

Clinical NDA Review

Brand Name: Zelapar

Generic Name: Zydys selegiline

Sponsor: Elan Pharmaceuticals, Inc.

Indication: Parkinson's Disease

NDA Number: 21479

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1. EXECUTIVE SUMMARY

Background and Introduction

Conventional selegiline is currently approved (1989) in the U.S. as well as in several other countries for the treatment of patients with Parkinson's disease (PD) who are receiving levodopa/L-DOPA (LD) therapy (with or without a peripheral decarboxylase inhibitor) and who are experiencing deterioration in their therapeutic response to LD. Selegiline is thought to exert its therapeutic effect via inhibition of the monoamine oxidase (MAO) B enzyme and the decrease in dopamine metabolism and turnover. Selegiline is marketed in the U.S. as Eldepryl®, a formulation that is swallowed.

Zydis selegiline (ZS) is a rapidly-dissolving oral dosage formulation of selegiline consisting of an open matrix of water-soluble ~~_____~~. This formulation dissolves quickly (e.g. beginning within seconds) in saliva on the tongue, releasing selegiline into the saliva, and does not require added water to aid disintegration, dissolution or absorption. Major theoretical advantages of the ZS formulation include : 1) improved patient compliance with the easily administered tablet that rapidly dissolves on the tongue, especially for patients with swallowing difficulties; 2) reduced variability in absorption relative to orally-administered standard tablets, with potentially more predictable clinical effects; and 3) reduced overall exposure to selegiline and metabolites (based on administered dose), and reduced production of potentially active metabolites. b(4)

The NDA presents data (text, tables, listings) from the clinical development program for ZS. Original data collected during the clinical development program were derived from 6 Parkinson's disease studies including two identical, double-blinded, placebo controlled trials (Z/SEL/97/025 and Z/SEL/97/026), a randomized, open-label, parallel group active control trial, a one day/single ZS exposure, randomized, placebo-controlled cross-over trial, and 2 open-label extension trials.

Indication

ZS is indicated as an adjunctive treatment for management of symptoms in patients with Parkinson's disease who exhibit deterioration of their response to levodopa/carbidopa.

Efficacy

The efficacy assessment was based upon two identical, phase 3 randomized, double-blind, placebo-controlled, parallel group multi-center studies comparing the efficacy and safety of ZS 2.5 mg/d (after 6 weeks treatment with Zs 1.25 mg/d) with placebo as an adjunct in the management of patients with Parkinson disease who were treated with LD and who exhibited deterioration in the quality of their response to this therapy. The two studies (Z/SEL/97/026, Z/SEL/97/025) were conducted at U.S. centers with the exception of one Canadian center.

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In Study Z/SEL/97/025, a total of 150 patients were randomized and 148 were in the intent-to-treat population. In Study Z/SEL/97/026, a total of 155 patients were randomized and 140 were in the intent-to-treat (ITT) population. Patients were randomized to treatment with placebo for 12 weeks or ZS for 12 weeks (1.25 mg/d for weeks 1 - 6; 2.5 mg/d for weeks 7-12). The primary efficacy endpoint was based on the change from baseline of reduction in percentage average daily "OFF" time during waking hours reported from patient/caregiver completed diary cards (averaged from 10 and 12 weeks). Study Z/SEL/97/026 was positive (-13.1 % reduction for ZS; -3.9 % reduction for placebo) and showed a robust result with a $p < 0.001$ in ITT LOCF population. Study Z/SEL/97/025 was negative (-12.1% reduction for ZS; -7.4% reduction for placebo) and did not show a statistically significant improvement ($p < 0.127$) in ITT LOCF population. These statistical analyses were conducted by the DNDP statistical reviewer because the sponsor had not conducted the appropriate primary analysis of the primary efficacy endpoint using the appropriate population (i.e. ITT LOCF) and appropriate implementation of the LOCF. The sponsor's analyses of the primary endpoint using various datasets (including LOCF but with an inappropriate implementation of the LOCF algorithm) of the ITT population were statistically consistent (i.e. positive result for study Z/SEL/97/026 and negative result for Z/SEL/97/025) with the analyses conducted by the DNDP statistical reviewer. DNDP had previously informed the sponsor that a single adequately controlled trial that exhibited robust efficacy for the primary efficacy endpoint could be evidence for substantial efficacy.

The sponsor's re-analysis of the primary efficacy analysis of the primary endpoint and secondary endpoints and new analysis of the completer ITT dataset (that was supposed to be analyzed but never was) were submitted by the sponsor very late, approximately 1 month before the action letter date. These analyses have not yet been reviewed.

Safety

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

There were 8 deaths (7 ZS and 1 conventional selegiline/Eldepryl) in the original NDA submission reflecting deaths up to the data cut-off date. Four additional deaths that occurred after the cut-off date for the Safety Update were noted in the Safety Update. None of the deaths were thought to be related to ZS and these deaths were not necessarily unexpected in this patient population. There were 4 cases with a cardiovascular cause of death (i.e. coronary artery thrombosis, myocardial infarction, ruptured abdominal aortic aneurysm, cardiorespiratory arrest). One patient with sideroblastic anemia and chronic myelocytic leukemia died (specific details surrounding death were unknown) several days after surgical evacuation of bilateral subdural hematomas. Causes of death in the other 3 cases were lung cancer, complications from sigmoid

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volvulus, and natural. Of interest, 3 patients with cardiovascular causes of death and the patient with the subdural hematomas had been on high dose ZS (10 mg/d).

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

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

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

Review of clinical laboratory analytes (clinical chemistry, hematology, urinalyses) during treatment with ZS did not reveal any remarkable findings with the exception of mild to moderate increments in serum BUN and creatinine above baseline in patients treated with high dose ZS (10 mg/d). Whereas there was no mean increment above baseline in serum BUN with ZS 1.25 mg/d or Eldepryl (5 mg BID) at 12 weeks, the mean increment high dose ZS (10 mg/d) was 11.2

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

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

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

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

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

Pharmacokinetics and Pharmacodynamics

The number of healthy subjects studied in pharmacokinetic (PK) and pharmacodynamic (PD) studies was 219 (108 single dose; 111 multidose). PK studies at steady state showed that the

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mean plasma C_{max} (4.4 ng/ml) with ZS (2.5 mg/d) was much higher than that (1.7 ng/ml) with Eldepryl (5 mg BID). but that mean AUC (6.5 ng/mL•hr) with ZS was somewhat lower than that (8.3 ng/mL•hr) with Eldepryl. Although mean plasma selegiline exposure (e.g. C_{max} and AUC) increased with increasing doses of ZS (1.25, 2.5, 5 mg daily), the increment was not dose proportional. Pre-gastric absorption of selegiline from the ZS formulations and avoidance of significant first-pass hepatic metabolism resulted in higher fractions of the administered dose being delivered to the systemic circulation and lower fractions of the administered dose being converted to metabolites (major metabolites = N-desmethylselegiline, L-methamphetamine, and L-amphetamine).

There are several shortcomings of the PK program that should be addressed by the sponsor.

- There are no mass balance studies to indicate quantitative routes of excretion of ZS.
- There are no studies of PK of ZS in subjects with various degrees of renal impairment or hepatic impairment. Neither is information known about the PK of conventional oral selegiline (e.g. Eldepryl) in subjects with various degrees of renal impairment or hepatic impairment.
- There are no PK studies of ZS in elderly subjects (≥ 65 years old).
- The sponsor did not analyze the PK data of ZS for a gender effect.
- The sponsor did not conduct any drug-drug interaction (DDI) studies.
- The results of the food interaction study are puzzling for both ZS (5 mg) and Eldepryl (10 mg). Considering that most ZS absorption should be pre-gastric, it is difficult to understand why food would alter the extent (but not T_{max}) of absorption. Furthermore, the sponsor found that food decreased the absorption of selegiline with Eldepryl treatment. This is contrary to the labeling for Eldepryl that notes that food can increase bioavailability by 3 to 4 fold.

Oral tyramine challenge studies were conducted to characterize the pharmacodynamic (PD) effect of ZS on inhibition of MAO-A enzyme activity in order to assess the risk of a tyramine-induced "cheese" reaction resulting in a hypertensive crisis. The most recently completed PK/PD tyramine challenge study in response to a DNDP request raised more questions than it answered. Both ZS 1.25 mg QD and Eldepryl 5 mg BID showed a similar increase in tyramine sensitivity such that the tyramine sensitivity factor was significantly raised (~ 6.7). Both treatments also showed significant percentages of subjects with high tyramine sensitivity as reflected by very low tyramine threshold doses (≤ 50 mg ZS ~ 43 %, Eldepryl ~ 59 %; 25 mg ZS 20 %, Eldepryl 20 %). There was no dose response of ZS for enhancing tyramine sensitivity and the 2.5 mg dose suggested less MAO-A inhibition than 1.25 mg. Altogether these results suggested significant MAO-A inhibition and a significant potential risk for a tyramine-induced "cheese" hypertensive reaction/crisis. Eldepryl results contrasted markedly with those in the literature, tyramine test results from Eldepryl's sponsor, and the general impression that there is no significant MAO-A inhibition with conventional doses of Eldepryl. ZS results in the most recent study stimulated significant concerns about potential safety risks in the absence of tyramine restrictions and were more alarming than those obtained in previous studies of ZS. Although there was no explanation for these surprising results for both ZS and Eldepryl, their significance cannot be dismissed. I do not believe that it would be appropriate to approve ZS with tyramine dietary restrictions if I am

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not convinced that the apparent MAO-A inhibition exhibited by ZS and Eldepryl is real. I am not convinced that MAO-A inhibition is real, thus additional study is clearly required.

1.1. Conclusions

1. ZS at 2.5 mg daily is an effective dose for the sponsor's desired indication/claim. The sponsor did not adequately study the 1.25 mg daily dose to receive a claim for this dose.
2. Although the safety review to date does not find reasons that preclude an approval for ZS, there are several safety issues that require clarification prior to approval. It is not clear if the safety issues (e.g. possible MAO-A inhibition, renal toxicity, QTc prolongation) that arose during the review of this NDA are completely specific to PK/PD relationships of ZS or if they also apply to Eldepryl (but had not been identified previously). Additional study should be conducted to characterize MAO-A inhibition, QTc prolongation, and PK and tolerability in subjects with various degrees of renal impairment. Finally, AEs/SAEs should be reviewed by the sponsor to collapse preferred terms systematically and group similar AEs/SAEs, especially those possibly reflecting orthostatic hypotension.
3. The most recently conducted tyramine challenge study suggests significant MAO-A inhibition and therefore a significant potential risk for a tyramine-induced "cheese" hypertensive reaction/crisis for both ZS and Eldepryl. A repeat study must be performed prior to approval.

1.2. Recommendations

Action Recommendation

I consider this application to be approvable but several safety issues must be addressed prior to granting an approval.

Requirements for Approval

1. The tyramine challenge study needs to be repeated as a condition for approval to confirm the results of the last study or to show that these results are spurious and that there is no need to require tyramine dietary restriction.
2. ECGs must be studied at multiple times after ZS dosing at steady state to exclude or characterize a QTc prolongation effect. This could be accomplished in a repeat study assessing the effect of tyramine challenge.
3. PK must be studied in patients with renal impairment to characterize the PK and tolerability of subjects with various degrees of renal impairment. Patients who are treated with ZS and have renal impairment could generate high PK levels after 2.5 mg ZS that could mimic levels

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obtained high dose ZS (10 mg) and these high levels could further impair renal function or result in increased toxicity. This information is important for dosing considering that excretion of ZS is believed to occur mainly via the kidney and that high dose ZS appears to impair renal function.

4. AEs/SAEs should be reanalyzed using a systematic collapsing of similar preferred terms. There was no systematic collapsing of COSTART Preferred Terms during the generation of the AE/SAE tables or listings for the ISS. Because this was not done, it is not possible to know if a certain phenomenon (e.g. especially 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 specify preferred terms for the AEs/SAE rather than indicating an organ system (e.g. special senses, skin and appendages, metabolic and nutritional) to which the preferred terms are related.

Other Recommendations (Not Required for Approval)

5. The sponsor should address shortcomings identified in the PK program
6. The sponsor should characterize cardiovascular effects of ZS on orthostatic VS (supine and standing blood pressure and pulse) at multiple times after dosing. This could be accomplished in a repeat study assessing the effect of tyramine challenge.
7. The sponsor should conduct animal and/or in vitro studies to characterize effects of ZS on cardiac repolarization.
8. The sponsor should conduct analyses/plots of QT (using the different correction formulae) vs heart rate in placebo and/or baseline patients to see that the slope of the plot is 0 and there is no correlation between QTc and heart rate.
9. The sponsor should conduct analyses of other safety parameters (e.g. VS, ECGs, clinical laboratory findings, etc.) for drug-demographic interactions (e.g. age, gender). The only drug-demographic interactions analyzed were for TEAEs according to age and gender.
10. The sponsor should conduct statistical analyses (possibly using a mixed effects statistical model) of the orthostatic VS collected in the last PK/PD study for treatment (ZS vs Eldepryl), time after dosing (i.e. over 24 hours), day of study (initial dosing at day 1 vs day 10 at PK steady state), and position (supine vs standing).
11. The sponsor should analyze the apparently increased incidence of accidental injury in ZS treated patients to try to determine if these injuries were related to somnolence and/or orthostatic hypotension related to ZS.

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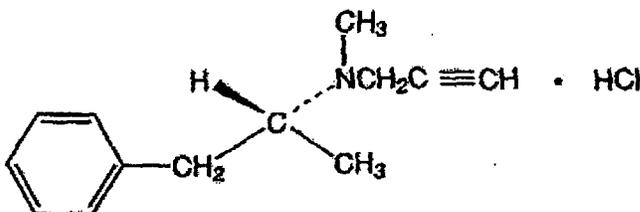
2. INTRODUCTION AND BACKGROUND

2.1. Background on Conventional Selegiline (Eldepryl ®)

Conventional selegiline is currently approved (1989) in the U.S. as well as in several other countries for the treatment of patients with Parkinson's disease (PD) who are receiving levodopa/L-DOPA (LD) therapy (with or without a peripheral decarboxylase inhibitor) and who are experiencing deterioration in their therapeutic response to LD. Selegiline is thought to exert its therapeutic effect via inhibition of the monoamine oxidase (MAO) B enzyme and the decrease in dopamine metabolism and turnover. Selegiline is marketed in the U.S. as Eldepryl ®, a formulation that is swallowed. Throughout this NDA conventional selegiline may also be referred to as Eldepryl. Although Eldepryl has also been studied to determine if it exerts a neuroprotective effect on dopaminergic neurons of Parkinson's disease patients, convincing evidence has not yet been generated.

ELDEPRYL (selegiline hydrochloride) is a levorotatory acetylenic derivative of phenethylamine. It is also commonly referred to in the clinical and pharmacological literature as 1-deprenyl.

The chemical name for selegiline is: (R)-(-)-N,N,2-dimethyl-N-2-propynylphenethylamine hydrochloride. It is a white to near white crystalline powder, freely soluble in water, chloroform, and methanol, and has a molecular weight of 223.75. The structural formula is as follows:



One very important safety concern with Eldepryl is the potential to produce hypertensive "cheese" reactions when tyramine-containing products are ingested and Eldepryl has exerted non-selective inhibition of MAO-A. Thus, the main warning in the Eldepryl label is against the use of higher than recommended doses (i.e. 5 mg BID). Severe syndromes with potentially a fatal outcome may also occur from a drug-drug interaction with various drugs such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and meperidine. Severe CNS toxicity associated with hyperpyrexia and death has been reported with the use of TCAs and conventional selegiline. Severe reactions consisting of diaphoresis, flushing, ataxia, tremor, hyperthermia, hypertension/hypotension, seizures, palpitation, dizziness, and/or mental changes (e.g. agitation, confusion, and hallucinations potentially progressing to delirium and coma) have

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been reported with the use of SSRIs and conventional selegiline. The occurrence of stupor muscular rigidity, severe agitation, and hyperthermia has been reported in some patients receiving the combination of meperidine and selegiline. Other main side effects from selegiline consist mainly of exacerbation of side effects produced by LD (e.g. nausea, vomiting, orthostatic hypotension, light headedness, syncope, hallucinations, dyskinesia, headache).

2.2. Regulatory History and Clinical Development of Zydis Selegiline

Zydis selegiline (ZS) is a rapidly-dissolving oral dosage formulation of selegiline, consisting of an open matrix of water-soluble ~~_____~~. This formulation dissolves quickly (e.g. beginning within seconds) in saliva on the tongue, releasing selegiline into the saliva, and does not require added water to aid disintegration, dissolution or absorption. Major theoretical advantages of the ZS formulation include : 1) improved patient compliance with the easily administered tablet that rapidly dissolves on the tongue, especially for patients with swallowing difficulties; 2) reduced variability in absorption relative to orally-administered standard tablets, with potentially more predictable clinical effects; and 3) reduced overall exposure to selegiline and metabolites (based on administered dose), and reduced production of potentially active metabolites. b(4)

The original IND (47005) for ZS was submitted to the FDA in 1994 by RP Scherer DDS. When the sponsor discovered and notified FDA that ZS was not bioequivalent to conventional selegiline, it was clear that clinical efficacy data would be required to support the registration of ZS. In 1996 the DNDP informed Scherer that an open-label, randomized, controlled study (Z/SEL/95/008) of parallel groups of low and high ZS and Eldepryl would not be sufficient to support efficacy. Elan Pharmaceuticals took over the clinical development of ZS from Scherer in 1997. DNDP had recommended that the sponsor conduct a single, pivotal, "large" double-blinded, placebo-controlled study of ZS in Parkinson's disease patients but the sponsor planned to conduct two smaller studies (double-blinded, placebo-controlled, parallel group) with identical designs. In February 1999, Elan Pharmaceuticals assumed ownership of ZS from Scherer and completed pivotal studies Z/SEL/97/025, and Z/SEL/97/026, and their extension phase (Z/SEL/97/027). On 11/7/01 Elan Pharmaceuticals had a pre-NDA meeting with DNDP to review mainly issues of format and content. Elan Pharmaceuticals and in addition to other Pre-NDA meetings previously for ZS. At the 11/01 meeting DNDP agreed that one positive, statistically robust study (e.g. study Z/SEL/97/026) could serve as the main basis for approval of ZS.

Early pharmacokinetic studies conducted in healthy volunteers indicated that ZS provided increased plasma concentrations of selegiline, generated a lower fraction of metabolites, and had a much higher relative bioavailability compared with standard oral tablets. Selegiline plasma concentrations were on the order of 5 - 8 times greater than that seen with the standard oral selegiline tables, suggesting a dose range of 1.25 to 2.5 mg was a potentially effective and therapeutically equivalent dose range. Based upon this information, ZS was administered in the pivotal trials at 1.25 mg daily initially and subsequently at 2.5 mg daily.

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ZS has been approved outside the U.S. ZS was first approved in 1998 in the United Kingdom, was subsequently approved in 9 other countries (see Foreign Marketing History section), and approval is pending in another country. Approval is for adjunctive therapy of Parkinson's disease with LD and for symptomatic relief or to delay the need for LD in early Parkinson's disease.

2.3. Pharmacology/Mechanism of Action of Selegiline

Selegiline (phenylisopropyl-N-methylpropylamine hydrochloride) belongs to the class of enzyme-activated irreversible inhibitors, also referred to as "suicide" substrates for monoamine oxidases (MAOs). MAOs are enzymes associated primarily with the outer mitochondrial membrane. MAOs are widely distributed throughout the body and are found in brain and in peripheral tissues such as the gut and heart. MAO catalyzes the deamination of monoamine neurotransmitters or neuromodulators among other substrates and occurs in two main forms, termed MAO-A and MAO-B. In humans, peripheral MAO is predominantly type A, while in the brain MAO is present as both forms; cortical MAO is predominantly type A, while in the striatum the predominant form is type B.

As a substrate selective for MAO-B, selegiline (L-selegiline isomer) acts in a two-step sequence, first binding to the enzyme active site then forming a covalent bond with the flavin moiety after deamination. After creation of the selegiline-enzyme combination, the MAO-B enzyme is permanently inactivated. The net result is a reduction in the ability of MAO-B to oxidize (degrade) amine neurotransmitters and neuromodulators. Restoration of MAO-B function can only be achieved through turnover of the inactivated enzyme and its replacement by synthesis of new enzyme, a process in humans that can take from two weeks up to 30-40 days to complete. When compared to other MAO-B inhibitors such as pargyline or moclobemide, and when given in therapeutically-relevant doses, selegiline displays a relatively high degree of selectivity for MAO-B. As a result, selegiline is expected to show improved tolerability and reduced potential for drug interactions than other, less selective MAO inhibitors.

Selegiline selectively and irreversibly inhibits monoamine oxidase Type B (MAO-B) and is used in Parkinson's disease patients to decrease the metabolism of dopamine and thereby enhance the effects of levodopa/L-DOPA (LD) and extend its effectiveness. In recent years, a number of other pharmacologic actions have also been identified for selegiline, including modulation of gene expression, modulation of apoptosis, and neuroprotective effects. The relationship of these potential actions of selegiline to its effectiveness in extending the action of LD in patients with Parkinson's disease is unclear.

2.4. Rationale for Selegiline Use

As LD has a relatively short half-life, requiring multiple doses during the day, the therapeutic approach to managing ON-OFF fluctuations is to pharmacologically extend the duration of each dose of LD by reducing the metabolism of the end product (dopamine) and its removal from the synapse via inhibition of MAO-B activity. This prolongation of dopamine's synaptic residence time essentially "smooths out" the rise and fall of dopaminergic stimulation delivered to the basal

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ganglia and is thought to reduce the stimulus driving the development of fluctuations in LD response.

