5% of the Patients in the Zydys selegiline 1.25/2.5 mg Group : Extension Studies**

	Previous Placebo <sup>a</sup>	Z SEL 1.25/2.5 mg <sup>b</sup>	Z SEL 10mg	Overall
Number Of Patients	83	307	24	331
Number of Patients With At Least One AE	76 (91.6%)	273 (88.9%)	24 (100.0%)	297 (89.7%)
Number Of AEs	416	1474	164	1638
Body as a Whole	40 (48.2%)	154 (50.2%)	17 (70.8%)	171 (51.7%)
Accidental Injury	14 (16.9%)	50 (16.3%)	7 (29.2%)	57 (17.2%)
Pain	8 (9.6%)	32 (10.4%)	3 (12.5%)	35 (10.6%)
Infection	8 (9.6%)	26 (8.5%)	5 (20.8%)	31 (9.4%)
Back Pain	6 (7.2%)	24 (7.8%)	1 (4.2%)	25 (7.6%)
Nervous	44 (53.0%)	154 (50.2%)	16 (66.7%)	170 (51.4%)
Dizziness	9 (10.8%)	34 (11.1%)	1 (4.2%)	35 (10.6%)
Insomnia	8 (9.6%)	34 (11.1%)	1 (4.2%)	35 (10.6%)
Depression	8 (9.6%)	21 (6.8%)	1 (4.2%)	22 (6.6%)
Dyskinesia	8 (9.6%)	20 (6.5%)	1 (4.2%)	21 (6.3%)
Abnormal Dreams	4 (4.8%)	16 (5.2%)	1 (4.2%)	17 (5.1%)
Hallucinations	7 (8.4%)	16 (5.2%)	1 (4.2%)	17 (5.1%)
Somnolence	7 (8.4%)	16 (5.2%)	0 (0.0%)	16 (4.8%)
Digestive	36 (43.4%)	131 (42.7%)	11 (45.8%)	142 (42.9%)
Stomatitis	9 (10.8%)	24 (7.8%)	3 (12.5%)	27 (8.2%)
Mouth Ulceration	7 (8.4%)	24 (7.8%)	2 (8.3%)	26 (7.9%)
Tongue Disorder	7 (8.4%)	21 (6.8%)	1 (4.2%)	22 (6.6%)
Nausea	6 (7.2%)	19 (6.2%)	2 (8.3%)	21 (6.3%)
Constipation	5 (6.0%)	18 (5.9%)	2 (8.3%)	20 (6.0%)
Cardiovascular	24 (28.9%)	81 (26.4%)	8 (33.3%)	89 (26.9%)
Respiratory	15 (18.1%)	79 (25.7%)	8 (33.3%)	87 (26.3%)
Pharyngitis	5 (6.0%)	21 (6.8%)	3 (12.5%)	24 (7.3%)
Metabolic and Nutritional	14 (6.9%)	52 (16.9%)	7 (29.2%)	59 (17.8%)
Peripheral Edema	6 (7.2%)	23 (7.5%)	2 (8.3%)	25 (7.6%)
Skin and Appendages	11 (13.3%)	52 (16.9%)	5 (20.8%)	57 (17.2%)
Rash	3 (3.6%)	16 (5.2%)	2 (8.3%)	18 (5.4%)
Musculoskeletal	18 (21.7%)	48 (15.6%)	5 (20.8%)	53 (16.0%)
Arthralgia	5 (6.0%)	16 (5.2%)	1 (4.2%)	17 (5.1%)
Urogenital	12 (14.5%)	44 (14.3%)	4 (16.7%)	48 (14.5%)
Urinary Tract Infection	4 (4.8%)	18 (5.9%)	1 (4.2%)	19 (5.7%)

Appears This Way  
On Original

	Previous Placebo <sup>a</sup>	Z SEL 1.25/2.5 mg <sup>b</sup>	Z SEL 10mg	Overall
Special Senses	7 (8.4%)	33 (10.7%)	9 (37.5%)	42 (12.7%)
Hemic and Lymphatic	8 (9.6%)	24 (7.8%)	5 (20.8%)	29 (8.8%)

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

Data Source: End-of-Text Table 4.1.7

Note: At each level of summarization, a patient was counted once if he /she reported one or more adverse events at that level.