2.5. Intended Use of Selegiline

LD, often combined with a peripheral decarboxylase inhibitor (PDI) such as carbidopa, is the primary therapy for Parkinson's disease. Patients newly diagnosed typically respond well and are stable on LD therapy for many years. As the disease progresses, however, many patients begin to lose their responsiveness to LD and develop a number of complications, especially motor complications. (e.g. end of dose wearing off, "ON-OFF", dyskinesias). Late complications of LD therapy may include the emergence of dysphagia, autonomic dysfunction, affective symptoms, or motor symptoms such as end-of-dose wearing off, ON-OFF fluctuations, and or dyskinesias.

Patients with ON-OFF fluctuations undergo disabling and unpredictable episodes during which patients normally responding to L-DOPA (the "ON" phase) experience a transient, sudden resurgence of PD symptoms such as freezing, tremor or bradykinesia (the "OFF" phase). The development of ON-OFF fluctuations has been linked to unfavorable changes in dopaminergic receptor function in the basal ganglia, primarily in response to the pulsatile nature of dopaminergic stimulation produced by intermittent dosing with LD. Estimates from the literature indicate nearly half of Parkinson's disease patients may experience motor fluctuations after 4-6 years of LD therapy. These symptoms also have a negative impact on the patient's affective state. Patients experiencing ON-OFF fluctuations are essentially disabled during the OFF periods, and form the target patient population (intended use) for ZS.

2.6. Clinical Evidence for Selegiline Effectiveness

Numerous clinical trials have been published demonstrating the effectiveness of selegiline in extending the efficacy of LD therapy in Parkinson's disease patients experiencing deteriorations in clinical benefit. In larger studies, short term therapy is associated with changes in LD response reflecting improved motor coordination, walking, ON-OFF fluctuations, and global improvement. Large, long-term studies appear to provide the best overall evaluation of response to selegiline as adjunctive therapy and, in general, support the efficacy and safety of selegiline, particularly in patients experiencing motor fluctuations. In the positive long-term studies, selegiline exerted an LD sparing effect and delayed progression to predetermined endpoints such as requiring increased LD or a dopamine agonist. Improvements in motor coordination, walking ability and motor fluctuations were also noted as well a improvements in patient disease status and performance on global scales and on various standardized assessment tools such as the Unified Parkinson's Disease Rating Scale (UPDRS) or others. These favorable outcomes for selegiline were consistent with those observed in the published short-term trials. In addition, some studies report improved survival with the addition of selegiline.

However, one large-scale open-label trial involving short-term selegiline monotherapy in early-

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stage Parkinson's disease followed by randomization to long-term therapy with either LD or LD plus selegiline found little benefit from the addition of selegiline and reported an increased mortality in the selegiline groups. The results of this study were reviewed and engendered much commentary, but little support for these discrepant findings. Several studies were subsequently published contradicting the findings, criticizing the open-label study design, re-assignments of patients to treatments, and deficiencies in the actual cause of death information gathered and the claim of increased mortality findings, including some longitudinal studies. Despite the extended evaluation of data from the negative trial, no clear reasons for the observed increase in mortality were identified. Thus, the safety of selegiline monotherapy or selegiline adjunctive therapy with LD in early-stage Parkinson's disease is still open to question. However, based on the weight of the numerous positive, published, short- and long-term trials cited above, the efficacy and safety of adjunct therapy in mid-to-late stage Parkinson's disease, particularly in patients experiencing LD wearing-off or ON-OFF fluctuations, seems clear.

2.7. Background on Conventional Selegiline (Eldepryl ®)

Conventional selegiline is currently approved (1989) in the U.S. as well as in several other countries for the treatment of patients with Parkinson's disease (PD) who are receiving LD therapy (with or without a peripheral decarboxylase inhibitor) and who are experiencing deterioration in their therapeutic response to LD. Selegiline is marketed in the U.S. as Eldepryl ®, a formulation that is swallowed. Throughout this NDA conventional selegiline may also be referred to as Eldepryl. Although Eldepryl has also been studied to determine if it exerts a neuroprotective effect on dopaminergic neurons of Parkinson's disease patients, convincing evidence has not yet been generated.

The main safety concern with Eldepryl is the potential to produce hypertensive "cheese" reactions when tyramine-containing products are ingested and Eldepryl has exerted non-selective inhibition of MAO-A. Thus, the main warning in the Eldepryl label is against the use of higher than recommended doses (i.e. 5 mg BID).

2.8. Regulatory History and Clinical Development of Zydis Selegiline

Zydis selegiline (ZS) is a rapidly-dissolving oral dosage formulation of selegiline consisting of an open matrix of water-soluble ~~_____~~. This formulation dissolves quickly (e.g. beginning within seconds) in saliva on the tongue, releasing selegiline into the saliva, and does not require added water to aid disintegration, dissolution or absorption. Major theoretical advantages of the ZS formulation include : 1) improved patient compliance with the easily administered tablet that rapidly dissolves on the tongue, especially for patients with swallowing difficulties; 2) reduced variability in absorption relative to orally-administered standard tablets, with potentially more predictable clinical effects; and 3) reduced overall exposure to selegiline and metabolites (based on administered dose), and reduced production of potentially active metabolites.

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The original IND (47005) for ZS was submitted to the FDA in 1994 by RP Scherer DDS. When the sponsor discovered and notified FDA that ZS was not bioequivalent to conventional selegiline, it was clear that clinical efficacy data would be required to support the registration of ZS. In 1996 the DNDP informed Scherer that an open-label, randomized, controlled study (Z/SEL/95/008) of parallel groups of low and high ZS and Eldepryl would not be sufficient to support efficacy. Elan Pharmaceuticals took over the clinical development of ZS from Scherer in 1997. DNDP had recommended that the sponsor conduct a single, pivotal, "large" double-blinded, placebo-controlled study of ZS in Parkinson's disease patients but the sponsor planned to conduct two smaller studies (double-blinded, placebo-controlled, parallel group) with identical designs. In February 1999, Elan Pharmaceuticals assumed ownership of ZS from Scherer and completed pivotal studies Z/SEL/97/025, and Z/SEL/97/026, and their extension phase (Z/SEL/97/027). On 11/7/01 Elan Pharmaceuticals had a pre-NDA meeting with DNDP to review mainly issues of format and content. Elan Pharmaceuticals and in addition to other Pre-NDA meetings previously for ZS. At the 11/01 meeting DNDP agreed that one positive, statistically robust study (e.g. study Z/SEL/97/026) could serve as the main basis for approval of ZS.

Early pharmacokinetic studies conducted in healthy volunteers indicated that ZS provided increased plasma concentrations of selegiline, generated a lower fraction of metabolites, and had a much higher relative bioavailability compared with standard oral tablets. Selegiline plasma concentrations were on the order of 5 - 8 times greater than that seen with the standard oral selegiline tables, suggesting a dose range of 1.25 to 2.5 mg was a potentially effective and therapeutically equivalent dose range. Based upon this information, ZS was administered in the pivotal trials at 1.25 mg daily initially and subsequently at 2.5 mg daily.

ZS has been approved outside the U.S. ZS was first approved in 1998 in the United Kingdom, was subsequently approved in 9 other countries (see Foreign Marketing History section), and approval is pending in another country. Approval is for adjunctive therapy of Parkinson's disease with LD and for symptomatic relief or to delay the need for LD in early Parkinson's disease.

3. FOREIGN MARKETING HISTORY

ZS was first approved for marketing on September 18, 1998 in the United Kingdom. A Mutual Recognition Application to the European Union member states was filed March 12, 1999

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ZS is currently approved in nine countries and is pending approval in one country. It has not been withdrawn from any market due to any reason related to safety or effectiveness. Zydis selegiline has been launched in four countries: the United Kingdom, Germany, Italy, and the Philippines. In Germany, Zydis selegiline (tradename Xilopar) is distributed by Cephalon and in Italy the product license holder is Segix.

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Zydis selegiline tablets, containing 1.25 mg selegiline hydrochloride, are approved for the following indications:

- Adjunctive therapy in combination with levodopa (with peripheral decarboxylase inhibitor) in the treatment of Parkinson's disease.
- For use alone in early Parkinson's disease for symptomatic relief and/or to delay the need for levodopa.

Table 1 provides the list of the countries, tradenames, approval dates, and as applicable the marketing introduction dates for ZS.

Table 1 Zelapar (Zydis selegiline) Global Marketing Status

Country	Tradename	Approval Date	Market Introduction Date
United Kingdom	Zelapar	September 1998	November 1998
Portugal	Xilopar	September 1999	NA
Denmark	Xilopar	October 1999	NA
Germany	Xilopar	October 1999	July 2000
Sweden	Xilopar	November 1999	NA
Austria	Xilopar	December 1999	NA
Italy	Xilopar	December 1999	September 2000
France	Otrasel	June 2000	NA
Philippines	Zelapar	June 2000	July 2000
			NA

NA = not applicable

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4. PRECLINICAL SUMMARY

I have provided a brief summary of preclinical data to support this NDA. For greater details, see the review of the Pharmacologist/Toxicologist (Dr. L. Freed).

In this 505(b)(2) submission, the sponsor makes reference to the nonclinical pharmacology and efficacy data contained in the submission for the innovator product selegiline HCl, Eldepryl tablets (NDA 19-334) and capsules (NDA 20-647) to support this NDA for ZS. No additional pharmacology studies have been performed in animals to confirm the effectiveness of selegiline as an inhibitor of MAO-B. However, based upon recommendations by DNDP, the sponsor has conducted a hamster buccal toxicity study and a dog toxicokinetic study to further support this NDA.

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The objective of the hamster buccal toxicity study was to assess the local toxicity of ZS, after 28 days of daily treatment, in both abraded and nonabraded cheek pouches. The highest concentration of selegiline tested (14 mg/mL) did not result in local toxicity after 28 consecutive days of treatment. This was a concentration of ZS that was approximately 10-fold higher than that which would be expected in patients receiving 2 x 1.25 mg tablets of ZS.

The objective of the dog toxicokinetic study was to estimate the exposure to selegiline in the Originator's dog toxicology studies. Based on the results of this 28-day toxicokinetic study in dogs, combined with data reviewed in the Originator's NDA, it is concluded that the oral administration of selegiline HCl in the Originator's toxicology studies resulted in sufficient systemic exposure to selegiline to support the proposed buccal route of clinical administration of ZS. Exposure of dogs to parent selegiline in the Originator's toxicology studies was greater than 20-fold above that expected in humans receiving 2 x 1.25 mg ZS tablets.

The sponsor has proposed that the two studies it conducted in combination with the nonclinical toxicology, pharmacology, and ADME studies in the NDAs for Eldepryl (selegiline HCl) tablets (NDA 19-334) and capsules (NDA 20-647) are sufficient to support the approval of ZS.

5. FINANCIAL DISCLOSURE

All principal investigators in the pivotal efficacy studies (i.e. Z/SEL/97/025, Z/SEL/97/026) and the most recently completed PK/PD study (AN17933-101) completed financial disclosure forms certifying that there were no financial conflicts. Considering the individuals who had completed the forms, there did not appear to be any instances involving a financial conflict. There were some subinvestigators (mostly physicians) who had not completed these forms. A brief explanation of why the form was not completed was provided in a table. However, inconsistent descriptions of the explanation why a form had not been completed were confusing.

The sponsor had as standard procedure of making 3 attempts to contact the investigators/subinvestigators and used a delivery service in addition to phone calls. I asked the sponsor to clarify the inconsistent descriptions of the explanation when a financial disclosure form had not been completed. The sponsor provided a submission that described specifically how the sponsor had attempted to contact each individual and the specific reasons why the financial disclosure form had not been completed. This response indicated that the sponsor had made valid attempts to obtain completed financial disclosure form. I have no reasons for concern about financial conflicts of interest for investigators who conducted studies that require submission of financial disclosure.

6. DATA SOURCE DESCRIPTION

The source of data for this NDA review was contained in the original NDA submission. In addition, the sponsor has made numerous submissions in response to my questions and requests

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for additional data, data presentations, and/or data analyses. The sponsor also submitted a 120 day Safety Update.

7. EXPOSURE TO ZYDIS SELEGILINE (ZS)

A total of 578 unique patients received at least one dose of ZS. There were 430 patients in the randomized/controlled or extension efficacy and safety studies (Z/SEL/97/025, Z/SEL/97/026, Z/SEL/97/027, Z/SEL/95/008, Z/SEL/95/008E). There were 148 patients in the clinical pharmacology taste preference study (Z/SEL/94/026) in which patients received a single dose of ZS and a single dose of conventional selegiline (i.e. Eldepryl).

Overall, the mean duration of exposure for all multiple-dose Parkinson's disease studies was 442 days. The maximal exposure to ZS was 1215 days. The number of patients who received ZS for ≥ 6 months was 283 and the number of patients who received ZS for ≥ 12 months/1 year was 227. **Error! Reference source not found.** shows patient accountability in all these studies and **Error! Reference source not found.** shows the number of patients who received ZS for a certain period and the ZS dose for that period.

Table 2 Patient Accountability - All Clinical Studies in Parkinson's Disease

Table 3.8-5: Patient Accountability—All Clinical Studies in Parkinson's Disease

Study	Initial Treatment in Study of Origin		Treated with Zydys Selegiline in Second Study, or Re-Entered from Previous Extension Study	Crossover Phase		Total	
	Zydys Selegiline	Placebo		Placebo to Zydys Selegiline	Zydys Selegiline to Placebo	Ever Received Zydys Selegiline	Ever Received Placebo
Z/SEL/97/026	94	48	123	41	0	135	48
Z/SEL/97/025	100	50	125	42	0	142	50
Z/SEL/95/008	127	71	0	0	0	127 ^c	0
Z/SEL/95/008E	77	0	77 ^a	0	0	77	0
Z/SEL/97/027	254	0	254 ^b	0	0	254 ^b	0
Z/SEL/94/026	148	148	0	74	74	148	148

^a includes 127 patients who received Zydys selegiline and 26 patients who received Eldepryl 10 mg in Study ZSEL/95/008.

^b includes 165 Zydys selegiline patients and 83 placebo crossovers from the placebo-controlled trials, plus 6 patients from Study Z/SEL/95/008E

^c includes 65 patients receiving 1.25 mg/day Zydys selegiline and 62 patients receiving 10 mg/day Zydys selegiline

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Table 3 Exposure Duration of Patients in All Studies

Table 3.2-6: Duration of Exposure to Zydys Selegiline in All Studies

	Z SEL 1.25 mg	Z SEL 2.5 mg	Z SEL 10 mg
Duration (days) ^{a,b}			
N	299	271	62
Mean (SD)	145.5 (197.80)	495.3 (350.97)	204.9 (178.84)
Median	45.0	482.0	88.0
Min, Max	1.0, 1101.0	7.0, 1152.0	14.0, 484.0
Cumulative Duration Categories			
<90 days	299 (100.0%)	271 (100.0%)	62 (100.0%)
≥90 days (3 months)	79 (26.4%)	218 (80.4%)	28 (45.2%)
≥180 days (6 months)	67 (22.4%)	193 (71.2%)	23 (37.1%)
≥270 days (9 months)	63 (21.1%)	179 (66.1%)	22 (35.5%)
≥365 days (1 year)	57 (19.1%)	151 (55.7%)	19 (30.6%)
≥730 days (2 years)	8 (2.7%)	91 (33.6%)	0 (0.0%)

^a For patients who were treated with Zydys selegiline in the randomized parallel studies, baseline was Day 0 or Visit 3 in the randomized studies. For patients who were assigned to Zydys placebo or traditional selegiline in the randomized parallel studies, baseline was the last visit in the randomized studies.

^b Six patients were rolled over from the Z/SEL/95/008 extension study to the Z/SEL/97/027 study. Their exposure in the Z/SEL/97/027 study was also added to the overall exposure.

Data Source: ISS End-of-Text Table 3.2. Data includes patients from Studies Z/SEL/97/025, Z/SEL/97/026, Z/SEL/97/027, Z/SEL/95/008, Z/SEL/95/008 Extension. Excludes Study Z/SEL/94/026 where 148 patients were exposed to one dose of Zydys selegiline at 5.0 mg.

The NDA also contains 9 PK and PK/PD studies of 219 healthy subjects who are not considered in the exposure numbers reviewed. The number of subjects who received a single dose of ZS was 108 and the number who participated in multidose studies (PK/PD tyramine challenge trials) was 111. These subjects received ZS (1.25, 2.5, 5, or 10 mg daily) or conventional selegiline (i.e., Eldepryl, 10 mg daily) for approximately 2 weeks.

8. HUMAN PHARMACOKINETICS

Brief Description of Studies

I have provided a relatively brief summary of human pharmacokinetic (PK) data to support this

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NDA. I reviewed the sponsor's summary of PK information and the final study reports for the 3 PK/PD studies involving tyramine challenges. For greater details, see the reviews of the Clinical Pharmacology/Biopharmaceutical reviewers, Dr. V. Tandon who conducted the comprehensive PK review and Dr. Andre Jackson who conducted a review of the population PK and PD results.

Nine studies were conducted in healthy volunteers to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of ZS. No pharmacokinetic studies were performed in patients with Parkinson's disease. These studies evaluated : 1) bioavailability and buccal absorption profile of ZS; 2) the bioequivalence of ZS and two standard oral tablets of conventional selegiline commercially available in Europe (Movergan[®] and Eldepryl[®], respectively); 3) absorption kinetics and the site of absorption of ZS; 4) single-dose pharmacokinetics of selegiline and its metabolites after administration of ZS compared to commercially-available formulations; 5) the effects of food on the PK of single doses of selegiline from the Zydis formulation (5 mg) and compares it to Eldepryl (10 mg); and 6) pharmacodynamics (PD) of ZS and Eldepryl for MAO-A inhibition as reflected in oral tyramine test in conjunction with PK of selegiline and metabolites during multiple dose administration.

Three studies evaluated both single and multiple dose pharmacokinetics of ZS in comparison to commercially available standard oral tablets (Z/SEI/95007, Z/SEL/96014, and AN17933-101). These studies also included assessment of the comparative pharmacodynamic activity of ZS and standard oral tablets after single and multiple doses, using the oral tyramine challenge test.

Pharmacokinetic Profiles of Selegiline and Metabolites

The best study for demonstrating PK parameters (e.g. C_{max}, AUC, T_{max}, peak to trough fluctuation-PTF) for different doses (1.25, 2.5, 5 mg daily) of ZS in a direct comparison with Eldepryl (5 mg BID) after initial dosing and after multiple dosing at steady state was study AN17933-101. High-performance liquid chromatography with electrochemical detection or gas chromatography with mass spectrometric or nitrogen phosphorus detection was used to quantitate selegiline, selegiline metabolites, and biomarkers for inhibition of MAO-A and MAO-B in plasma, urine and/or saliva. Selegiline metabolites included N-desmethylselegiline, L-methamphetamine, and L-amphetamine. Biomarkers reflecting MAO-B and MAO-A inhibition included 5-hydroxyindole-3-acetic acid (5-HIAA), 3-methoxy-4-hydroxyphenyl glycol (MHPG), and β-phenylethylamine (PEA).

PK parameters for selegiline for all selegiline treatments at initial dosing (day 1) and at steady state (day 10) are show in Table 4. Mean T_{max} for all ZS doses was similar at ~ 10 minutes and much faster than that (~ 4.5 hours) for Eldepryl. C_{max} for all ZS doses at both times was greater than that for Eldepryl. Although C_{max} and AUC progressively increased for all ZS doses, increments were not dose-proportional. Greater AUC at steady state than that observed initially for selegiline treatments indicated drug accumulation. PTF for all Z doses was greater than that for Eldepryl.

Pharmacokinetic parameters (C_{max}, AUC, T_{max}, PTF) for major metabolites (e.g. N-

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demethylselegiline, L-amphetamine, L-methylamphetamine) of selegiline for all selegiline treatments at initial dosing (day 1) and at steady state (day 10) are shown in Table 5, Table 6, and Table 7. Results are shown after initial dosing (day 1) and at steady state (day 10). Generation of these 3 metabolites and thus mean exposure to them was much lower for all doses of ZS compared to Eldepryl. This phenomenon was not unexpected considering the pregastric absorption for ZS and how such absorption minimizes first past hepatic effects. Although mean results for metabolites derived from ZS generally suggested dose proportionality, dose-proportionality was not shown by statistical analyses. These inconclusive results were thought to be related to high inter-subject variability. Greater AUCs for all 3 metabolites at steady state than those observed initially for selegiline treatments also indicated accumulation of metabolites. PTF for metabolites derived from all ZS treatments was also greater than that for Eldepryl as also had been seen for PTF for selegiline.

Table 4 Mean (SD) Day 1 and Day 10 Selegiline Pharmacokinetic Parameters

Treatment	Day 1			Day 10				
	C _{max} (ng/mL)	t _{max} (h)	AUC _t (ng·h/mL)	C _{ss,max} (ng/mL)	C _{ss,min} (ng/mL)	t _{ss,max} (h)	AUC _t (ng·h/mL)	PTF (%)
Zydis Selegiline 1.25 mg OD (N=15)	3.34 (1.68)	0.17 (0.17-0.27)	1.49 (0.77)	3.96 (1.90)	0.03 (0.03)	0.25 (0.17-0.50)	4.77 (2.29)	2051 (625)
Zydis Selegiline 2.5 mg OD (N=16 ^a)	4.47 (2.56)	0.18 (0.08-0.50)	2.44 (1.64)	4.37 (1.83)	0.05 (0.04)	0.25 (0.17-0.50)	6.52 (2.09)	1643 (533)
Zydis Selegiline 5.0 mg OD (N=15 ^a)	5.45 (3.24)	0.18 (0.10-0.50)	3.78 (2.03)	5.54 (3.01)	0.06 (0.04)	0.25 (0.17-0.78)	8.51 (2.74)	1485 (592)
Eldepryl® 5.0 mg BID (N=17)	1.12 (1.48)	4.55 (0.50-6.03)	1.93 (1.67)	1.73 (1.08)	0.09 (0.07)	1.00 (0.25-6.00)	8.32 (5.06)	604 (484)

* Median (range) for t_{max} and t_{ss,max}. ^a N=15 for Day 10, subject 35 withdrew on Day 9. ^b N=14 for Day 10, subject 46 withdrew on Day 9.

Data source: Tables 14.2.3.1 to 14.2.3.4

Table 5 Mean (SD) Day 1 and Day 10 N-Desmethylselegiline Pharmacokinetic Parameters

Treatment	Day 1			Day 10				
	C _{max} (ng/mL)	t _{max} (h)	AUC _t (ng·h/mL)	C _{ss,max} (ng/mL)	C _{ss,min} (ng/mL)	t _{ss,max} (h)	AUC _t (ng·h/mL)	PTF (%)
Zydis Selegiline 1.25 mg OD (N=15)	1.22 (0.48)	1.00 (0.75-1.50)	2.07 (0.71)	2.06 (0.69)	0.04 (0.05)	1.00 (0.75-2.00)	8.66 (4.39)	677 (338)
Zydis Selegiline 2.5 mg OD (N=16 ^a)	4.02 (2.05)	1.00 (0.75-3.00)	8.03 (3.64)	6.07 (3.39)	0.16 (0.09)	1.00 (0.50-1.52)	22.13 (10.09)	665 (246)
Zydis Selegiline 5.0 mg OD (N=15 ^a)	7.36 (3.16)	1.00 (0.50-2.00)	17.14 (5.16)	10.10 (4.24)	0.19 (0.12)	1.00 (0.50-3.00)	32.29 (10.28)	758 (230)
Eldepryl® 5.0 mg BID (N=17)	10.65 (5.09)	1.50 (0.50-8.00)	64.03 (38.56)	14.56 (6.44)	1.00 (0.85)	1.50 (0.25-6.17)	100.96 (56.22)	363 (158)

* Median (range) for t_{max} and t_{ss,max}. ^a N=15 for Day 10, subject 35 withdrew on Day 9. ^b N=14 for Day 10, subject 46 withdrew on Day 9.

Data source: Tables 14.2.3.5 to 14.2.3.8

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Table 6 Mean (SD) Day 1 and Day 10 L-Amphetamine Pharmacokinetic Parameters

Treatment	Day 1			Day 10				
	C _{max} (ng/mL)	t _{max} (h)	AUC _t (ng-h/mL)	C _{ss,max} (ng/mL)	C _{ss,min} (ng/mL)	t _{ss,max} (h)	AUC _t (ng-h/mL)	PTF (%)
Zydis Selegiline 1.25 mg OD (N=15)	0.20 (0.09)	1.80 (1.00-6.02)	1.49 (1.54)	1.19 (1.68)	0.28 (0.09)	3.00 (1.00-12.13)	11.92 (5.13)	156 (236)
Zydis Selegiline 2.5 mg OD (N=16 ^a)	0.58 (0.15)	4.00 (0.75-12.00)	8.00 (1.48)	1.78 (0.82)	0.60 (0.26)	3.00 (1.00-6.00)	26.92 (7.92)	107 (51)
Zydis Selegiline 5.0 mg OD (N=15 ^a)	1.33 (0.28)	3.00 (1.00-6.00)	19.94 (3.78)	3.24 (0.60)	1.14 (0.39)	3.00 (0.92-6.00)	50.63 (10.42)	112 (38)
Eldepryl® 5.0 mg BID (N=17)	2.69 (0.65)	8.00 (4.50-23.93)	44.17 (8.28)	5.30 (1.07)	2.62 (0.59)	8.00 (0.50-12.00)	95.25 (16.98)	69 (22)

* Median (range) for t_{max} and t_{ss,max}. ^a N=15 for Day 10, subject 35 withdrew on Day 9. ^b N=14 for Day 10, subject 46 withdrew on Day 9.
Data source: Tables 14.2.3.9 to 14.2.3.12

Table 7 Mean (SD) Day 1 and Day 10 L-Methamphetamine Pharmacokinetic Parameters

Treatment	Day 1			Day 10				
	C _{max} (ng/mL)	t _{max} (h)	AUC _t (ng-h/mL)	C _{ss,max} (ng/mL)	C _{ss,min} (ng/mL)	t _{ss,max} (h)	AUC _t (ng-h/mL)	PTF (%)
Zydis Selegiline 1.25 mg OD (N=15)	0.62 (0.23)	1.50 (1.00-3.00)	5.68 (2.44)	1.78 (0.84)	0.51 (0.21)	2.00 (1.00-12.13)	24.45 (11.79)	125 (25)
Zydis Selegiline 2.5 mg OD (N=16 ^a)	1.86 (0.49)	1.50 (0.75-4.00)	20.17 (4.27)	4.29 (1.63)	0.93 (0.50)	2.02 (0.75-6.00)	53.88 (15.56)	151 (45)
Zydis Selegiline 5.0 mg OD (N=15 ^a)	5.00 (1.53)	1.50 (1.00-4.02)	57.49 (12.63)	8.76 (1.51)	2.17 (0.85)	1.26 (0.50-6.12)	113.76 (36.91)	150 (46)
Eldepryl® 5.0 mg BID (N=17)	8.37 (1.28)	8.00 (5.00-12.53)	131.34 (21.83)	16.23 (2.72)	5.12 (1.55)	6.00 (1.50-12.00)	254.98 (66.55)	109 (26)

* Median (range) for t_{max} and t_{ss,max}. ^a N=15 for Day 10, subject 35 withdrew on Day 9. ^b N=14 for Day 10, subject 46 withdrew on Day 9.
Data source: Tables 14.2.3.13 to 14.2.3.16

Plasma Concentrations Following Therapy

Plasma samples obtained from the two studies Z/SEL/97/025 and Z/SEL/97/026 indicate that trough levels of selegiline were very low in the majority of patients, with median plasma concentrations of 0.246 ng/mL at Week 4 (1.25 mg/day) and 0.8380 ng/mL at Week 12 (2.5 mg/day). Corresponding placebo values were below the limit of quantitation for both sampling points. These observations are consistent with steady-state half-life values reported in PK/PD studies (which ranged from 7.8 hours in study AN17933-101 to 13.3 hours in study Z/SEL/97/005). Also, plasma concentrations fell below quantifiable limits within 4 hours of administration of ZS 1.25 mg and within 12 hours for the 2.5 mg dose in study AN17933-101, again consistent with the observations from studies Z/SEL/97/025 and Z/SEL/97/026.

The design of the primary efficacy trial Z/SEL/97/026 and the supportive trial Z/SEL/97/025 required the evaluation of patients prior to taking their daily dose of study medication, and again after taking the daily dose. This resulted in close clustering of values for dosing interval (time since last dose) on clinic days around 24 hours, as most patients came to the clinic in the

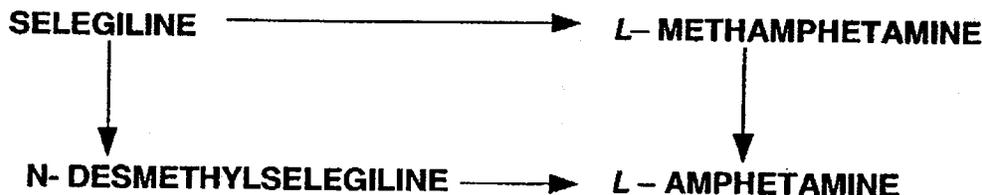
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morning for assessment. As plasma samples for selegiline were to be taken prior to the patient's daily dose of study medication, this limited the opportunity to obtain samples to a small window around 24 hours after the last dose and rendered attempts to generate population pharmacokinetic analyses unreliable. Nevertheless, a population PK analysis was performed. Median AUC values for selegiline were 3.33 ng/mL•hr at week 4 (1.25 mg/day) and 6.66 ng/mL•hr at week 12 (2.5 mg/day), and were similar to mean AUC values found at steady state in Study AN17933-101 (4.77 ng/mL•hr for 1.25 mg/day and 6.52 ng/mL•hr for 2.5 mg/day).

Metabolism of Zydys Selegiline

Selegiline is metabolized to L-methamphetamine and N-desmethylselegiline, both of which are further metabolized to L-amphetamine as shown in the diagram below. Although little is known about quantitative excretion of selegiline and metabolites after ZS administration because the sponsor did not perform mass balance studies, the PK reviewer (Dr. V. Tandon) noted that we can consider that results of study of excretion of conventional selegiline as an approximation for ZS. Selegiline (i.e. Eldepryl) and its principal metabolites are excreted primarily in urine. More specifically, based upon a literature review, approximately 85% of an oral dose of selegiline given as a standard tablet was recovered as L-methamphetamine (59%) and L-amphetamine (26%).



Metabolism of selegiline typically exhibits high inter-patient variability. Peak serum concentrations of selegiline metabolites may occur anywhere within 0.5 to 2 hours, and C_{max} varies widely. Selegiline is a small molecule with a pK_a that allows significant absorption of the drug through the buccal mucosal surface directly into the systemic circulation, avoiding first-pass metabolism that occurs after administration of standard oral tablets. Thus while the metabolic profile of selegiline is not altered by the Zydys dosage forms, a higher fraction of the administered dose is delivered to the systemic circulation. The fraction of selegiline transformed to metabolites is reduced by approximately an 80% compared to oral Eldepryl.

Pharmacokinetic Conclusions

- Pre-gastric absorption of selegiline from the ZS formulations and avoidance of significant first-pass hepatic metabolism resulted in higher fractions of the administered dose being delivered to the systemic circulation and lower fractions of the administered dose being converted to metabolites.

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- In several studies, selegiline bioavailability, based on plasma selegiline AUC, was 6-8 fold greater after Zydis selegiline 2 x 5.0 mg than after Eldepryl 2 x 5.0 mg, suggesting that an equivalent dose for Zydis selegiline would lie much lower than 2 x 5.0 mg/day, possibly in the 1.25 to 2.5 mg/day range.
- Selegiline exhibited consistent dose-dependent kinetics after administration of ZS, with single-dose C_{max} values of 3.96 ± 1.90 ng/mL (1.25 mg), 4.37 ± 1.83 ng/mL (2.5 mg), and 5.54 ± 3.01 ng/mL (5.0 mg), compared to 1.73 ± 1.08 ng/mL for Eldepryl 2 x 5.0 mg. T_{max} values were consistently earlier for ZS (15 minutes after administration, all three doses) than for Eldepryl (1.0 hour after administration).
- The mean exposure to selegiline, as measured by AUC at steady state, was lower for Zydis selegiline 1.25 mg/day (4.77 ± 2.29 ng/mL, hr) and 2.5 mg/day (6.52 ± 2.09 ng/mL•hr) than for Eldepryl 2 x 5.0 mg/day (8.32 ± 5.06 ng/mL•hr).
- There are several shortcomings of the PK program that should be addressed by the sponsor.
 - There are no mass balance studies to indicate quantitative routes of excretion of ZS.
 - There are no studies of PK of ZS in subjects with various degrees of renal impairment or hepatic impairment. Neither is information known about the PK of conventional oral selegiline (e.g. Eldepryl) in subjects with various degrees of renal impairment or hepatic impairment.
 - There are no PK studies of ZS in elderly subjects (≥ 65 years old).
 - The sponsor did not analyze the PK data of ZS for a gender effect.
 - The sponsor did not conduct any drug-drug interaction (DDI) studies.
 - The results of the food interaction study are puzzling for both ZS (5 mg) and Eldepryl (10 mg). Considering that most ZS absorption should be pre-gastric, it is difficult to understand why food would alter the extent (but not T_{max}) of absorption. Furthermore, the sponsor found that food decreased the absorption of selegiline with Eldepryl treatment. This is contrary to the labeling for Eldepryl that notes that food can increase bioavailability by 3 to 4 fold.

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9. PHARMACODYNAMICS

I have reviewed the pharmacodynamic (PD) data to support this NDA. I reviewed the sponsor's summary of PK/PD information and the final study reports for the 3 PK/PD studies involving tyramine challenges. For greater details, see the reviews of the Clinical Pharmacology/Biopharmaceutical reviewers, Dr. V. Tandon who conducted the comprehensive PK review and Dr. Andre Jackson who conducted a review of the population PK and PD results.

9.1. Background / Introduction

Monoamine oxidases (MAOs) are intracellular enzymes distributed widely throughout the body with highest concentrations found in liver, kidney, stomach, intestine, and brain. Selegiline is a selective inhibitor of central monamine oxidase type B (MAO-B), an enzyme responsible for dopamine metabolism in brain. With increasing doses, many drugs, including selegiline lose their selectivity for inhibiting a specific enzyme. For example, increasing doses of selegiline may be associated with increasing inhibition of MAO-A, an enzyme predominant in human intestine.

Norepinephrine, tyramine, and epinephrine are substrates for MAO-A and to a lesser extent, MAO-B. With significant inhibition of MAO-A, the metabolism of tyramine diminishes and significant amounts of tyramine may reach the systemic circulation and ultimately result in a hypertensive reaction or even crisis. This result is believed to occur via the "false-neurotransmitter" hypothesis whereby tyramine is converted to a octopamine that is taken up at noradrenergic synapses. This uptake of octopamine is associated with increased synaptic release of norepinephrine and various cardiovascular actions including hypertensive effects, and increments in vascular constriction, heart rate, and cardiac contractility. A clinical model for testing inhibition of MAO-A is the oral tyramine test that evaluates the pressor response to tyramine challenge. Tyramine is known to be present in significant quantities in cheese (and other foods and certain alcoholic beverages) and is believed to be responsible for the "cheese reaction" that can produce a hypertensive crisis, especially when taking MAO inhibitors with little or no selectivity.

The WARNINGS section of the Eldepryl label notes that the selectivity of selegiline for MAO-B may not be absolute even at the recommended daily dose of 10 mg daily. This section of the label also

Metabolism of various substances may be altered with inhibition of MAO-B and MAO-A. Correspondingly, changes in metabolic profiles can indirectly show these inhibitory effects. Considering that MAO-B primarily degrades dopamine and phenylethylamine (PEA), inhibition of MAO-B leads to increased dopamine and PEA and increased urinary excretion of PEA (normally PEA is not measurable in urine), a reflection of such inhibition. Along these lines,

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MAO-A primarily degrades serotonin (5-hydroxytryptamine-5 HT) to 5-hydroxyindoleacetic acid (5-HIAA) that is excreted in urine. MAO-A also degrades norepinephrine to 3-methoxy-4-hydroxyphenyl glycol (MHPG). Analogously, inhibition of MAO-A results in decreased plasma MHPG and 5-HIAA as well as decreased urinary 5-HIAA.

The purpose of the main PK/PD study AN17933-101 was to assess MAO-B and MAO-A inhibition for the two ZS doses (e.g. 1.25 and 2.5 mg QD) included in the pivotal efficacy trials, and a higher ZS dose (5.0), and compare results to those for the marketed formulation of selegiline (i.e. Eldepryl) taken according to the U.S. label twice daily (after breakfast and lunch). MAO-A inhibition would be assessed by evaluating changes in the sensitivity of blood pressure changes (i.e. pressor responses) to oral tyramine challenge and changes (i.e. decrements) in metabolic profiles of products (e.g. plasma MHPG and urinary 5-HIAA) of substrates (e.g. norepinephrine and serotonin, respectively) of MAO-A. Increments in tyramine sensitivity are determined by noting the magnitude of the lowering of the mean tyramine threshold dose after treatment, the number of subjects who exhibit threshold low tyramine doses (e.g. < 100 mg, and especially \leq 50 mg), and the increment in the Tyramine Sensitivity Factor (TSF). The TSF is calculated by dividing the control/pre-treatment tyramine threshold dose by the post-treatment tyramine threshold dose for each subject. MAO-B inhibition would be assessed by changes (i.e. increments) in the metabolic profile of a substrate of MAO-B (e.g. urinary PEA).

ZS results in decreased generation of its main metabolites (e.g. N-demethylselegiline, L-amphetamine, L-methylamphetamine) via its pre-gastric absorption in the mouth that minimizes hepatic first-pass effects which contribute to generation of these metabolites. These PK/PD also assessed PK profiles of selegiline metabolites for the various selegiline treatments.

At a pre-NDA meeting (1/30/01) with the sponsor, DNDP had requested that the sponsor conduct a pharmacodynamic study to assess MAO-B and MAO-A inhibition for ZS 2.5 mg (the dose studied for primary efficacy analysis) with a commercial dosing of Eldepryl (5 mg BID) to overcome shortcomings of previously conducted pharmacodynamic studies. Study AN17933-101, conducted in response to DNDP's request, is the most relevant pharmacodynamic study in this NDA and is therefore the most important pharmacodynamic study. Study AN17933-101 investigated not only the dose for which approval is desired (i.e. 2.5 mg daily) but also a higher (5.0 mg daily) and lower (1.25 mg daily) dose of ZS and compared all these doses of ZS with conventional selegiline/Eldepryl as commercially dosed (5 mg BID; 4 hours apart at breakfast and lunch times). Therefore, this study is reviewed and presented in greatest detail.

Other similar pharmacodynamic studies assessing MAO-B and MAO-A inhibition were also performed. Study Z/SEL/96/014 and Z/SEL/95/007 had studied a lower (i.e. 1.25 mg) and higher (i.e. 10 mg ZS daily) dose respectively in comparison to 10 mg of Eldepryl given at a single dosing as two capsules in the morning before breakfast. These studies also assessed changes in sensitivity to oral tyramine-induced hypertensive responses and changes in the metabolic profiles of a substrate for MAO-B inhibition, products of substrates for MAO-A, and selegiline and metabolites.

9.2. Study AN17933-101 (Study of Pharmacodynamic Effects on Tyramine Testing and Pharmacokinetics)

Principal Investigator : Paul Rolan, MB BS MD FRACP FFPM DCPSA

Study Site : Medeval Limited
Skelton House
Manchester Science Park
Lloyd Street North
Manchester M15 6SH
UK

9.2.1. Description of Protocol AN17933-101 (Amendment 4; 9/17/01)

Title of Study :

Comparison of the Pressor Effect of tyramine Following repeat Dose Administration of Zydis Selegiline 1.25, 2.5, and 5.0 mg QD and Eldepryl (Conventional Selegiline) 5.0 mg BID in Healthy Volunteers

Study initiation date : 7/20/01

Study completion date : 12/6/01

Objectives :

Primary : Assess the relative selectivity of Zydis selegiline (ZS; 1.25, 2.5, and 5.0 mg, once daily-QD) and Eldepryl (conventional selegiline) 5.0 mg twice daily (BID) for MAO-A and MAO-B by investigating pressor responses to orally administered tyramine

Secondary : Assess the pharmacokinetics (PK), pharmacodynamics (PD), and tolerability of each formulation of selegiline

STUDY DESIGN and SCHEDULE :

The study was an open-label, partially randomized, parallel dose group trial designed to assess the effects of ZS (1.25, or 2.5, or 5.0 mg QD before breakfast) an Eldepryl 5.0 mg BID (first dose after a light breakfast and second dose 4 hours later after lunch) on the tyramine challenge test (to increase blood pressure) as an indirect measure of MAO-A inhibition. Effects on metabolic profiles of substrates of MAO-B (phenylethylamine-PEA) and MAO-A (3-methoxy-4-hydroxyphenyl glycol-MHPG and 5-hydroxyindoleacetic-5-HIAA) in plasma and/or urine will also be studied to assess the selectivity of MAO inhibition by the various selegiline treatments. Approximately 60 male healthy volunteers were to be studied. Changes in the sensitivity to tyramine threshold testing (e.g. increase in sensitivity to tyramine to meet threshold systolic blood pressure increment of > 30 mm Hg) would indicate nonspecific inhibition of MAO-A by a

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selegiline treatment. Up to 68 male subjects were to be studied at a single center with a goal of obtaining at least 60 evaluable subjects. Subjects would sign an informed consent document and be randomized to Eldepryl or one dose of ZS for 14 days after applying inclusion and exclusion criteria to each subject in the screening period. However, the protocol was subsequently amended so that all subjects who satisfied screening were not randomized to all 4 treatment groups. Because assignment to Eldepryl treatment would require spending significantly more time in the clinical unit than for subjects assigned to ZS, subjects were given the option of selecting ZS treatment (i.e. receiving one of the ZS doses) or Eldepryl treatment. Thus, during the study the protocol was amended so that subjects opting for ZS would only be randomized to one of 3 doses.

Key Inclusion Criteria :

- males age 18 - 45 years
- body weight within 20 % of appropriate range as defined by Metropolitan Life tables
- no history of clinically significant diseases
- no history of clinically significant abnormalities of hematology, chemistry, urinalysis, or positive serology for hepatitis B or C or HIV

Key Exclusion Criteria :

- history of sensitivity to tyramine or selegiline
- family history of premature (< 50 years age of onset) coronary artery disease or cerebral hemorrhage
- history of undiagnosed chest pain, stroke, transient ischemic attack, intracranial hemorrhage, or asymptomatic intracranial aneurysm or other vascular malfunction
- history of a clinical condition that may affect drug absorption, metabolism, or excretion
- history of mental illness, drug addiction, drug abuse, or alcoholism
- resting blood pressure > 140/90 within the past 3 months
- blood donation within past 3 months
- use of an investigational drug within past 3 months
- use of a prescription drug within 21 days before day 1 or an over the counter medication within 11 days before day 1
- use of an MAO inhibitor, fluoxetine, other SSRI or tricyclic antidepressant within past 3 months

The screening period was from day -21 until day -1. The treatment period was from day -1 until day 14. The post-study period was from day 14 until day 21. Subjects were to be admitted to the clinical study unit on the evening (e.g. day -8 and day -11) prior to each tyramine testing period (day -7 up to day -5 and day 12 up to day 14) and tyramine testing each day unless there was a reason for an overnight stay. All other testing was to be conducted on an "outpatient" basis not involving overnight stays. The schedule for performing various evaluations including blood and urine sampling, tyramine testing, and other procedures is shown in Table 8.