<sup>a</sup> Previous Placebo Patients<sup>a</sup> refers to patients who were randomized to Zydys placebo in the original studies and started on Zydys selegiline in the extension study.

<sup>b</sup> The initial dose of Zydys selegiline in the Extension Studies was 1.25 mg for 53 patients and 2.5 mg for 254 patients.

## CLINICAL REVIEW

### Clinical Review Section

#### 14.6.2. Treatment Emergent Adverse Events (TEAEs) by Age

The sponsor presented a subgroup analysis of TEAEs (including oropharyngeal events) by age (< 55 yo, 56-64 yo, > 65 yo) for AEs occurring in  $\geq 5\%$  of patients in the double-blind placebo controlled studies in the ISS using a table format similar to Table 69. From such a table I created Table 73 that shows the relative risk for the TEAE according to various age subgroups whenever the relative risk for a TEAE for any treatment was  $> 1.0$ . Relative risk is calculated as : incidence of body system or specific TEAE for ZS treatment 1.25 or 2.5 mg/ incidence of body system or specific TEAE for Placebo treatment. This analysis suggested that the oldest age ( $\geq 65$  yo) subgroup exhibited an increased risk for nausea, stomatitis, headache, back pain, and dizziness, and AEs related to cardiovascular, respiratory, skin and appendages, and digestive systems. The middle age subgroup (56 – 64 yo) exhibited an increased risk for pain, and AEs related to respiratory, musculoskeletal, skin and appendages, metabolic and nutritional, and hematological and lymphatic systems. The youngest age subgroup ( $\leq 55$  yo) exhibited an increased risk for back pain, dizziness, dyskinesia, and rhinitis, and AEs related to metabolic and nutritional, and hematological and lymphatic systems. The sponsor presented more detailed analyses of TEAEs by age subgroups in the end-of-text tables in the ISS.

**Table 73 Relative Risk (ZS %/ Placebo %) for Body System and Specific TEAEs by Treatment and Age Subgroups Occurring in  $\geq 5\%$  of the Total Patient Population in Double-Blind Placebo Controlled Studies Whenever Relative Risk Exceeds 1.0**

Age	$\leq 55$ yo		56 – 64 yo		$\geq 65$ yo	
	ZS-24	Placebo-19	ZS-42	Placebo-27	ZS-128	Placebo-52
Digestive system	1.0		1.0		1.7	
nausea	0.4		0.6		2.2	
stomatitis	0 % / 0 %		0.6		1.7	
Body as a whole	0.9		0.9		1.1	
pain	0.4		3.9		0.9	
headache	0.8		0.3		1.5	
back pain	4.2 % / 0 %		0.6		1.7	
Nervous system	1.2		1.0		1.3	
dizziness	2.4		0.5		2.0	
dyskinesia	12.5 % / 0 %		1.3		1.4	
Cardiovascular syst.	0.8		0.5		1.8	
Respiratory system	0.8		1.8		1.5	
rhinitis	8.3 % / 0 %		1.1		0.8	
Skin and Appendages	1.2		2.6		2.2	
Musculoskeletal	1.6		1.6		1.2	
Metabolic+Nutritional	8.3 % / 0 %		1.9		1.0	
Urogenital system	1.6		0.7		0.1	
Hemic + Lymphatic	4.2 % / 0 %		2.4 % / 0 %		0.8	

## CLINICAL REVIEW

### Clinical Review Section

For oropharyngeal TEAEs, 7 of 8 patients, who experienced shifts in mouth pain from none to mild, were elderly (i.e. > 65 years old). In addition, 9 of 9 patients, who had shifts from none to mild for discrete areas of focal reddening of the left cheek, were elderly.