Subjects receiving ZS took ZS approximately 30 minutes after starting breakfast while upright . They were not supposed to eat or drink for at least 5 minutes before and after taking ZS and were

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also supposed to refrain from swallowing while ZS dissolved. Subjects were supposed to fast for at least 10 hours beginning on the evenings of day -1 and day -9. Subjects receiving Eldepryl could eat lunch 15-30 minutes prior to the second tyramine test.

Subjects also were supposed to be asked to refrain from alcohol consumption from 48 hours prior to day 1 completion of the study. Caffeine intake was supposed to be restricted to no more than 3 cups of coffee or tea or 12 ounces of soda. Although tobacco use was permitted during the study, subjects were not supposed to take caffeine or use nicotine from midnight prior to performing tyramine testing until completion of that day's testing.

Oral Tyramine Threshold Test Procedure

Subjects, who were given a list of tyramine containing products at screening, were supposed to abstain from consuming tyramine containing products from at least 5 days prior to the initial tyramine testing until completion of the study. An oral tyramine threshold challenge test was to be performed on days -7 to -5 prior to beginning study drug and again on days 12 to 14 after dosing with study drug and achieving steady state. Prior to administration of tyramine on each test day, the reference measurements of blood pressure and pulse would be made by obtaining 3 sets of measurements and taking the average of the 3 for each day to serve as the reference value. The reference value for each day would be used to determine when the subject met the threshold tyramine response and when it was acceptable to administer a repeat dose of tyramine. The tyramine test would be performed by administering increasing doses (maximum of 3 doses/day) of oral tyramine on up to 3 consecutive days. Subjects were supposed to fast and abstain from cigarette smoking from midnight prior to each testing day, to continue to fast until completion of tyramine testing each day to remain at rest in the supine position during procedures on each test day. Doses of 100, 200, 300, 400, 500, 600, and 700 mg of tyramine (with 150 mls of water) were to be given during the baseline threshold testing. During the testing at steady state selegiline treatment, tyramine treatment was to start with ascending doses of 25 and 50 mg and continue up to the same higher doses given at the baseline/pre-treatment testing until the threshold result was achieved. On each test day, tyramine doses were to be given at 2 hour intervals beginning at 30 minutes following administration of the total daily selegiline treatment. A repeat tyramine dose was to be administered only if blood pressure returned to < 10 mm Hg above the pre-dose reference value for that day. Tyramine dosing was to be stopped once the threshold cardiovascular response (i.e. rise of systolic blood pressure > 30 mm Hg above pre-dose reference value of that test day) was observed. Treatment with labetalol or phentolamine was to be given if systolic blood pressure rose > 60 mm Hg above baseline

On each tyramine test day, heart rate and blood pressure were to be measured at 5 minute intervals from 10 minutes before each tyramine dose until 120 minutes after treatment (or longer if blood pressure remains ≥ 10 mm Hg above the pre-dose reference value for that day). Blood pressure was recorded using a _____ automated blood pressure monitor. Each subject was to remain supine during this time and was to be asked immediately after the blood pressure measurement to lie on the right side and only to return to the supine position one minute before the next blood pressure measurement. **The reference point for calculation of change in blood pressure and heart rate, after all 3 doses on each day, was to be the mean of 3 pre-dose values before any tyramine dosing.**

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Safety and tolerability of treatment was to be assessed by oropharyngeal examinations, measurement of orthostatic vital signs (VS), routine blood chemistry and urine analyses and monitoring of adverse events. For orthostatic VS measurements of blood pressure (via automated monitor) and pulse, VS were measured after being supine for at least 3 minutes and then immediately upon standing. Regarding oropharyngeal examinations, the oropharynx was supposed to be examined for signs of mucosal pathology on day -1 (requirement to be performed before first selegiline treatment on day 1) and at the post-study visit (occurring between day 14 to 21). The assessor was to be a qualified dental or oral surgeon who was independent of all other aspects of the study. Subjects were to be told to alert the treating physician if they developed mouth ulcers, abnormal pain or soreness in their mouths and to arrange to be seen as soon as possible. The oropharyngeal examination was to comprise visual inspection of the inside of each cheek, the inside of each lip, the surface of the tongue, and the pharynx. Any discrete areas of focal reddening, multiple foci of reddening, edema, and ulceration were to be noted and graded (e.g. absent, mild, moderate, or severe). Standard source data collection forms were to be provided to the assessor.

Table 8 Study Schedule of Events

Procedure	Screen	Day											Post-study		
		-8	-7 to -5	-1	1	2	3 to 7	8	9	10	11	12 to 14			
Informed consent	✓														
Med. history	✓														
Inclusion/Exclusion	✓	✓		✓											
Physical Exam	✓														✓
Vital signs ¹	✓	✓		✓	✓ ²	24 h			✓		✓ ²		✓		✓
Height and Weight	✓														Weight
ECG	✓														✓
Hem./Chem./UA	✓			✓											✓
Hepatis B, C, HIV	✓														
Breath alcohol & urine drug screen	✓	✓		✓					✓						
Overnight stay		✓	As required	✓	✓				✓	✓	✓	✓	As required		
Overnight fast				✓					✓	✓	✓	✓			
Administer study drug (section 6.5)					✓	✓	✓	✓	✓	✓	✓	✓	✓		
PK blood samples for Zydys Selegiline					✓ ³	24 h		Pre-dose	Pre-dose	✓ ³	24 h	1 hour post-dose			
PK blood samples for Eidepryl®					✓ ⁴	24 h		Pre-dose	Pre-dose	✓ ⁴	24 h	1 hour post-dose			
MHPG blood samp.				✓	✓				✓	✓					
24 h urine ⁵				Start	Finish/ Start	Finish			Start	Finish/ Start	Finish				
Tyramine test			✓											✓	
Oropharynx Irr.				✓											✓
Adverse events		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Con. Meds.	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

¹Oral Temperature, blood pressure & pulse supine after three minutes & immediately upon standing. ²Treatments A-C: BP and pulse at pre-dose, 1, 2, 4, 8, 12, 16 & 24 hours post-dose; oral temperature pre-dose, 12 & 24 hours post-dose; Treatment D: BP and pulse at pre-dose, 1, 2, 4, 5, 6, 8, 12, 16 & 24 hours post-dose; oral temperature pre-dose, 12 & 24 hours post-dose. ³PK samples pre-dose, 5, 10, 15, 30, 45, 60 min. & 1.5, 2, 3, 4, 6, 12, & 24 hours post-dose ⁴PK samples pre-dose, 15, 30, 60 min., 1.5, 2, 4, 4.25, 4.50, 5, 6, 8, 12, & 24 hours post-dose. ⁵24-hour urine for PEA and 5-HIAA were collected in 6 hour aliquots from 0-6 & 6-12 hours, then a 12 hour aliquot from 12-24 hours

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Table 8 showing the schedule of events indicates when samples of blood were to be obtained for PK characterization of selegiline and its major metabolites (e.g. N-demethylselegiline, L-amphetamine, L-methylamphetamine). Table 8 also indicates when blood and urine samples were to be obtained for characterizing changes in profiles of substrates of MAO-B (e.g. urinary PEA) and MAO-A (plasma MHPG and urinary 5-HIAA) as indices of inhibition of these enzymes by different selegiline treatments.

Analyses : Pharmacodynamic tyramine test results will be tabulated and summarized and incorporated into a survival analysis. The survival analyses and tyramine pressor ratios will be analyzed statistically. Pharmacokinetic parameters and results of metabolic profiles of a substrate of MAO-B and products of substrates for MAO-A will also be tabulated, summarized descriptively, and analyzed statistically. Demographic and safety data will be tabulated and summarized descriptively. Analysis of safety and tolerability of treatment would be based upon vital signs, routine laboratory test results, adverse events and oropharyngeal examinations.

Protocol Amendments

There were no significant protocol amendments worthy of discussion except for amendments deemed worthy of description and already described within the protocol.

9.2.2. Results of Study AN17933-101

Patient Disposition

A total of 66 subjects enrolled but only 63 subjects were assigned to one of 4 treatment groups because 3 subjects failed the screening tyramine threshold testing. At screening, subjects were given the option of being randomized to receive one of 3 ZS doses or Eldepryl. The disposition of all subjects is shown in Figure 1. Sixty subjects completed the study. One subject in each of 3 treatment arms (total n = 3) withdrew for protocol deviation/non-compliance because of a positive test for alcohol. Although it was later discovered after completion of study that one subject violated an exclusion criterion by having received an investigational drug within 3 months prior to day 1 of study, this subject was included in data analyses.

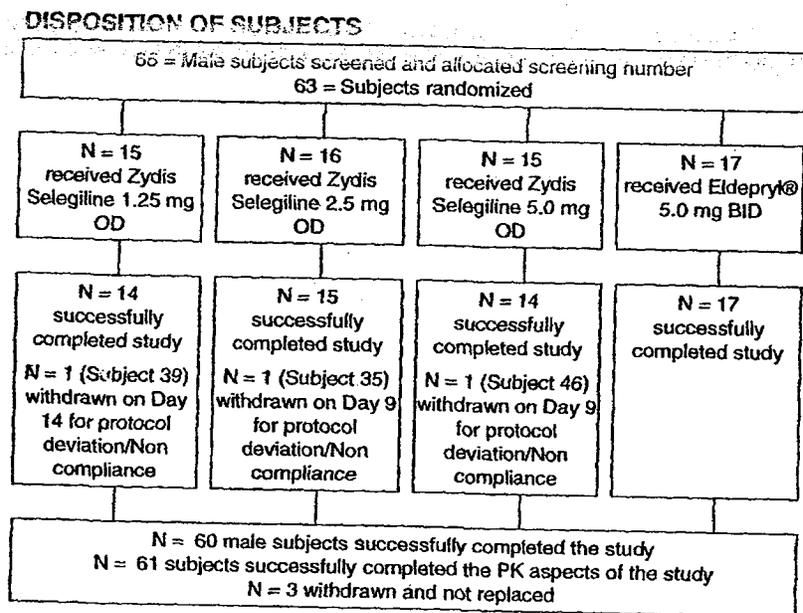
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Figure 1



Protocol Violations, Deviations, and Prohibited Concomitant Medications

The sponsor described errors in conducting the study as protocol deviations. However, the sponsor did not define protocol deviation nor make a distinction between protocol violation and protocol deviation. A total of 271 protocol deviations were recorded. The sponsor noted that the majority of these violations were not considered to be of a serious nature that would compromise the achievement of the study objectives. This reviewer does not consider any of these violations sufficiently significant or relevant to be described here.

Demographic Characterizations

There did not appear to be notable differences among the 4 selegiline treatment groups with regard to certain demographic characteristics (i.e. age, race, height, or weight).

9.2.2.1. Pharmacodynamic Results

Tyramine Testing

No subjects in any selegiline treatment group appeared to experience a hypertensive crisis.

Three subjects(# 39-ZS 1.25 mg group; # 35-ZS 2.5 mg group; # 46 ZS-5.0 mg group) were not included in the survival analysis of tyramine threshold doses during treatment because they did not achieve a threshold dose during testing at steady state selegiline. Each subject was withdrawn prior to steady state testing because of a positive alcohol breath test result.

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Table 9, Table 10, Table 11, and Table 12 show tyramine threshold results for individual subjects in each treatment group for the pre-treatment/baseline state and during steady state treatment between days 12-14. Tabulated arithmetic means and SD, % CV, median, minimum and maximum for each group are also shown in these tables.

Results (see Figure 2) from survival analysis could not detect any differences in the survival curves of the tyramine threshold doses amongst the 4 treatment groups at baseline prior to treatment administration. According to the log rank test the p value was 0.1211 and according to the Wilcoxon test the p value was 0.1617.

Similarly, during steady state selegiline treatment, there was no statistically significant difference (i.e. $p > 0.05$) amongst the 4 treatment groups with a survival analysis (see Figure 3). Although the p value using the log rank test was borderline and approached statistical significance with a value = 0.0538, there was no evidence for statistical significance according to the Wilcoxon test in which the p value was 0.1182.

The Wilcoxon matched pairs signed rank sum test tested the null hypothesis that the median difference between the pre-treatment tyramine threshold dose and that during steady state treatment equaled zero indicating no effect of treatment on tyramine threshold doses. All four treatment groups showed a highly statistically significant reduction in tyramine threshold doses with p values < 0.0002 indicating that each selegiline treatment reduced the threshold of the cardiovascular/pressor effects of tyramine. Thus, all treatments indirectly via tyramine testing showed evidence for MAO-A inhibition.

Analyses of the ratios (pre-treatment threshold dose/steady state threshold dose) of the tyramine threshold doses were also performed to assess differences amongst the 4 treatment groups by making pairwise comparisons of all potential combinations of treatment groups. Results of these analyses including least square means for each treatment group, differences between groups and corresponding 95 % confidence intervals and respective p values are shown in Table 13. The mid-dose (i.e. 2.5 mg QD) ZS group mean ratio (2.65) was statistically lower ($p = 0.0230$) than that (6.74) for the conventional Eldepryl treatment group. The mid-dose (i.e. 2.5 mg QD) ZS group mean ratio (2.65) was also statistically lower ($p = 0.0292$) than that (6.91) for the low-dose (i.e. 1.25 mg QD) ZS group. All other pairwise comparisons between treatment groups were not statistically significant with relatively high p values ($p \geq 0.2533$). These statistically significant results suggested that there was less MAO-A inhibition with the 2.5 mg daily ZS treatment than that with treatment of a lower dose of ZS (i.e. 1.25 mg daily) and conventional Eldepryl treatment (5.0 mg BID).

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Table 9 Tyramine Threshold Doses and Tyramine Pressor Ratios: ZS 1.25 mg QD

Subject	Pre-Treatment Tyramine Threshold Dose (mg)	During Treatment Tyramine Threshold Dose (mg)	Tyramine Pressor Ratio
1	400	50	8.00
2	200	25	8.00
6	400	50	8.00
8	500	100	5.00
9	300	100	3.00
22	600	300	2.00
23	500	300	1.67
31	500	300	1.67
36	700	400	1.75
39	500	NV	NR
41	600	25	24.00
50	500	400	1.25
55	300	25	12.00
57	500	400	1.25
61	400*	25	16.00
N	15	14	14
Arithmetic Mean	460	179	6.69
SD	130	160	6.75
CV%	28	89	101
Median	500	100	4.00
Min	200	25	1.25
Max	700	400	24.00

NV = No value, as subject withdrawn prior to attainment of threshold dose for a positive ABT.

NR = No result

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

Table 10 Tyramine Threshold Doses and Tyramine Pressor Ratios: ZS 2.50 mg QD

Subject	Pre-Treatment Tyramine Threshold Dose (mg)	During Treatment Tyramine Threshold Dose (mg)	Tyramine Pressor Ratio
5	200*	25	8.00
14	300	200	1.50
15	300	300	1.00
16	300	200	1.50
18	400	200	2.00
19	400	400	1.00
21	100	25	4.00
24	600	500	1.20
25	300	200	1.50
27	400	200	2.00
29	400	300	1.33
34	300	200	1.50
35	400	ND	NR
44	300*	25	12.00
54	500	400	1.25
60	500	300	1.67
N	16	15	15
Arithmetic Mean	356	232	2.76
SD	121	141	3.12
CV%	34	61	113
Median	350	200	1.50
Min	100	25	1.00
Max	600	500	12.00

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

NR = No result

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

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Table 11 Tyramine Threshold Doses and Tyramine Pressor Ratios: ZS 5.0 mg QD

Subject	Pre-Treatment Tyramine Threshold Dose (mg)	During Treatment Tyramine Threshold Dose (mg)	Tyramine Pressor Ratio
4	300	50	6.00
10	400	200	2.00
11	400	200	2.00
17	500	200	2.50
26	600	50	12.00
28	300	200	1.50
30	400	200	2.00
38	400	200	2.00
40	300	200	1.50
43	300	25	12.00
46	400	ND	NR
47	300*	25	12.00
51	300	200	1.50
53	500	300	1.67
58	200	25	8.00
N	15	14	14
Arithmetic Mean	373	148	4.76
SD	103	92	4.35
CV%	28	62	91
Median	400	200	2.00
Min	200	25	1.50
Max	600	300	12.00

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

NR = No result

Table 12 Tyramine Threshold Doses and Tyramine Pressor Ratios: Eldepryl 5.0 mg BID

Subject	Pre-Treatment Tyramine Threshold Dose (mg)	During Treatment Tyramine Threshold Dose (mg)	Tyramine Pressor Ratio
3	200	100	2.00
7	200	25	8.00
12	200	25	8.00
13	400	50*	8.00
20	300	25	12.00
32	500	100	5.00
33	400	50	8.00
37	500*	50	10.00
42	300	50	6.00
45	500	50	10.00
48	600	200	3.00
49	200	100	2.00
52	300	300	1.00
56	500	400	1.25
59	200	25	8.00
63	500	25	20.00
65	600	200	3.00
N	17	17	17
Arithmetic Mean	376	104	6.78
SD	148	109	4.82
CV%	39	104	71
Median	400	50	8.00
Min	200	25	1.00
Max	600	400	20.00

NA = Not applicable, as subject was withdrawn prior to Day 12.

NR = No result

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

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Figure 2 Tyramine Threshold Doses at Pre-Treatment

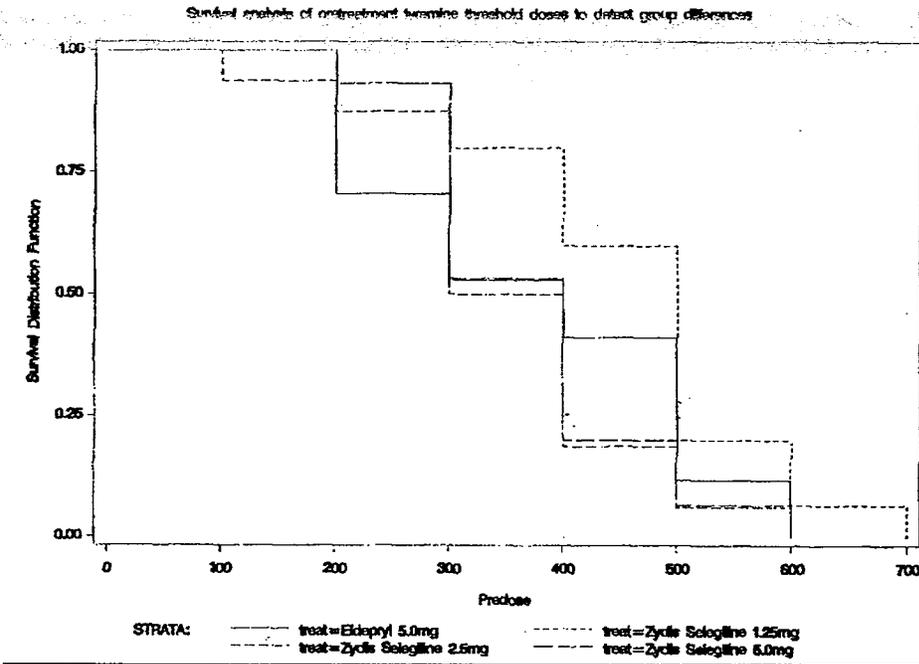
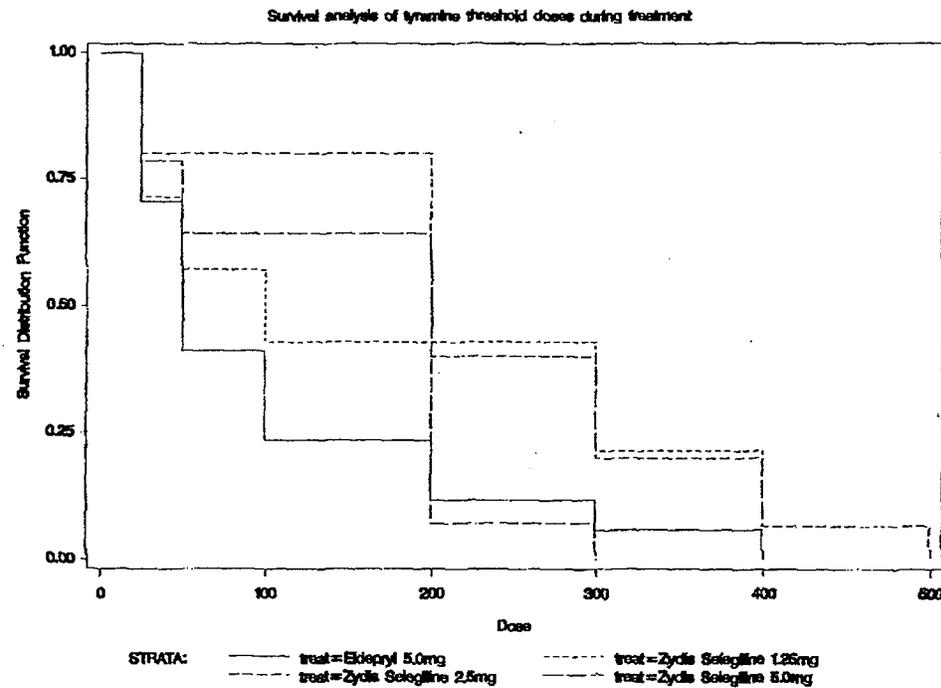


Figure 3 Tyramine Threshold Doses During Steady State Treatment



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Table 13 Summary of the Statistical Comparison of the Tyramine Pressor Ratios

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

Data source: Appendix 16.2.7.10

Table 14 Number and Percent of Subjects Showing Significant Sensitivity to Low Tyramine Doses at Steady State Selegiline Treatment

Tyramine Threshold Dose	ZS 1.25 mg n = 14	ZS 2.5 mg n = 15	ZS 5.0 mg n = 15	Eldepryl 5 mg BID n = 17
< 50 mg	6 (42.9 %)	3 (20 %)	5 (33.3 %)	10 (58.8 %)
25 mg	4 (28.6 %)	3 (20 %)	3 (20 %)	5 (29.4 %)

Metabolic Profiles for Substrate of MAO-B and Products of Substrates of MAO-A

A statistical comparison between 2 pre-treatment measurements of plasma free on day -1 and day 1 (pre-dose) showed a statistically significant overall effect ($p = 0008$). There was considerable intrasubject variability and few statistically significant differences amongst the 4 treatment groups at different times before and after treatment. Table 15 shows the results of various selegiline treatments on least square mean plasma free MHPG concentration. Although MHPG concentrations were lower on day 10 vs baseline/pre-treatment (mean of day -1 and day 1 before dosing) for all treatments, statistical differences occurred only for the higher dose treatments (i.e. ZS 5 mg QD and Eldepryl 5 mg BID). The magnitude of the decrement from baseline was greater for higher dose selegiline treatments (approximately 20 % and 22 % for ZS 5 mg and Eldepryl treatments respectively) and smaller for lower dose selegiline treatments (approximately 16 % and 10 % for ZS 1.25 mg and Zs 2.5 mg respectively). Overall, these results showing a modest decrease in generation of MHPG are consistent with modest inhibition of MAO-A.

Table 16 shows the effect of different selegiline treatments on 24 hour urinary excretion of 5-HIAA over time (e.g. pre-treatment day-1 to day 1, initial treatment day 1 to day 2, and steady

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state treatment day 9 to 10 and day 10 to 11). Although there were no statistically significant differences, there was a trend for an increase in amounts of 5-HIAA over time for all ZS treatments and a trend for a decrease in amounts of 5-HIAA for Eldepryl. Results of this indirect measure of MAO-A inhibition suggest possible inhibition of MAO-A by Eldepryl but no apparent inhibition by any ZS treatment.

Table 16 also shows a progressive increase in urinary excretion of PEA for all treatments and reflects inhibition of MAO-B. These increments were dose-dependent for ZS. The increment produced by Eldepryl was most similar to the increments produced by 2.5 mg ZS.

Table 15 Effect of Treatment on Plasma Free MHPG (LS mean) Over Time

Treatment	Baseline/Pre-treatment (mean Day -1 & Day 1)	Day 9	Day 10
ZS 1.25 mg QD	0.89	0.93	0.75 *
ZS 2.5 mg QD	1.22	1.11	1.10
ZS 5.0 mg QD	0.93	0.89	0.74 # **
Eldepryl 5.0 mg BID	1.15	1.03	0.90 ##

* p = 0.0356 vs ZS 2.5 mg QD Day 10

** p = 0.0363 vs ZS 5.0 mg QD Day 10

p = 0.0498 vs ZS 5.0 mg QD Baseline

p = 0.0054 vs Eldepryl 5.0 mg BID Baseline

Table 16 Mean (SD) Pre-treatment and During Treatment PEA and 5 -HIAA 24 Hour Urinary Excretion

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

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

Data source: Tables 14.3.4.1 to 14.3.4.4

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9.2.2.2. Pharmacokinetic Profiles of Selegiline and Metabolites

Pharmacokinetic parameters (C_{max}, AUC, T_{max}, peak to trough fluctuation-PTF) for selegiline and major metabolites for all selegiline treatments at initial dosing (day 1) and at steady state (day 10) in this study are presented (Table 4, Table 5, Table 6, Table 7) in the PK section of this review.

9.2.2.3. Safety

All selegiline treatments were generally tolerated well. There were no deaths, serious adverse events (SAEs), nor discontinuations for AEs. Treatment AEs (TEAEs) for all selegiline treatments were generally similar in frequency, nature, and severity. Overall, the most frequent TEAEs were headache, palpitations, somnolence, fatigue, and dizziness. The number of TEAEs and subjects experiencing them is shown in Table 17. There was no clear suggestion of a dose-dependent occurrence of AEs for the different doses of ZS. The sponsor did note that the proportions of AEs judged to be study treatment related appeared to be less for all doses of Zs compared to Eldepryl treatment. However, the open-label nature of the study makes this observation a useless one of unknown significance.

Table 17 Overall Summary of Adverse Events in Study

	Number of Subjects (% receiving treatment)	Number of AEs
Overall Total	49 (78 %)	129
Pre-treatment AEs Total	26 (41 %)	38
<i>Treatment emergent AEs Total</i>	<i>40 (63 %)</i>	<i>91</i>
Zydis Selegiline 1.25 mg OD Total	8 (53 %)	14
Zydis Selegiline 2.5 mg OD Total	13 (81 %)	25
Zydis Selegiline 5.0 mg OD Total	10 (67 %)	21
Eldepryl 5.0 mg BID Total	9 (53 %)	31

Data source: Appendix 16.2.8, Tables 14.4.1.1, and 14.4.1.2

In general, the sponsor noted that there were no clinically relevant changes in orthostatic VS (i.e. supine and standing blood pressure and pulse). It is not clear upon what basis the sponsor makes this statement, particularly when "clinically relevant changes" are not defined. The sponsor has collected many orthostatic VS measurements for all treatment subjects before treatment and throughout treatment including at various designated timepoints over two 24hour periods (on initial dosing on day 1 and at PK steady on day 10). These VS data are presented descriptively (e.g. N, mean, SD, min, max, median, % CV) as summary statistics for all treatment groups. These data were not analyzed for any effects (e.g. treatment, orthostatic changes, changes over the treatment period, etc.) and were not subjected to statistical analyses.

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

There were no significant changes in ECGs nor physical examinations that were noted at the post-study visit.

A total of 281 clinical laboratory abnormalities (i.e. outside reference range) were observed in all subjects from pre-treatment, treatment, and post-treatment periods. Although the sponsor noted that there were 5 potentially clinically significant laboratory abnormalities in 4 subjects, only 3 of these abnormalities in 2 subjects were treatment-emergent. Subject # 19 (ZS 2.5 mg) experienced a mild elevation of serum ALT (86 IU/mL; normal 5-40) and AST (48 IU/ml; normal 5-45) at the post-study visit. Three days later a repeat test showed that AST became normal and that ALT (54) was decreasing. The persisting ALT elevation was not considered to be of clinical significance. Subject # 23 (ZS 1.25 mg) experienced a minimal elevation of serum bilirubin (26 $\mu\text{mol/L}$; normal ≤ 21) at a post-study visit. A repeat test three days later show a similarly, mildly elevated value (25). This was not considered to be of clinical significance. Of interest, one pre-treatment screening result was also similarly elevated (25) for this subject and a repeat test before initiating treatment was normal. This reviewer did not consider any other treatment-emergent laboratory abnormalities worthy of description.

Open-label oropharyngeal examinations did not reveal any serious abnormalities from treatment (ending between day 12 – 14 depending when the tyramine threshold dose was achieved) at the post-study visit that could have occurred between days 14 –21. There were 3 subjects with mild treatment-emergent changes. Two subjects (# 21-ZS 2.5 mg; # 30-ZS 5.0 mg) experienced aphthous ulcers in the mucolabial/mucobuccal folds) and one subject (# 40-ZS 5.0 mg) exhibited cold sores in the perioral area.

9.2.3. Discussion of Study Results

Pharmacodynamics

There are some potentially important issues to be noted relative to the design of this study. This study did not contain a placebo control and was not blinded. Thus, not only is there no ideal placebo control group for comparison of results, but results are potentially subject to some bias regarding blood pressure readings for determining tyramine sensitivity thresholds. Subjects and

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investigators would know if subjects received Eldepryl or ZS because subjects were given the option of receiving Eldepryl or being randomized to one of the 3 ZS doses. Conceivably, investigators, could unconsciously or even consciously record blood pressure readings that would suggest less tyramine sensitivity for ZS, the experimental drug under study compared to Eldepryl. Neither is it clear what effect, if any, this partial randomization might have had on results. Finally, only young to middle age males were studied. Although this reviewer did not find any data suggesting a differential sensitivity to tyramine and MAO inhibition for males and females or older subjects, it is possible results could show that females and/or older subjects exhibit somewhat lesser sensitivity to tyramine after selegiline treatment. Of interest, both of the sponsor's other PK/PD studies investigating tyramine challenges (i.e. studies Z/SEL/096/014 and Z/SEL/095/007) included both older (38 – 70 years old) male and female subjects and their results suggested less MAO-A inhibition (reflected by tyramine challenge results) for similar doses than results in study AN17933-101. In these other studies, mean TSF ratios for Eldepryl (3.4 and 3.7) were lower than that (6.8) obtained for Eldepryl in study AN17933-101. Similarly, the mean TSF for ZS 1.25 mg (2.8) in study Z/SEL/096/014) was much lower than that (6.7) observed for the same dose in study AN17933-101. This observation argues for including older male and female subjects in a repeat study.

All ZS selegiline treatments appeared to lower the sensitivity to tyramine relative to baseline/pre-treatment results. Tyramine pressor ratios (i.e. TSFs) for all ZS doses were similar to or less than that observed with conventional Eldepryl treatment. Although these results indirectly reflected MAO-A inhibition also by ZS (as occurred for Eldepryl), MAO-A inhibition appeared to be either less than that or similar to that occurring with Eldepryl because ratios were not higher than that of Eldepryl. Of interest, the tyramine pressor ratio/TSF for ZS 2.5 mg was statistically less than that for Eldepryl, possibly suggesting less MAO-A inhibition. However, the fact that the mean tyramine pressor ratio for the lowest dose of ZS 1.25 was similar to the mean value for Eldepryl and was also statistically greater than that for ZS 2.5 mg argues against the idea that MAO-A inhibition, as reflected by tyramine testing, is less. The tyramine pressor ratio for the lowest ZS dose was also higher (but not statistically greater) than that of the highest ZS dose suggesting perhaps that the occurrence of the statistically significant difference may have been a chance event. If there was dose-dependent MAO-A inhibition with the ZS doses studied, one would have predicted seeing a direct correlation between tyramine pressor ratio and ZS dose such that the lowest ratio occurred with the lowest dose and the highest ratio occurred with the highest dose. However, a dose-dependent effect was not observed.

The absence of a dose-dependent effect of ZS on increasing sensitivity to oral tyramine as a reflection of MAO-A inhibition could be related to one or any combination of 4 potential interpretations : 1) maximal but limited MAO-A inhibition occurs at a relatively low threshold (e.g. ZS doses \geq 1.25 mg daily); 2) the slope of dose-response curve for MAO-A inhibition is actually very shallow over a relatively wide range of the ZS doses studied and you cannot see a slight upward trend because of relatively small numbers of subjects per group; 3) there is a U-shaped dose-response MAO-A inhibition curve or 4) these results are spurious for unknown reasons. **Overall, based upon the tyramine testing in this study, my conclusion is that MAO-A inhibition from ZS doses ranging between 1.25 to 5 mg daily is similar to each other and at the least, not greater than that observed with Eldepryl. These results do not allow one to**

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draw a conclusion that MAO-A inhibition, with respect to tyramine testing, is less than that occurring with conventional Eldepryl treatment (when administered 5 mg BID according to the FDA label in the morning)

b(4)

It is important to put these results into perspective by comparing them with tyramine testing results in the literature and on file with FDA. **Of interest, the increased tyramine sensitivity shown in this study during Eldepryl treatment contrasts with reports of specific oral tyramine test results in the literature and the overall impression conveyed in various publications that there is little or no significant inhibition of MAO-A associated with 10 mg daily of Eldepryl.** However, surprisingly, I was only able to find 1 study (from a search of the literature and FDA files) that seemed comparable to study AN17933-101 in terms of important study design variables. The Somerset Pharma Study SP9303-P9934 Report (Blob et al., 2001, contained in NDA 21336 for transdermal selegiline) conducted by Somerset Pharma (i.e. the sponsor for Eldepryl) appears to be a reasonably comparable to study AN17933-101 in important design variables because the Somerset study investigated the effect of 10 mg daily Eldepryl (given as 5 mg BID) on healthy subjects and utilized a tyramine pressor dose threshold that was similar (i.e. a rise in systolic blood pressure \geq 30 mm of Hg). The Somerset Pharma study found a mean TSF of 1.7, a mean tyramine threshold dose of 355 mg after treatment but no subjects exhibited a tyramine threshold below 100 mg. These results stand in marked contrast to those in the Elan study under discussion in which ZS (1.25 mg) and Eldepryl (5 mg BID) showed respective mean TSFs of 6.7 and 6.8, mean tyramine threshold doses after treatment of 179 mg and 104 mg, and percentages of subjects with very low treatment threshold doses (i.e. \leq 50mg) of 42.9 % and 58.8 % that were much higher. Such results suggest considerable MAO-A inhibition. Potentially relevant design differences in the Somerset study that may account for the different results compared to study AN17933-101 are :1) the shorter 9 day Eldepryl treatment period (vs 12 days); 2) the use of 2 pre-treatment tyramine tests that were averaged to provide a more integrated control test; and 3) the requirement that 3 consecutive systolic blood pressure increments (measured at 5 minute intervals) be obtained to achieve the tyramine threshold. I believe that studying Eldepryl dosing as 5 mg BID according to the label is an important issue because there is some suggestion that greater MAO-A inhibition may be obtained when a 10 mg daily dose of Eldepryl is taken BID instead of as a single dose. It is also of interest to note that mean TSF is typically $>$ 20 in subjects treated with non-selective MAO inhibitors that result in significant MAO-A inhibition and are associated with serious hypertensive "cheese" reaction.

A further surprise was that I was only able to find only 5 published studies (Elsworth et al., Psychopharm, 57:33, 1978; Prasad et al., Psychopharm, 95:540, 1988; Bieck et al., J Neural Transm, Suppl, 28: 21, 1989; Schultz et al. Clin Pharm Ther, 46:528, 1988; Warrington et al., J Psychopharm, 5:82, 1991) that contained potentially relevant data for comparison of oral tyramine testing results after treatment with oral selegiline (i.e. Eldepryl). **However, these studies contained various, potentially important study design differences including ; 1) Eldepryl dose of 10 mg as a single dose or lower or higher daily doses; 2) treatment duration of a stable Eldepryl dose before tyramine testing; 3) study population such as healthy subjects or depressed or Parkinson's disease patients; 4) specific definitions for determining tyramine threshold such as systolic response greater than 20 or 25 mm Hg or a certain diastolic rise or a certain pulse decrease; and 5) other requirements/conditions for establishing the threshold dose**

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such as single baseline VS reference, position during VS collection and frequency of collecting VS.

In these studies mentioned above, mean TSFs ranged from 1.7 - 4.1, mean tyramine treatment threshold dose ranged from 111 mg to 250 mg, and the percentage of subjects with very low tyramine threshold doses (i.e. ≤ 50 mg) ranged from 0 % to 14.3 %. In one study (Bieck et al., J Neural Transm, Suppl, 28: 21, 1989) that investigated the effect of 20 mg daily of selegiline (after 5 mg x 2 weeks and then 20 mg x 2 weeks) on the oral tyramine systolic pressure ratio (PD30), the change in tyramine sensitivity based upon changes in median threshold dose was 4.6, but no information was provided about individual TSFs nor about specific threshold doses. **Although tyramine challenge results in these publications tend to suggest less MAO-A inhibition than results of study AN17933-101, the many differences in potentially important study design variables outlined earlier for these studies may be sufficiently important to suggest a misleading conclusion that MAO-A inhibition with the approved dose of Eldepryl (5 mg BID) is minimal or insignificant.** One can only speculate what results might have been obtained by these other investigators if they had performed tyramine testing after treatment with Eldepryl as 5 mg BID for a period approaching 2 weeks and utilized a similar definition/procedure for determining tyramine threshold (e.g. > 30 mm Hg rise in systolic blood pressure relative to an integrated baseline reference value) as used in study AN17933-101.

Results in study AN17933-101 also appear to contrast somewhat with those derived from other oral tyramine studies (Study Z/SEL/96-014 investigating 10 mg Eldepryl as a single dose and ZS 1.25 mg; and Study Z/SEL/95-007) investigating 10 mg Eldepryl as a single dose and ZS 10 mg) contained in this NDA and presented later in this review. In study 96-014, respective results for ZS (1.25 mg) and Eldepryl (10 mg QD) were 2.7 and 3.6 for mean TSFs, were 332 mg and 225 mg for mean tyramine treatment thresholds, and 9.1 % and 18.2 % for percentage of subjects with very low tyramine threshold doses (i.e. ≤ 50 mg). In study 95-007, respective results for ZS (10 mg) and Eldepryl (10 mg QD) were 3.7 and 4.5 for mean TSFs, were 121 mg and 131 mg for mean tyramine treatment thresholds, and 8.3 % and 16.7 % for percentage of subjects with very low tyramine threshold doses (i.e. ≤ 50 mg). **Thus, results in general from Study AN17933-101 not only appear to suggest more MAO-A inhibition for all ZS doses and Eldepryl (5 mg BID) according to oral tyramine testing than is suggested by the preponderance of other data contained in the literature or in the Somerset Pharma study but also somewhat greater MAO-A inhibition than is suggested from earlier studies submitted by the sponsor.**

Of interest, the ratio for mean control tyramine threshold dose/mean treatment tyramine threshold dose is not usually presented nor discussed in studies of oral tyramine testing after selegiline treatment. Furthermore, mean TSF results (determined by averaging individual results of control tyramine threshold dose/treatment tyramine threshold dose) may be much different and higher than results presented as mean control tyramine threshold dose/mean treatment tyramine threshold dose for the specific treatment group. For example, in study AN17933-101 mean TSF for ZS (1.25 mg) and Eldepryl (5 mg BID) was 6.7 and 6.8 respectively, but the ratio of mean control tyramine threshold dose/mean treatment tyramine threshold dose for these groups was only 2.6 and 3.6 respectively. When these ratios are compared to the ratio in the Somerset study (1.5), the relative difference in this parameter is not as great as when mean TSFs

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are compared. In the other 5 oral tyramine testing studies discussed, this ratio ranged between 1.5 to 3.7.

The sponsor notes that the increase in tyramine sensitivity produced by ZS and Eldepryl in study AN17933-101 is not clinically significant. However, a close look at test results in this study tends to suggest otherwise. The range (148 - 232 mg) of the mean tyramine threshold doses on ZS treatment is relatively low in absolute terms, is much lower than that (355 mg) observed in the most comparable study (Somerset Pharma) in which Eldepryl was given 5 mg BID, and is only modestly higher than that (104 mg) observed for Eldepryl 5 mg BID in the same study. Of great potential importance, the percentage of individuals exhibiting a threshold treatment dose of tyramine ≤ 50 mg after ZS and also after Eldepryl was considerable. This percentage for ZS doses ranged between 20 - 42.9 % and this percentage for Eldepryl was 58.8 %. The percentage of individuals also exhibiting a threshold treatment dose of tyramine ≤ 25 mg was even more disconcerting. **More specifically, the fact that 42.9 % of the 1.25 mg ZS group % showed a treatment tyramine threshold dose that was ≤ 50 mg (vs 56.8 % for Eldepryl) and 28.6 % showed a treatment tyramine threshold dose of 25 mg (vs 29.4 % for Eldepryl) seems alarming and contrasts greatly with any other data for which I am aware.** The other 2 Elan studies (96-014 and 95-007) also showed small percentages of subjects with a very low threshold doses (≤ 50 mg). In study 96-014 the percentage of subjects showing a tyramine threshold of 50 mg was 9.1 % for ZS (1.25 mg) and 18.2 % for Eldepryl (10 mg QD) and the percentage of subjects showing a tyramine threshold of 25 mg was 9.1 % for Eldepryl. In study 95-007 the percentage of subjects showing a tyramine threshold of 50 mg was 8.3 % for ZS (10 mg) and 16.7 % for Eldepryl (10 mg QD) and the percentage of subjects showing a tyramine threshold of 25 mg was 8.3 % for Eldepryl. **I am unable to find any study of Eldepryl treatment and oral tyramine testing that showed very low tyramine threshold doses (e.g. ≤ 50 mg) of tyramine except for the Elan studies and one study (Warrington et al., J Psychopharm, 5:82, 1991) in which one subject exhibited a very low (≤ 25 mg; 12.5 % of subjects). Considering that a diet consisting of 10-50 mg of tyramine is considered a significant tyramine load and that dietary products containing 10 - 25 mg of tyramine have been associated with serious hypertensive reactions as a manifestation of the "cheese effect", there is concern that these results could have clinical relevance regarding MAO-A inhibition.** It is difficult to avoid this consideration based upon the results of the Elan trials, especially study AN17933-101. It is also relevant to note that the sponsor did not conduct any studies assessing the effect of tyramine rich meals on vital signs to diminish concerns about the risk of ZS.