#### 14.6.3. Treatment Emergent Adverse Events (TEAEs) by Gender

The sponsor presented a subgroup analysis of TEAEs by gender (male and female) for AEs occurring in  $\geq 5\%$  of patients in the double-blind placebo controlled studies in the ISS using a table format similar to Table 69. From such a table I created Table 74 that shows the relative risk for the TEAE according to gender whenever the relative risk for a TEAE for any treatment was  $> 1.0$ . Relative risk is calculated as : incidence of body system or specific TEAE for ZS treatment 1.25 or 2.5 mg/ incidence of body system or specific TEAE for Placebo treatment. This analysis suggested that females exhibited an increased risk for nausea, back pain, and rhinitis, and AEs related to skin and appendages system. In contrast, males appeared to exhibit an increased risk for pain, headache, insomnia, and dizziness, and AEs related to musculoskeletal, metabolic and nutritional, and hematological and lymphatic systems.

**Table 74 Relative Risk (ZS %/ Placebo %) for Body System and Specific TEAEs by Treatment and Gender Subgroups Occurring in  $\geq 5\%$  of the Total Patient Population in Double-Blind Placebo Controlled Studies Whenever Relative Risk Exceeds 1.0**

Gender	Male		Female	
	ZS-128	Placebo-66	ZS-66	Placebo-32
# Subjects/ Rx Grp				
Digestive system		1.3		1.3
nausea		0.8		1.6
stomatitis		1.2		1.5
Body as a whole		1.0		1.0
pain		1.4		0.8
headache		1.4		0.8
back pain		0.9		7.6 % / 0 %
Nervous system		1.3		1.1
dizziness		2.3		0.8
insomnia		2.3		1.0
dyskinesia		2.1		1.9
Cardiovascular system		1.1		1.2
Respiratory system		1.3		1.8
rhinitis		1.0		1.5
Skin and Appendages		1.3		3.4
Musculoskeletal		2.8		0.4
Metabolic + Nutritional		1.8		0.7
Hemic + Lymphatic		2.1		1.0

## CLINICAL REVIEW

### Clinical Review Section

#### 14.6.4. Treatment Emergent Adverse Events (TEAEs) by Race

The overwhelming majority (~ 91 %) of total patients (n = 194) in the double blind, placebo controlled patients were of the Caucasian race. This minimal percentage (~ 9 %) of patients of non-Caucasian race made any subgroup analysis of TEAEs based upon race meaningless. Thus, no subgroup analysis of TEAEs by race was conducted.

#### 14.6.5. Drug Plasma Concentration TEAE Relationships

The sponsor did not collect PK samples in Parkinson's disease patients. Thus, it was not possible to present any analyses of TEAEs in which there were plasma selegiline levels to assess relationships between plasma drug level and AEs.

#### 14.7. TEAES in Healthy Subjects

The NDA contains 9 PK and PK/PD studies of 219 healthy subjects. The number of subjects who received a single dose of ZS was 108 and the number who participated in multidose studies (PK/Parkinson's disease tyramine challenge trials) was 111. ZS was generally well-tolerated in both groups of subjects and TEAEs that occurred were consistent with those potentially expected according to the known safety profile for ZS and Eldepryl. TEAEs in these healthy subjects (without Parkinson's disease) are presented here separately from TEAEs of patients in clinical studies. The sponsor did not incorporate TEAEs of healthy subjects in the tables, data listings, text presentations, and discussion of the ISS.

There were no deaths in the healthy volunteer studies. Two subjects discontinued for AEs. One subject (#018 in Study Z/SEL/95/003) withdrew because of a severe urinary tract infection after receiving Eldepryl and ZS on two different days. In follow-up, the subject had an uneventful recovery and the event was not considered related to study treatment. Another subject (#020 in Study Z/SEL/95/007) who had not yet received an study medication withdrew after tyramine challenge because of nausea and "feeling woozy." One subject (#013 in Study Z/SEL/95/023) experienced an SAE consisting of hospitalization for rectal surgery to treat a prolapsed hemorrhoid after treatment with ZS (1.25 mg) and Eldepryl (5 mg BID).. This SAE was not considered related to study medication in this subject who recovered uneventfully and had a history of hemorrhoidectomy.

Verbatim terms for TEAEs were used. The most frequent TEAE in healthy subjects was headache. Other more common TEAEs in the multidosing PK/PD studies included palpitations, somnolence, fatigue, and dizziness. Other TEAEs included nausea/vomiting, anorexia, postural dizziness, light-headedness, and postural hypotension.