The literature also contains several studies (Mendis et al., Psychopharm, 73:87, 1981; Sunderland et al., Psychopharm, 86:432, 1985; Prasad et al., Psychopharm, 95:540, 1988; Korn et al., Pharmacodynamics, 49: 273, 1996) that provide results of IV tyramine testing for selegiline. I mention these studies for comparison with results of oral tyramine testing. Because these studies do not have direct relevance to study results in this NDA, I will focus on considering and comparing results of oral tyramine testing. **IV tyramine testing appears to be less sensitive than oral tyramine testing based upon a study (Schultz et al. Clin Pharm Ther, 46:528, 1988) in which the same subjects underwent both oral and IV tyramine testing after similar treatment periods with Eldepryl.** Whereas, the mean TSF for IV tyramine testing was 1.4 and 2.1 after 5 and 20 mg of Eldepryl respectively, the mean TSF was

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1.8 and 4.0 in response to the same respective doses of Eldepryl (Schultz et al. Clin Pharm Ther, 46:528, 1988). In addition, one study (Sunderland et al., Psychopharm, 86:432, 1985) that investigated the effect of a wide range of Eldepryl doses (10 mg, 30 mg, 60 mg) showed that with increasing doses of Eldepryl there is increasing MAO-A inhibition as reflected by increasing mean TSFs such that the highest dose showed a similar mean TSF that was similar that of a non-selective MAO inhibitor.

Overall, examinations of profiles of products of substrates for MAO-A did not show major changes during steady state treatment. Measurements of plasma MHPG showed relatively small decrements at steady state treatment for all ZS doses and Eldepryl and were statistically significant for the highest dose of ZS (5.0 mg) and Eldepryl relative to baseline. In addition, 24 hour measurements of urinary 5-HIAA excretion for all ZS doses did not decrease during treatment but suggested a slight upward trend. In contrast, urinary 5-HIAA measurements suggested a decreasing trend with treatment with Eldepryl. Although statistically significant changes were not observed with any treatment over time, these contrasting trending patterns might suggest mild MAO-A inhibition with Eldepryl with respect to this indirect measure of MAO-inhibition. Conceivably, different indices of MAO-A inhibition may be associated with different sensitivities for showing MAO-A inhibition.

Despite results suggesting potentially considerable MAO-A inhibition from studies in the NDA, there were no instances of hypertensive crisis associated with any ZS treatment and exposure to gradually increasing test doses of tyramine in these Elan studies. Neither were there any examples of hypertensive crisis associated with Eldepryl treatment and exposure to gradually increasing test doses of tyramine nor cases of hypertensive crises described within this NDA. However, rare cases of hypertensive crisis are known to occur, albeit rarely, with Eldepryl treatment and sympathomimetic drugs such as pseudoephedrine even at the recommended labeled dose of 5 mg BID. Considering that MAO-A inhibition with 2.5 mg ZS may actually be similar to that occurring with Eldepryl when one considers the totality of all pressor ratio data for all ZS treatments and Eldepryl, it would not seem unreasonable to expect rare occurrences of hypertensive crisis when large numbers of patients using 2.5 mg ZS are exposed to tyramine containing products ranging between 10-50 mg. A search of AERS Datamart (FDA post-marketing database reflecting AERs) using various hypertensive terms and selegiline revealed 49 cases. Unfortunately, most of these cases did not show a narrative to describe precisely the adverse reaction. Thus, it is not possible to know what these cases represent. A few cases appeared to reflect a serious drug-drug interaction reactions associated Eldepryl use and other drugs including SSRIs, tricyclic antidepressants, and nalbuphine. One case was also reported as a published letter (Amano et al., J Neurol, 248: 533, 2001) describing a patient who exhibited paroxysmal hypertensive crises (soon after starting Eldepryl titrated up to 10 mg daily) and that prompted a negative evaluation for a pheochromocytoma. This patient's hypertensive crises resolved after Eldepryl was discontinued.

It is difficult to understand why hypertensive crises would not be reported more frequently if Eldepryl inhibited MAO-A to the extent suggested from study AN17933-101. Some studies suggest that oral tyramine challenges administered with food and known tyramine content in food products may produce less blood pressure stimulation than oral tyramine administered

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during fasting. Conceivably, this phenomenon could explain why hypertensive crises from dietary "cheese" reactions of tyramine containing foods or beverages are relatively rare with Eldepryl 5 mg BID even if it did result in MAO-A inhibition suggested by results from study AN17933-101.

There is also some information contained within NDA 21-336 (for transdermal selegiline; sponsor - Somerset Pharma) that bears consideration to results contained within the NDA under review. Studies in NDA 21-336 showed a mean TSF of 1.7 for 20 mg transdermal selegiline, the dose for which approval was requested. However, no subjects exhibited low tyramine threshold doses below 100 mg. This product bears relevance to ZS because both products purport to minimize unwanted inhibition of MAO-A in intestine and liver via absorption primarily into the systemic circulation to avoid first pass hepatic effects. In terms of considering PK/PD relationships (from multidosing studies at steady state) for these products, mean C_{max} for transdermal selegiline (~ 3.5 ng/ml) is lower than C_{max} for the 3 doses ZS (~ 4.0 ng/ml for 1.25 mg ZS; ~ 4.4 for 2.5 mg ZS; ~ 5.5 ng/ml for 5 mg ZS) but is higher than C_{max} (~ 1.7 ng/ml) for Eldepryl (5 mg BID). In contrast, AUC for transdermal selegiline (~ 65 ng/mL•hr) is much higher than AUC for Eldepryl (~8.3 ng/mL•hr) and for all ZS doses (~ 4.8 ng/mL•hr for 1.25 mg ZS; ~ 6.5 ng/mL•hr for 2.5 mg ZS; ~ 8.5 ng/mL•hr for 5 mg ZS). In view of these results, MAO-A inhibition would be greatest with transdermal selegiline if MAO-A was related to AUC of selegiline. Mean T_{max} for ZS, Eldepryl, and transdermal selegiline was approximately 11, 1, and 0.3 hours respectively. However, if MAO-A inhibition was related to C_{max} and T_{max} (and thus shape of the PK curve) of selegiline, MAO-A inhibition from these doses of ZS and Eldepryl might be somewhat similar and less than that observed with transdermal selegiline. However, it is not clear from the literature what selegiline PK parameters and kinetic relationships correlate with MAO-A inhibition. Furthermore, consideration of these PK parameters for these formulations of selegiline and their kinetics do not help explain results of oral tyramine testing in study AN17933-101.

The question has been raised from suggestions in the literature whether MAO-B selectivity decreases with increased duration of exposure to selegiline and MAO-A inhibition increases. In NDA 21-336 the sponsor presented data about the effect of increasing duration of exposure on oral tyramine testing with transdermal selegiline after treatment for 9-10, 21, and 33 days. There were progressive increments in mean TSF and ratio of mean control tyramine threshold dose/mean treatment tyramine threshold dose and progressive decrements in the mean tyramine threshold dose. These results consisted of pooled data across studies. However, these results were of sufficient concern to DNDP that DNDP recommended that the sponsor conduct a trial assessing the chronic safety of transdermal selegiline by studying serial oral tyramine threshold testing over 3 months. The sponsor has submitted a protocol to perform this study. A similar potential concern about the chronic safety of ZS can also be raised and consideration should be given to whether Elan should also perform such a study, particularly in light of results suggesting the extent of MAO-A inhibition associated with ZS treatment for a short period.

Results of measurements of urinary PEA excretion served as a positive control for bioactivity of all study treatments. All doses of selegiline significantly increased urinary excretion of PEA and

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thereby showed evidence of significant MAO-B inhibition, the pharmacological action believed to contribute to the therapeutic effect of selegiline on dopamine metabolism.

In summary, these data suggest that the change in oral tyramine sensitivity from Eldepryl dosed according to the label (i.e. 5 mg BID) in study AN17933-101 reflects inhibition of MAO-A activity to a greater extent than any other known result and the impression derived from all other studies investigating Eldepryl under various design conditions. However, the reference standard for comparison is extremely limited because I can only find one unpublished study (Somerset Pharma) that is very comparable to study AN17933-101 for the most important design variables. Thus, one is left with the question why such apparently discrepant results were observed in study AN17933-101 and whether results from this study or the impression derived from other studies reflects the true extent of MAO-A inhibition produced by conventional selegiline (i.e. Eldepryl). **If results of study AN17933-101 are real, it would be difficult to avoid considering that tyramine restriction should be instituted when such selegiline treatments are used. The only way to resolve these most critical questions regarding both formulations of selegiline is for the sponsor to conduct another, better designed study of oral tryamine testing for all ZS doses (1.25, 2.5, 5, ? 10 mg) and Eldepryl (5 mg BID).** Important improvements in design of a future study could include : 1) double-blinding; 2) addition of placebo and also possibly higher ZS dose group of 10 mg to allow one to see a possible dose response; 3) incorporating a positive control group involving treatment with a non-selective MAO inhibitor as a positive comparator; 4) addition of second control/pre-treatment testing to obtain an average control tyramine threshold dose for individuals; 5) requirement that the threshold dose be established when 3 consecutive systolic blood pressures collected at 5 minute intervals exceed 30 mm Hg; and 6) studying both males and females of older ages (e.g. 40 – 70 years old) who would resemble more closely the population to receive treatment with ZS.

Finally, all results of oral tyramine sensitivity testing for the lowest daily dose of ZS (i.e. 1.25 mg) in study AN17933-101 were consistently very similar to those of Eldepryl, and results of higher ZS doses were somewhat similar to those of Eldepryl. After reviewing all these data, it seems reasonable to entertain one of two possible conclusions. **The sponsor's results in their totality suggest that MAO-A inhibition related to ≤ 2.5 mg daily ZS is similar (in a worst case scenario) to that occurring with Eldepryl, or it may actually be less than that occurring with Eldepryl.**

Pharmacokinetics

There were no unusual, unexpected results observed from the data generated in this study for selegiline and its metabolites. Thus study did, however, provide results for permitting direct comparison of PK parameters within a single study for ZS doses of 1.25, 2.5 and 5.0 mg daily with Eldepryl 5 mg BID.

Safety

There were no unusual nor unexpected safety findings from this study. Neither were there any safety findings worthy of comment or discussion. However, it does appear that the sponsor has

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collected a significant, extensive body of safety data that remains to be explored and analyzed with respect to orthostatic VS (systolic and diastolic blood pressures and pulse in both supine and standing positions) Although this study involved open-label treatment without a placebo group, the sponsor collected several sets of VS prior to treatment and during treatment (at initial dosing over the first 24 hours and over another 24 hour period at steady state) for 3 ZS doses and conventional Eldepryl treatment. It is relatively unusual to have such an extensive amount of data that may show group differences in orthostatic blood pressure and/or pulse at various timepoints after dosing with initial dosing and later at PK steady state.

I have asked the sponsor to perform statistical analyses of these orthostatic VS data to characterize effects of ZS more comprehensively and to assess if my impression that ZS raises blood pressure and pulse is real. Clearly these data could help characterize pharmacological effects of ZS on orthostatic VS both early and later in the dosing scheme and at various times after dosing in supine and standing positions. An argument for requesting more extensive analyses of these data is based upon considerations that : 1) patients with Parkinson's disease frequently exhibit hypertension, tachycardia, and orthostatic hypotension related to age, disease, and/or other treatments; 2) controlled trials investigating ZS did not collect such data; and 3) analyses of these data might result in important insights into cardiovascular effects of ZS that otherwise would not be known and which could be described in labeling.

By allowing the oropharyngeal exam to span up to 7 days after the last Rx, conceivably some subjects examined later may have experienced partial or complete resolution of oral pathology that had been present earlier as a result of ZS treatment. Thus, one must be cautious about concluding the ZS did not result in any oropharyngeal abnormalities in this PK/PD study.

9.2.4. Conclusions

Sponsor's Conclusions :

Pharmacokinetics

1. ZS 1.25 mg and 2.5 mg QD has lower drug and metabolite exposure at steady state compared to Eldepryl® 5.0 mg BID.
2. Similar steady state exposure to selegiline was obtained following ZS 5.0 mg QD and the conventional treatment (Eldepryl® 5.0 mg BID), while exposure to amphetamine-type metabolites is reduced by 50 to 70% for ZS.
3. Pre-gastric absorption of selegiline from the Zydys formulations, thus avoidance of first pass metabolism was indicated, by higher levels of selegiline and lower levels of the metabolites compared to Eldepryl®.

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4. Concentrations of selegiline and its metabolites increased with increasing doses of ZS, but dose proportionality could not be concluded for selegiline, and for the metabolites the results were inconclusive due to high variability in the data.

Pharmacodynamics

5. ZS 2.5 mg QD decreased the tyramine pressor threshold dose relative to baseline, but MHPG and 5-HIAA indicators do not show clinically relevant MAO-A inhibition.
6. Overall the tyramine threshold dose for the reference 5.0 mg Eldepryl® BID treatment was lower than those of the three ZS treatments, thus suggesting that Eldepryl® inhibits MAO-A to a greater extent than the ZS treatments.
7. No differences could be concluded between the three ZS treatments and Eldepryl® in the extent of MAO-A inhibition, as assessed by a decrease in MHPG levels and 5-HIAA urinary excretion.
8. The amount of PEA in urine was similar following Eldepryl® 5.0 mg BID and ZS 2.5 mg OD for all days. Additionally, similar amounts of PEA was excreted in urine following ZS 2.5mg and 5.0 mg QD at steady state on Days 9 and 10.

Safety

9. The ZS and Eldepryl® treatments were well tolerated with no deaths or adverse events of a serious nature during the study.
10. Smaller proportions of subjects who received each of the ZS treatments reported treatment related adverse events compared to subjects who received the 5.0 mg BID Eldepryl® treatment.

Reviewer's Conclusions :

Pharmacodynamics

This reviewer agrees with most conclusions of the sponsor but disagrees with conclusions #5 and # 6. I will describe my disagreement with these conclusions.

The sponsor noted that although ZS 2.5 mg lowered the tyramine threshold dose relative to baseline, results of plasma MHPG and urinary 5-HIAA do not indicate clinically relevant MAO-A inhibition (i.e. Conclusion # 5). It is difficult to know what represents "clinically relevant MAO-A inhibition." These indices (e.g. metabolic profiles of products of substrates for MAO-A) may not be as sensitive as another index of MAO-A inhibition such as tyramine testing. This reviewer thinks that it may be an overstatement to say that 2.5 mg ZS does not produce "clinically relevant MAO-A inhibition."

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The sponsor also noted that the tyramine threshold dose for Eldepryl was lower than those for all ZS treatments and concluded that this indicates that the extent of MAO-A inhibition occurring with all doses of ZS studied is less than that occurring with Eldepryl (i.e. Conclusion # 6). Despite the fact that the tyramine threshold dose for Eldepryl was lower than those for all ZS treatments, the fact that there were no statistically differences in mean tyramine threshold doses amongst all 4 selegiline treatments at steady state does not permit one to accept the sponsor's conclusion that tyramine testing revealed less MAO-A inhibition with ZS treatments than with Eldepryl treatment.

Based upon results of this study, it seems safer to draw the more conservative conclusions that ≤ 2.5 mg ZS (the doses that could be used if approved) : 1) produces significant MAO-A inhibition that may increase the risk of hypertensive "cheese" reactions from ingesting tyramine containing products; and 2) does not appear to inhibit MAO-A to a greater extent than that which appears to occur with conventional selegiline (i.e. Eldepryl).

I do not believe that it would be appropriate to approve ZS with tyramine dietary restrictions if I am not convinced that the apparent MAO-A inhibition exhibited by ZS and Eldepryl is real. I am not convinced that MAO-A inhibition is real, **thus I believe that another pharmacodynamic study of oral tyramine testing is clearly needed to confirm or refute results of study AN17933-101.** A repeat, improved study investigating the same ZS doses (and possibly including also a higher dose of 10 mg) and Eldepryl (5 mg BID) in a placebo-controlled, double-blind study should clarify if the results of study AN17933-101 are real and whether the impression in the literature is incorrect about the extent of MAO-A inhibition that occurs with the labeled dose of Eldepryl. Without such a repeat study, it would be difficult to avoid requiring tyramine dietary restrictions for patients treated with ZS. The practical implication of such a restriction would be that ZS would not be considered a useful product added to the armamentaria for anti-parkinsonian medications. If a repeat study confirmed results observed for Eldepryl (5 mg BID), ~~_____~~

b(5)

Pharmacokinetics

This reviewer agrees with sponsor's PK conclusions that have been outlined with one exception. There is no clear basis for stating that dose proportionality could not be shown for selegiline, and for the metabolites the results due to high variability in the data. This is a speculative comment. There is no clear reason why dose proportionality could not be shown.

Safety

This reviewer agrees with the sponsor's conclusion that all selegiline treatments were well tolerated and that TEAEs were not medically serious in nature. However, I disagree with conclusion # 10 that notes that ZS treatment results in a lower frequency of adverse events judged to be related to study medication. The open-label nature of the study does not permit any conclusions to be drawn about the frequency with which specific treatments were judged to be related to study medication.

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9.3. Study Z/SEL/96/014 (Study of Pharmacodynamic Effects on Tyramine Testing and Pharmacokinetics)

Principal Investigator : Dr. S Warrington MA, MD, FRCP, FFPM, DCPSA

Study Site : Hammersmith Medicines Research
Ward 2
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Park Royal
London NW10 7NS
UK

9.3.1. Description of Protocol Z/SEL/96/014

Title of Study :

A Repeat Dose Study to Assess Tolerability and Pharmacokinetics of 1.25 mg Zydis Selegiline Compared with 10 mg Eldepryl and to Assess Indirect Measures of Inhibition of Monoamine Oxidases A and B

Conducted at a single site : Central Middlesex Hospital, London, UK

Final Study Report date : 1/23/98

Objectives : To assess the pharmacokinetics, tolerability, and monoamine oxidase (MAO) selectivity of repeated daily doses of ZS 1.25 mg in comparison with conventional selegiline (Eldepryl) by evaluating pressor responses to oral tyramine and by measuring metabolic profiles of a substrate of MAO-B (phenylethylamine-PEA) and products (e.g. 3-methoxy-4-hydroxyphenyl glycol-MHPG and 5-hydroxyindoleacetic-5-HIAA in plasma and/or urine) of substrates of MAO-A.

STUDY DESIGN :

This study was an open-label, randomized, parallel dose group trial designed to assess the effects of ZS (1.25 mg QD before breakfast without water) and Eldepryl (10 mg QD before breakfast with 150 mL of water) on the tyramine challenge test (to increase blood pressure) as an indirect measure of MAO-A inhibition. Twenty-four healthy volunteers (male and female) were to be studied. This study was conducted similarly (including tyramine pressor testing procedure) as Study AN17933-101 described earlier. Differences in oral tyramine testing procedure in this study compared to the procedure described for Study AN17933-101 were shorter intervals (90 minutes) between tyramine treatments and subjects were to remain supine throughout testing. The reference/pre-treatment value for determining the tyramine threshold response was identical to the described in Study AN17933-101.

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Safety and tolerability of treatment was to be assessed throughout the study by oropharyngeal examinations, measurement of vital signs (supine blood pressure and pulse), routine blood and urine analyses and monitoring of adverse events.

Key Inclusion Criteria were similar to Study AN17933-101 with the main exceptions being that older subjects (i.e. age 40-70 years) were to participate in this study and this study would also enroll healthy female volunteers.

Key Exclusion Criteria were similar to Study AN17933-101 with the main exception being that the exclusionary period for particular medications was different (in this study : no prescription medications within 14 days and no over the counter medications within 48 hours of tyramine testing; no SSRI; no SSRIs within 5 weeks of study enrollment).

Analyses : Pharmacodynamic tyramine test results will be tabulated and summarized and incorporated into a survival analysis. The tyramine pressor ratios will be analyzed statistically. Pharmacokinetic parameters and results of metabolic profiles of a substrate of MAO-B and products of substrates of MAO-A will also be tabulated, summarized descriptively, and analyzed statistically. Demographic and safety data will be tabulated and summarized descriptively. Analysis of safety and tolerability of treatment would be based upon vital signs, routine laboratory test results, adverse events and oropharyngeal examinations.

Protocol Amendments

There were no protocol amendments during the study.

9.3.2. Results of Study Z/SEL/96/014

Results from this study have limited relevance to the NDA under review because this trial studied only a low dose (1.25 mg) of ZS and compared results with that of 10 mg Eldepryl administered as a single dose instead of Eldepryl dosed according to the label at 5 mg BID (at breakfast and lunch). The only ZS dose studied appropriately for efficacy in a pivotal trial was 2.5 mg daily. Thus, results from this study will not be presented as comprehensively as those presented and discussed for study AN17933-101 that investigated 2.5 mg ZS along with 1.25 and 5 mg doses and the labeled dosing of Eldepryl (i.e. 5 mg BID).

Patient Disposition

A total of 24 subjects (11 females and 13 males; age 48 - 70 years) enrolled and all these subjects completed the study.

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Protocol Violations, Deviations, and Prohibited Concomitant Medications

The sponsor did not present a discussion about protocol violations or deviations or prohibited concomitant medications. However, the sponsor did note that there were minor anomalies in taking study medication in 3 subjects,

Demographic Characterizations

There did not appear to be notable differences between the 2 selegiline treatment groups with regard to certain demographic characteristics (i.e. age, race, height, or weight) with the exception of gender. Five males and seven females received Eldepryl and eight males and four females received ZS.

9.3.2.1. Pharmacodynamic Results

Tyramine Testing

Tyramine pressor ratio threshold data for individual subjects and study groups are shown in Table 18 and Figure 4 (survival analysis presentation). The sponsor noted in the study report that two subjects (#3 and #4; one in each treatment group) were "excluded from the analysis" because the profile of the tyramine pressor response was atypical during selegiline treatment. These "atypical" response occurred much later than expected (e.g. at 205 minutes) in contrast to most responses that occurred within 100 minutes and often earlier. Including data from all subjects, mean (SD) tyramine pressor ratio for ZS was 2.83 (3.68) and mean (SD) tyramine pressor ratio for Eldepryl was 3.37 (4.23). When data from both subjects were excluded, mean (SD) tyramine pressor ratio for ZS was 2.73 (3.85) and mean (SD) tyramine pressor ratio for Eldepryl was 3.58 (4.36). The majority of tyramine pressor ratios in both treatment groups was < 2. One subject in each group had a very high ratio (14-ZS; 16-Eldepryl) and appeared to be an "outlier" relative to other subjects in the treatment group.

The dose of tyramine at which 50 % of subjects had not reached a threshold pressor effect (i.e. PD₅₀) was compared for each treatment. The PD₅₀ for ZS was 400 mg for both pretreatment and study drug treatment testing. In contrast, the PD₅₀ for Eldepryl was 400 mg for pretreatment testing and was 200 mg for study drug treatment testing. Thus, the ratio of the pre-treatment/treatment PD₅₀ was 1 for ZS and 2 for Eldepryl. Nevertheless, there were no statistically significant differences between treatment groups.

Metabolic Profiles for a Substrate of MAO-B and Products of Substrates of MAO-A

Figure 5 shows individual and median plasma MHPG in both treatment groups over time. Day 1 results of plasma MHPG were prior to dosing and therefore represent the pre-treatment value for comparison to treatment. Although, there appeared to be a trend toward lower values toward the

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end of the study for the Eldepryl group, there were no statistically significant differences for either treatment. Thus there no clear evidence for MAO-A inhibition by this index.

Figure 6 shows individual and median urinary 5-HIAA in both treatment groups over time. There were no statistically significant decrements indicating MAO-A inhibition by this index.. Neither was there any trend suggesting a possible change for either treatment.

Figure 7 shows individual and median urinary PEA in both treatment groups over time. There were marked increments in PEA excretion for both treatments indicating MAO-B inhibition.

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Table 18 Tyramine Thresholds for Pre-Treatment and Days 14, 15, 16

Subject No.	Treatment group	Tyramine threshold dose (mg)	Tyramine threshold dose (mg)	Tyramine Pressor Ratio
		Pre-treatment	Day 14/15/16	
96/014/001	Eldepryl 10mg	500	200	2.5
96/014/003		100	100	1
96/014/006		400	300	1.3
96/014/008		300	50	6
96/014/009		500	300	1.7
96/014/011		400	300	1.3
96/014/014		500	300	1.7
96/014/017		400	100	4
96/014/018		400	25	16
96/014/019		400	200	2
96/014/023		700	500	1.4
96/014/024		300	200	1.5
Mean			408.33 (436.36)	14.58 (225.00)
SD		144.34 (112.01)	135.03 (136.47)	4.23 (4.36)
Median		400 (400)	200 (200)	1.7 (1.7)
Minimum		100 (300)	25 (25)	1 (1.3)
Maximum		700 (700)	500 (500)	16 (16)
95/014/002	Zydis 1.25mg	400	400	1
96/014/004		400	100	4
96/014/005		400	100	4
96/014/007		400	400	1
96/014/010		400	200	2
96/014/012		600	400	1.5
96/014/013		300	500	0.6
96/014/015		400	400	1
96/014/016		700	400	1.8
96/014/020		700	500	1.4
96/014/021		700	50	14
96/014/022		500	300	1.7
Mean			491.67 (500.00)	312.50 (331.82)
SD		144.34 (148.32)	159.72 (152.11)	3.68 (3.85)
Median		400 (400)	400 (400)	1.6 (1.5)
Minimum		300 (300)	50 (50)	0.6 (0.6)
Maximum		700 (700)	500 (500)	14 (14)

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

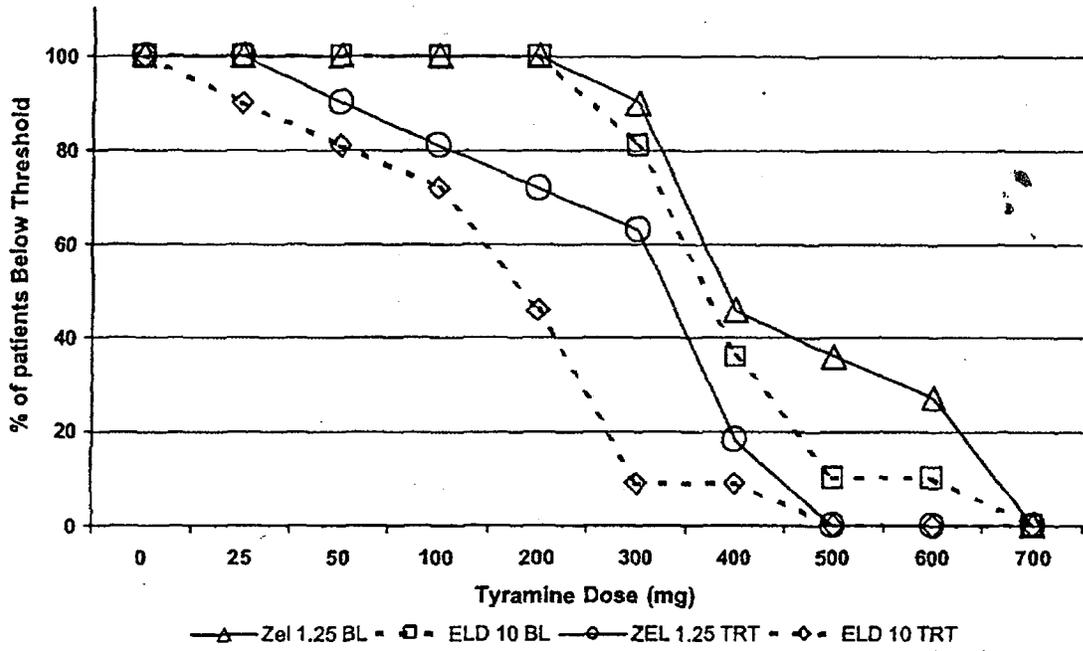
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Figure 4 Survival Analysis of Tyramine Challenge Threshold At Baseline and After PK Steady State Treatment with ZS (1.25 QD) or Eldepryl (10 mg QD)

Survival Analysis - Tyramine Challenge Study 96014

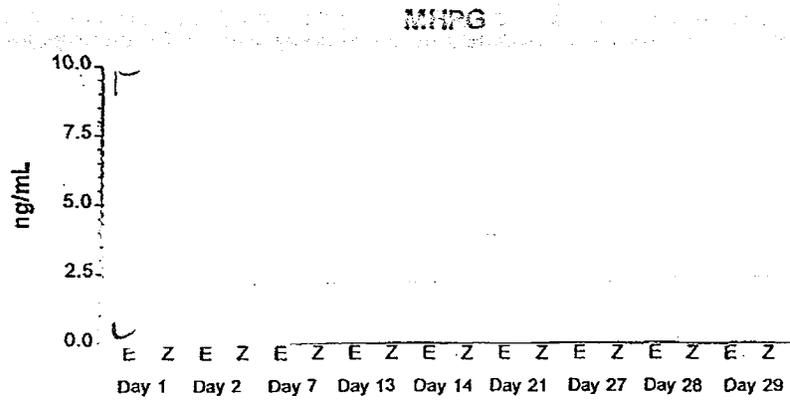


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Figure 5 Individual and Median Plasma MHPG Concentrations



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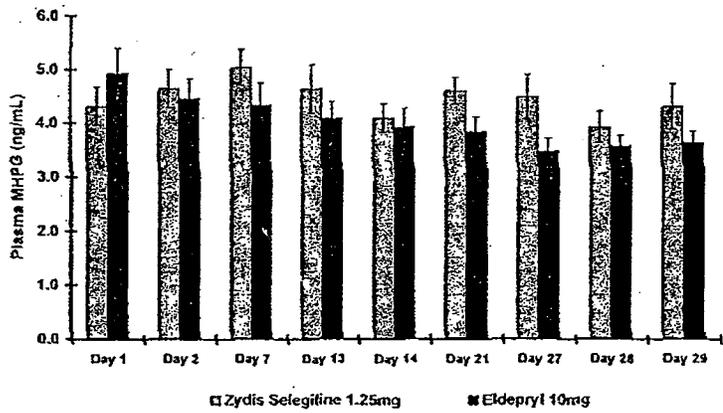
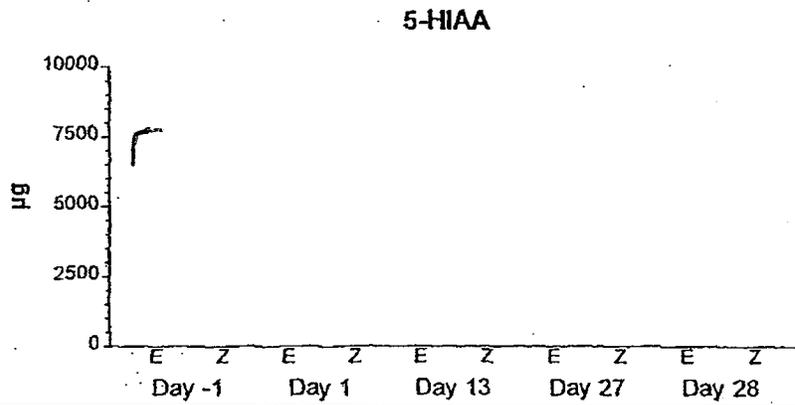


Figure 6 Urinary Excretion of 5-HIAA

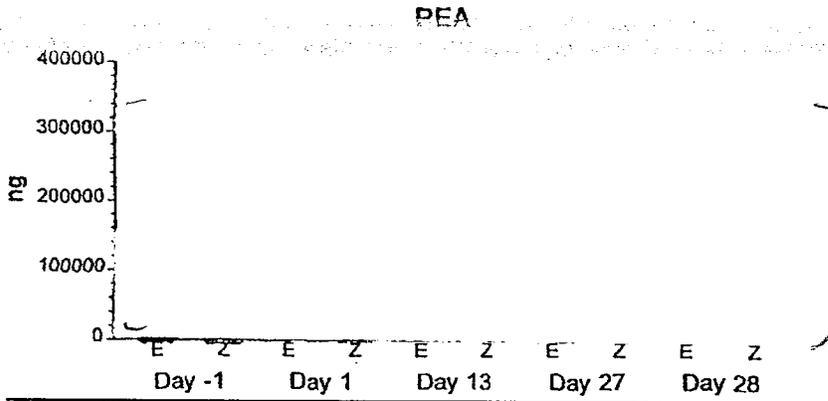


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Figure 7 Individual and Median Urinary PEA Excretion



9.3.2.2. Pharmacokinetic Profiles of Selegiline and Metabolites

Specific results of PK profiles of selegiline and its metabolites in this study will not be presented because PK results of ZS and major metabolites were presented in the PK section (Table 4, Table 5, Table 6, Table 7) of this review. The main purpose of this study was to assess pharmacodynamic actions of 2 selegiline treatments on MAO-A and MAO-B inhibition and this reviewer does not see value in presenting such PK data again.

9.3.2.3. Safety

Both treatments were tolerated relatively well with respect to the incidence, nature and severity of adverse events. Treatment AEs (TEAEs) for both selegiline treatments were generally similar in frequency, nature, and severity. There were no deaths, serious adverse events (SAEs), nor discontinuations for AEs.

There were no significant changes in ECGs nor physical examinations that were noted at the post-study visit.

In general, the sponsor noted that there were no clinically meaningful changes in VS (i.e. supine blood pressure and pulse) for either treatment between day 1 and day 29. Mean systolic and diastolic blood pressure and pulse rates were slightly lower on treatment than pre-treatment and post-study measurements for both treatment groups. Post-study results were similar to those of the pre-study visit.

There were no significant changes in ECGs nor physical examinations that were noted at the post-study visit.

There were no significant clinical laboratory abnormalities that occurred with either treatment that this reviewer deems worthy of presentation or discussion.

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Open-label oropharyngeal examinations did not reveal any serious abnormalities from either treatment.

9.3.3. Discussion of Study Results

Pharmacodynamics

ZS 1.25 mg QD treatment showed similar changes in tyramine pressor ratios as did treatment with Eldepryl 10 mg QD suggesting similar inhibition of MAO-A. Other indices of MAO-A inhibition such as plasma MHPG and urinary 5-HIAA were less sensitive and did not show a clear change (i.e. decrement over time). Although the sponsor speculates that if a larger number of subjects had been studied the survival plot may have shown a statistically significant shift to the left (i.e. increased sensitivity to tyramine threshold testing, this is purely speculation. It is not clear if the results would have been different and suggested that Eldepryl inhibited MAO-A to a greater extent than ZS 1.25. Thus, this study showed a similar tyramine pressor ratio with 1.25 mg QD ZS as was observed with 10 mg QD Eldepryl. This finding essentially replicates the observation in Study AN17933-101 that showed similar tyramine pressor ratios in healthy, younger males treated with ZS 1.25 mg QD and Eldepryl 5 mg BID (but still a total 10 mg daily dose).

I have provided a detailed discussion of various issues related to oral tyramine testing and results of testing effects of selegiline and ZS in the Discussion section (Pharmacodynamics) of Study AN17933-101 and will not repeat the discussion here. Refer to that section for review of relevant issues worthy of discussion.

Pharmacokinetics

PK results showed generally similar results as previous studies with the exception that the levels of selegiline from 1.25 mg ZS were higher than expected

Safety

There was nothing remarkable nor unexpected with regard to tolerability and safety results for both selegiline treatments.

9.3.4. Conclusions

Sponsor's Conclusions :

Pharmacodynamics

Both treatment produced significant MAO-B inhibition as reflected by the markedly increased excretion of urinary PEA, a substrate of MAO-B.

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There was no definite effect of either treatment on indices of MAO-A inhibition such as plasma MHPG and urinary excretion of 5-HIAA, products of substrates for MAO-A.

There was no distinct difference in the sensitivity to pressor effects of tyramine shown by subjects treated with ZS 1.25 mg QD and Eldepryl 10 mg QD. The sponsor did not specify that this was evidence for MAO-A inhibition by 1.25 mg QD of ZS.

Pharmacokinetics

This study showed that plasma selegiline levels from 1.25 mg ZS were higher than those observed with 10 mg Eldepryl and that much smaller quantities of metabolites were generated from ZS than were generated from Eldepryl. The difference on metabolite generation was expected because of the decrease in first pass hepatic extraction that occurs with buccal absorption of ZS. The sponsor noted that the levels of selegiline from 1.25 mg ZS were higher than expected.

The sponsor believes that higher AUCs at PK steady state for subjects treated with Eldepryl was due to the chance randomization of slow metabolizers of selegiline to the Eldepryl group.

Safety

Both treatments were well tolerated and showed similar safety profiles with regard to the incidence, nature, and severity of adverse events.

There were no findings suggesting effects of ZS on oropharyngeal examinations.

There were no abnormal clinical laboratory results from study treatment that prompted any significant concerns.

Reviewer's Conclusions :

This reviewer agrees with the conclusions of the sponsor with the exception of the sponsor's speculation that by chance more slow metabolizers of selegiline were randomized to the Eldepryl group. This may or may not be the case. However, it is speculative to draw this conclusion.

In addition, this reviewer interprets the statistically indistinguishable and similar tyramine threshold pressor ratios of both treatments as evidence for similar MAO-A inhibition and thus a similar risk for developing a hypertensive reaction to tyramine containing products.

9.4. Study Z/SEL/95/007 (Study of Pharmacodynamic Effects on Tyramine Testing and Pharmacokinetics)

Principal Investigator : Dr. S Warrington MA, MD, FRCP, FFPM DCPSA

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Study Site : Hammersmith Medicines Research
Ward 2
Central Middlesex Hospital
Park Royal
London NW10 7NS
UK

9.4.1. Description of Protocol

Title of Study :

A Repeat Dose Study to Assess Tolerability and Pharmacokinetics of Zydys Selegilene Compared with Selegiline Administered as a Standard table and to Assess Indirect Measures of Inhibition of Monoamine Oxidases A and B

Conducted at a single site : Central Middlesex Hospital, London, UK
Final Study Report date : January 1996

Objectives : To assess the pharmacokinetics, tolerability, and monoamine oxidase (MAO) selectivity of repeated daily doses of ZS 10 mg in comparison with the standard French selegiline tablet (l-deprenyl/selegiline) by evaluating pressor responses to oral tyramine and by measuring metabolic profiles of a substrate of MAO-B (e.g. phenylethylamine-PEA) and products (e.g. 3-methoxy-4-hydroxyphenyl glycol-MHPG and 5-hydroxyindoleacetic-5-HIAA in plasma and/or urine) of substrates of MAO-A.

STUDY DESIGN :

This study was an open-label, randomized, parallel dose group trial designed to assess the effects of ZS (10 mg QD before breakfast without water) and l-deprenyl/selegiline (10 mg QD before breakfast with 150 mL of water) on the tyramine challenge test (to increase blood pressure) as an indirect measure of MAO-A inhibition. Twenty-four healthy volunteers (male and female) were to be studied. This study would be conducted essentially similarly as Study AN17933-101 and Study Z/SEL/96/014 described earlier. Of potential importance, it should be noted that the oral tyramine test procedure involved some differences compared the procedure performed in Studies AN17933-101 and Z/SEL/96/014 and described in the review of Study AN17933-101. Differences involving Study Z/SEL/95/007 include : 1) study while on treatment over a maximal period of 2 days (not 3 days); 2) the highest dose of tyramine administered for the pre-treatment period is 600 mg (not 700 mg); 3) the highest dose of tyramine administered while on study drug is 300 mg (not 700 mg); 4) the lowest dose of tyramine administered while on study drug is 10 mg (not 25 mg); 5) blood pressure and pulse are measured up to 90 minutes (not 120 minutes after the last tyramine dose); and 6) additional criteria such as a diastolic blood pressure rise > 110 mm Hg or decrease of pulse to > 20 % of the reference/pre-treatment value for the day could constitute a positive tyramine threshold response (not solely a rise in systolic blood pressure to a threshold value in excess of the reference/pre-treatment value for the day).

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Safety and tolerability of treatment was to be assessed throughout the study by oropharyngeal examinations, measurement of vital signs (supine blood pressure and pulse), routine blood and urine analyses and monitoring of adverse events.

Key Inclusion Criteria and Key Exclusion Criteria were similar to those of Study Z/SEL/96/014.

Analyses : Pharmacodynamic tyramine test results will be tabulated and summarized and incorporated into a survival analysis. The tyramine pressor ratios will analyzed statistically. Pharmacokinetic parameters and results of metabolic profiles of a substrate of MAO-B and products of substrates of MAO-A will also be tabulated, summarized descriptively, and analyzed statistically (using two-tailed tests with performance at 5 % level. Demographic and safety data will be tabulated and summarized descriptively. Analysis of safety and tolerability of treatment would be based upon vital signs, routine laboratory test results, adverse events and oropharyngeal examinations.

Protocol Amendments

There were no significant protocol amendments worthy of discussion.

9.4.2. Results of Study Z/SEL/95/007

Results from this study have limited relevance to the NDA under review because this trial studied only a high dose (10 mg) of ZS and compared results with that of 10 mg Eldepryl administered as a single dose instead of Eldepryl dosed according to the label at 5 mg BID (at breakfast and lunch). The only ZS dose studied appropriately for efficacy in a pivotal trial was 2.5 mg daily. Thus, results from this study will not be presented as comprehensively as those presented and discussed for study AN17933-101 that investigated 2.5 mg ZS along with 1.25 and 5 mg doses and the labeled dosing of Eldepryl (i.e. 5 mg BID).

Patient Disposition

A total of 24 subjects (11 females and 13 males; age 39 - 68 years) enrolled and all these subjects completed the study.

Protocol Violations, Deviations, and Prohibited Concomitant Medications

The sponsor did not present a discussion about protocol violations or deviations or prohibited concomitant medications. However, the sponsor did note that there were minor anomalies in taking study medication in 3 subjects,

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Demographic Characterizations

There did not appear to be notable differences between the 2 selegiline treatment groups with regard to certain demographic characteristics (i.e. age, gender race, height, or weight).

9.4.2.1. Pharmacodynamic Results

Tyramine Testing

Tyramine pressor ratio threshold data for individual subjects and study groups are shown in Table 19. The sponsor noted in the study report that two subjects (#11 and #13; both in ZS group) did not achieve a positive tyramine threshold response for blood pressure or pulse in the pre-treatment period. For these subjects, 600 mg was the dose used as the pre-treatment dose in calculating the tyramine pressor ratio. Including data from all subjects, mean (SD) tyramine pressor ratio for ZS was 3.67 (1.3) and mean (SD) tyramine pressor ratio for Deprenyl was 4.5 (4.05). The vast majority of tyramine pressor ratios in both treatment groups was ≥ 2 . No subjects in either treatment group had a very high ratio (e.g. > 6). Tyramine pressor ratios were not statistically significant different between treatment groups. Neither was there any statistically significant difference between treatment groups for survival plots.

Metabolic Profiles for a Substrates of MAO-B and Products of Substrates of MAO-A

Table 20 and Table 21 show mean plasma MHPG in both treatment groups over time. ANOVA statistical analysis of pre-dose plasma MHPG on days 1, 2, 7, 13, 14, 21, and 28 revealed the changes (i.e. decrements) apparent with time were statistically significant and qualitatively similar for both treatments.

Table 22 and Table 23 show mean total and cumulative urinary excretion of 5-HIAA in both treatment groups over time. There were no statistically significant decrements indicating MAO-A inhibition by this index for any comparisons.

Table 24 and Table 25 show mean total and cumulative urinary excretion of PEA in both treatment groups over time. There were marked, statistically significant increments in urinary PEA excretion for both treatments indicating MAO-B inhibition. In addition, increments in urinary PEA excretion on day was statistically greater with ZS than those due to l-deprenyl/selegiline.

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Table 19 Tyramine Thresholds for Pre-Treatment and Days 14, 15

Subject No.	Treatment group	Tyramine threshold dose	Tyramine threshold dose	Tyramine Pressor Ratio	
		(mg) Pre-treatment	(mg) Day 14/15		
95/007/001	Tablet	500	200	2.5	
95/007/004		400	200	2	
95/007/006		400	100	4	
95/007/007		400	50	8	
95/007/010		300	200	1.5	
95/007/012		300	200	1.5	
95/007/015		400	100	4	
95/007/016		500	100	5	
95/007/017		300	100	3	
95/007/018		400	100	4	
95/007/021		500	200	2.5	
95/007/023		400	25	16	
Mean			400	131.25	4.5
SD		73.85	64.95	4.05	
Median		400	100	3.5	
Minimum		300	25	1.5	
Maximum		500	200	16	
95/007/002	Zydis	300	100	3	
95/007/003		400	200	2	
95/007/005		300	50	6	
95/007/008		300	100	3	
95/007/009		200	100	2	
95/007/011		600*	200	3	
95/007/013		600*	200	3	
95/007/014		400	100	4	
95/007/019		600	100	6	
95/007/022		400	100	4	
95/007/024		400	100	4	
95/007/026		400	100	4	
Mean			408.33	120.83	3.67
SD			131.14	49.81	1.3
Median		400	100	3.5	
Minimum		200	50	2	
Maximum		600	200	6	

NOTE: * = these values were >600mg, but the exact value is not known

See Appendix III* for results of statistical analyses

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Table 20 Descriptive Statistics for Plasma MHPG (ng/mL) During 28 Days Treatment with Zydys Selegiline (10 mg)

Day	Time (h)	N	Mean	SD	CV (%)	Minimum	Median	Maximum
1	0.00	12	4.53	1.70	37.52	2.98	4.19	9.02
1	1.00	11	4.20	1.55	36.86	2.91	3.56	7.83
1	2.00	11	4.24	1.51	35.69	2.72	3.46	7.21
1	3.00	10	3.95	1.22	30.90	2.67	3.64	6.80
1	4.00	10	4.27	1.42	33.29	2.90	3.70	6.83
1	6.00	7	4.24	0.98	23.17	3.24	4.15	5.37
1	12.00	10	4.27	1.34	31.48	2.28	4.27	5.90
1	24.00	12	4.55	1.40	30.70	2.32	4.30	6.73
7	0.00	12	4.96	2.27	45.78	2.78	4.32	10.90
13	0.00	11	3.30	0.60	18.09	2.36	3.25	4.35
13	1.00	12	3.35	0.96	28.58	2.22	3.05	4.91
13	2.00	11	3.19	0.79	24.90	2.40	2.69	4.52
13	3.00	9	3.16	0.83	26.16	2.16	3.03	4.62
13	4.00	12	3.23	0.95	29.31	2.21	3.04	5.35
13	6.00	10	3.23	1.03	31.97	1.99	3.10	5.05
13	12.00	11	3.31	0.92	27.73	2.20	2.99	5.11
13	24.00	12	3.44	1.10	32.03	2.37	2.95	5.39
21	0.00	11	4.33	1.54	35.46	2.32	3.85	7.62
28	0.00	12	3.67	0.86	23.39	2.32	3.48	5.29

See Appendix III for results of statistical analyses.

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Table 21 Descriptive Statistics for Plasma MHPG (ng/mL) During 28 Days Treatment with Deprenyl (10 mg)

Day	Time (h)	N	Mean	SD	CV (%)	Minimum	Median	Maximum
1	0.00	11	3.64	1.24	34.13	1.85	3.36	6.02
1	1.00	10	4.04	0.99	24.46	2.54	3.80	5.80
1	2.00	11	4.69	2.53	53.98	3.47	3.70	12.00
1	3.00	10	4.35	1.65	37.90	2.67	3.75	8.11
1	4.00	11	4.61	1.67	36.13	2.37	4.01	8.14
1	6.00	9	4.41	0.97	21.96	3.38	4.05	6.17
1	12.00	8	4.95	1.69	34.24	3.13	4.62	8.38
1	24.00	11	4.40	1.62	36.75	2.78	3.87	8.01
7	0.00	11	4.55	1.66	36.59	2.09	4.74	8.34
13	0.00	11	3.58	1.19	33.31	1.75	3.63	6.42
13	1.00	11	3.91	1.07	27.35	2.84	3.85	6.84
13	2.00	12	3.85	1.35	35.21	2.16	3.57	7.61
13	3.00	11	3.84	1.33	34.67	2.48	3.56	7.45
13	4.00	11	3.67	0.93	25.33	2.09	3.47	5.17
13	6.00	10	3.93	1.16	29.58	2.82	3.77	6.82
13	12.00	12	4.16	1.37	32.85	2.51	3.84	7.40
13	24.00	12	3.81	1.66	43.62	2.18	3.78	8.23
21	0.00	12	4.68	1.70	36.27	2.49	4.69	9.10
28	0.00	12	3.92	1.43	36.48	2.09	4.08	7.29

See Appendix III for results of statistical analyses.

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Table 22 Descriptive Statistics for Total and Cumulative Urinary Excretion (mg) of 5-HIAA on Days 1 and 13 of Treatment with Zydys Selegiline (10 mg)

Day	Time (h)	N	Mean	SD	CV (%)	Minimum	Median	Maximum
1	-12 to -6	12	0.783	0.184	23.527	0.482	0.844	1.042
1	-6 to 0	12	0.719	0.319	44.338	0.362	0.661	1.564
1	0 to 6	11	0.707	0.197	27.863	0.451	0.669	1.095
1	6 to 12	11	0.688	0.281	40.808	0.238	0.682	1.242
1	12 to 18	12	0.798	0.376	47.137	0.511	0.668	1.828
1	18 to 24	12	0.686	0.195	28.453	0.248	0.724	0.922
Cumulative -12 to 0h		12	1.502	0.430	28.632	0.980	1.171	1.719
Cumulative 0 to 12h		12	1.431	0.342	23.919	0.900	1.097	1.663
Cumulative 12 to 24h		12	1.485	0.499	33.634	0.769	1.266	1.551
Cumulative 0 to 24h		12	2.916	0.683	23.417	2.122	2.798	4.388
13	-12 to -6	12	0.959	0.472	49.263	0.567	0.886	2.276
13	-6 to 0	12	0.646	0.273	42.209	0.035	0.668	1.076
13	0 to 6	12	0.641	0.135	21.106	0.433	0.646	0.832
13	6 to 12	12	0.754	0.284	37.599	0.202	0.778	1.156
13	12 to 18	12	0.810	0.414	51.046	0.460	0.668	1.955
13	18 to 24	12	0.605	0.262	43.375	0.069	0.699	0.871
Cumulative -12 to 0h		12	1.604	0.688	42.883	0.644	1.164	1.853
Cumulative 0 to 12h		12	1.395	0.338	24.204	0.678	1.222	1.641
Cumulative 12 to 24h		12	1.415	0.385	27.200	0.908	1.103	1.756
Cumulative 0 to 24h		12	2.810	0.542	19.279	1.587	2.722	3.509

See Appendix III for results of statistical analyses.

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Table 23 Descriptive Statistics for Total and Cumulative Urinary Excretion (mg) of 5-HIAA on Days 1 and 13 of Treatment with Deprenyl (10 mg)

Day	Time (h)	N	Mean	SD	CV (%)	Minimum	Median	Maximum
1	-12 to -6	12	0.900	0.358	39.828	0.442	0.817	1.725
1	-6 to 0	12	0.717	0.289	40.332	0.173	0.735	1.389
1	0 to 6	12	0.861	0.382	44.315	0.485	0.759	1.973
1	6 to 12	12	0.690	0.437	63.347	0.181	0.669	1.850
1	12 to 18	12	0.764	0.350	45.777	0.214	0.733	1.346
1	18 to 24	12	0.591	0.149	25.191	0.234	0.607	0.798
Cumulative -12 to 0h		12	1.617	0.614	37.972	0.615	1.363	1.913
Cumulative 0 to 12h		12	1.551	0.478	30.825	0.912	1.183	1.695
Cumulative 12 to 24h		12	1.355	0.367	27.056	0.772	1.125	1.625
Cumulative 0 to 24h		12	2.906	0.673	23.163	1.684	2.912	3.970
13	-12 to -6	12	0.862	0.303	35.102	0.450	0.786	1.311
13	-6 to 0	12	0.683	0.224	32.837	0.349	0.623	1.170
13	0 to 6	12	0.672	0.243	36.150	0.396	0.634	1.269
13	6 to 12	12	0.882	0.531	60.207	0.338	0.684	1.998
13	12 to 18	12	0.832	0.344	41.362	0.367	0.806	1.646
13	18 to 24	12	0.744	0.205	27.575	0.348	0.765	1.029
Cumulative -12 to 0h		12	1.545	0.470	30.415	0.840	1.157	1.845
Cumulative 0 to 12h		12	1.554	0.659	42.404	0.786	1.141	1.868
Cumulative 12 to 24h		12	1.577	0.486	30.820	0.715	1.333	1.821
Cumulative 0 to 24h		12	3.131	0.940	30.025	1.501	3.047	4.539

See Appendix III for results of statistical analyses.

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Table 24 Descriptive Statistics for Total and Cumulative Urinary Excretion (mg) of PEA on Days 1 and 13 of Treatment with Zydys Selegiline (10 mg)

Day	Time (h)	N	Mean	SD	CV (%)	Minimum	Median	Maximum
1	-12 to -6	12	4.53	12.21	269.34	0.00	0.72	43.13
1	-6 to 0	12	2.83	7.35	259.72	0.00	0.65	26.09
1	0 to 6	11	16.76	18.53	110.57	1.45	10.56	69.94
1	6 to 12	11	21.08	17.85	84.66	2.23	28.04	53.77
1	12 to 18	12	18.80	12.61	67.08	5.41	17.46	47.45
1	18 to 24	12	16.19	27.67	170.89	1.91	9.29	103.16
Cumulative -12 to 0h		12	7.36	19.56	265.60	0.00	0.62	2.25
Cumulative 0 to 12h		12	41.08	31.10	75.72	3.68	23.26	47.14
Cumulative 12 to 24h		12	34.99	38.40	109.74	7.33	14.14	34.74
Cumulative 0 to 24h		12	76.07	67.77	89.09	13.79	67.54	274.32
13	-12 to -6	12	52.94	29.50	55.72	9.95	54.23	98.08
13	-6 to 0	12	21.98	14.69	66.84	0.84	17.79	52.02
13	0 to 6	12	25.94	12.53	48.29	7.82	24.44	47.06
13	6 to 12	12	50.88	24.10	47.36	6.60	56.75	80.05
13	12 to 18	12	51.83	23.22	44.79	20.46	52.66	86.56
13	18 to 24	12	30.86	18.72	60.65	2.09	28.99	61.15
Cumulative -12 to 0h		12	74.92	42.14	56.24	18.80	39.69	97.95
Cumulative 0 to 12h		12	76.83	31.60	41.13	14.42	63.07	101.00
Cumulative 12 to 24h		12	82.69	35.42	42.84	40.87	57.88	104.23
Cumulative 0 to 24h		12	159.52	61.50	38.55	65.17	154.13	252.35

See Appendix III for results of statistical analyses.

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Table 25 Descriptive Statistics for Total and Cumulative Urinary Excretion (mg) of PEA on Days 1 and 13 of Treatment with Deprenyl (10 mg)

Day	Time (h)	N	Mean	SD	CV (%)	Minimum	Median	Maximum
1	-12 to -6	12	2.26	3.26	143.79	0.00	1.25	11.72
1	-6 to 0	12	2.13	3.43	160.79	0.34	0.99	12.57
1	0 to 6	12	5.62	7.38	131.32	0.78	3.14	26.77
1	6 to 12	12	6.83	6.17	90.32	0.73	5.76	19.54
1	12 to 18	12	5.90	4.22	71.61	1.01	5.81	13.51
1	18 to 24	12	4.30	4.29	99.94	0.55	3.22	14.93
Cumulative -12 to 0h		12	4.40	6.65	151.21	0.63	1.34	2.97
Cumulative 0 to 12h		12	14.69	11.03	75.11	1.76	2.72	23.57
Cumulative 12 to 24h		12	10.19	7.50	73.56	1.57	2.95	13.62
Cumulative 0 to 24h		12	22.65	17.23	76.06	4.05	21.85	47.07
13	-12 to -6	12	23.25	17.22	74.09	1.30	19.24	57.77
13	-6 to 0	12	13.78	10.38	75.31	2.08	12.57	36.02
13	0 to 6	12	19.83	16.70	84.22	2.13	14.29	50.58
13	6 to 12	12	29.32	21.72	74.07	5.08	21.55	65.13
13	12 to 18	12	30.69	20.36	66.33	4.11	23.96	67.98
13	18 to 24	12	17.58	12.47	70.91	2.54	15.10	49.18
Cumulative -12 to 0h		12	37.03	25.53	68.96	3.40	19.87	52.92
Cumulative 0 to 12h		12	49.74	37.19	74.76	7.57	21.32	78.81
Cumulative 12 to 24h		12	48.27	30.49	63.17	6.65	28.21	64.82
Cumulative 0 to 24h		12	97.42	65.38	67.11	14.21	75.95	224.18

See Appendix III for results of statistical analyses.

9.4.2.2. Pharmacokinetic Profiles of Selegiline and Metabolites

Specific results of PK profiles of selegiline and its metabolites in this study will not be presented because PK results of ZS and major metabolites were presented in the PK section (Table 4, Table 5, Table 6, Table 7) of this review. The main purpose of this study was to assess pharmacodynamic actions of 2 selegiline treatments on MAO-A and MAO-B inhibition and this reviewer does not see value in presenting such PK data again.

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Higher plasma levels of selegiline occurred after ZS than after the same dose of l-deprenyl/selegiline. Despite that difference, the major metabolites (e.g. N-demethylselegiline, L-amphetamine, L-methylamphetamine) increased with repeated dosing to a similar extent for both selegiline treatments.

9.4.2.3. Safety

Both treatments were tolerated relatively well with respect to the incidence, nature and severity of adverse events. Treatment AEs (TEAEs) for both selegiline treatments were generally similar in frequency, nature, and severity. There were no deaths, serious adverse events (SAEs), nor discontinuations for AEs.

There were no significant changes in ECGs nor physical examinations that were noted at the post-study visit.

In general, the sponsor noted that there were no clinically meaningful changes in VS (i.e. supine blood pressure and pulse) for either treatment between day 1 and day 29. ANOVA statistical analysis of changes in supine systolic blood pressure, diastolic blood pressure, pulse rate, and oral temperature between days 1 and 28 did not reveal as statistically significant differences between ZS and l-deprenyl/selegiline treatments.

There were no significant changes in ECGs nor physical examinations that were noted at the post-study visit with the exception of subject # 9 (ZS group) who exhibited right bundle branch block and sinus bradycardia. The right bundle branch block persisted on a repeat ECG three weeks later.

There were no significant clinical laboratory abnormalities that occurred with either treatment that this reviewer deems worthy of presentation or discussion.

Oropharyngeal examinations showed that 3 of 12 subject who received ZS developed mouth ulcers that were consistent with aphthous ulcers.

9.4.3. Discussion of Study Results

Pharmacodynamics

ZS 10 mg QD treatment showed similar changes in tyramine pressor ratios as did treatment with l-deprenyl/selegiline 10 mg QD suggesting similar inhibition of MAO-A. Measurement of plasma MHPG over time also suggested similar MAO-A inhibition for both treatments.

Measurement of another index of MAO-A inhibition such as urinary 5-HIAA was less sensitive and did not show a clear change (i.e. decrement over time) suggesting MAO-A inhibition

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Tyramine pressor ratios indicated that both treatments increased the sensitivity to tyramine to a similar extent as also did the survival analysis. However, there were no statistically significant differences between these 2 treatments.

I have provided a detailed discussion of various issues related to oral tyramine testing and results of testing effects of selegiline and ZS in the Discussion section (Pharmacodynamics) of Study AN17933-101 and will not repeat the discussion here. Refer to that section for review of relevant issues worthy of discussion.

Pharmacokinetics

This study showed that plasma selegiline levels from 10 mg ZS were higher than those observed with 10 mg l-deprenyl/selegiline and that significant quantities of major metabolites were generated from both treatments although a smaller fraction of metabolites was generated from ZS. This fractional difference in metabolite generation was expected because of the decrease in first pass hepatic extraction that occurs with buccal absorption of ZS.

Safety

There was nothing remarkable nor unexpected with regard to tolerability and safety results for both selegiline treatments with the exception of 3 aphthous-like ulcers occurring in subjects treated with ZS.

9.4.4. Conclusions

Sponsor's Conclusions :

Pharmacodynamics

Both treatment produced significant MAO-B inhibition as reflected by the markedly increased excretion of urinary PEA, a substrate of MAO-B. There was evidence of MAO-A inhibition for both treatments according to decrements in plasma MHPG. There was no definite

MHPG. There was no definite effect of either treatment on another, apparently less sensitive index of MAO-A inhibition such as urinary excretion of 5-HIAA.

There was no distinct difference in the sensitivity to pressor effects of tyramine shown by subjects treated with ZS 10 mg QD and l-deprenyl/selegiline 10 mg QD. The sponsor did not specify that this was evidence for MAO-A inhibition by 10 mg QD ZS.

I have provided a detailed discussion of various issues related to oral tyramine testing results of testing effects of selegiline and ZS in the Discussion section (Pharmacodynamics) of Study AN17933-101 and will not repeat the discussion here. Refer to that section for review of relevant issues worthy of discussion.

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Pharmacokinetics

This study showed that plasma selegiline levels from 10 mg ZS were higher than those observed with 10 mg Eldepryl and that significant quantities of major metabolites were generated from both treatments

Safety

Both treatments were well tolerated and showed similar safety profiles with regard to the incidence, nature, and severity of adverse events.

There were no findings suggesting effects of ZS on oropharyngeal examinations.

There were no abnormal clinical laboratory results from study treatment that prompted any significant concerns.

Reviewer's Conclusions :

I agree with the conclusions of the sponsor except that it is not possible to exclude the possibility that the oral ulcers that developed in 3 of 12 subjects treated with 10 mg of ZS may have been related to this relatively high dose of ZS.

10. FDA BIORESEARCH MONITORING PROGRAM INSPECTIONS

Two study sites (principal investigators : Paul Nausieda, M.D., Milwaukee, Wisconsin; and Maureen Leehey, M.D., Denver, Colorado) from the positive pivotal study (Z/SEL/97/026) were inspected by FDA's Division of Scientific Investigations (DSI). These sites enrolled a large number of patients. At Dr. Nausieda's site, 24 patients were screened 20 patients subjects were randomized to study treatment, and 18 patients completed the study. At Dr. Leehey's site, 27 patients enrolled and 18 subjects completed the study. Although there were some deviations from the regulations as described above, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, that all enrolled subjects received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol. Overall, the data from Drs. Leehey and Nausieda's sites appear acceptable for use in support of this NDA.

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11. TABULAR SUMMARY OF KEY PIVOTAL STUDIES

Table 26 Pivotal Double-Blind, Placebo Controlled Key Efficacy Study (Z/SEL/97/026)

Study Number Phase (Start Date) Status	Design	Main Inclusion Criteria	Treatment Groups	Patients in the ITT Population	Age Range Sex (M/F) Race (C/B/O)	Duration	Report Location Vol.	CRT Location Vol.	CRF Location Vol.
Randomized Parallel Safety and Efficacy Studies in Patients with PD (cont'd)									
Z/SEL/97/026 Phase III (Dec 1997) Complete 16 U.S. sites	Multicenter Double-Blind Randomized Placebo-Controlled Parallel-Group	>30 years of age with affirmed diagnosis of idiopathic Parkinson's disease who responded to levodopa therapy and experiencing end of levodopa dose deterioration with predictable, mild to moderate ON-OFF fluctuations	Placebo 1.25 mg Zydis selegiline (Weeks 1 to 6) 2.5 mg Zydis selegiline (Weeks 7 to 12)	Placebo (N = 46) Zydis selegiline (N = 94)	38-85 yrs 89/51 129/1/10	12 weeks			

M = male, F = female, C = Caucasian, B = Black, O = Other

Table 27 Pivotal Double-Blind, Placebo Controlled Key Efficacy Study (Z/SEL/97/025)

Study Number Phase (Start Date) Status	Design	Main Inclusion Criteria	Treatment Groups	Patients in the ITT Population	Age Range Sex (M/F) Race (C/B/O)	Duration	Report Location Vol.	CRT Location Vol.	CRF Location Vol.
Randomized Parallel Safety and Efficacy Studies in Patients with PD									
Z/SEL/97/025 Phase III (Dec 1997) Complete 14 U.S. sites 1 Canadian site	Multicenter Double-Blind Randomized Placebo-Controlled Parallel-Group	>30 years of age with affirmed diagnosis of idiopathic Parkinson's disease who responded to levodopa therapy and experiencing end of levodopa dose deterioration with predictable, mild to moderate ON-OFF fluctuations	Placebo 1.25 mg Zydis selegiline (Weeks 1 to 6) 2.5 mg Zydis selegiline (Weeks 7 to 12)	Placebo (N = 50) Zydis selegiline (N = 98)	41-83 yrs 104/44 142/3/3	12 weeks			

M = male, F = female, C = Caucasian, B = Black, O = Other

12. SUMMARY DESCRIPTION OF CLINICAL STUDIES

The ISS (text, tables, listings) consists of safety data derived from 6 Parkinson's disease studies including two identical, double-blinded, placebo controlled trials (Z/SEL/97/025 and Z/SEL/97/026), a randomized, open-label, parallel group active control trial (Z/SEL/95/008), a one day/single ZS exposure, randomized, placebo-controlled cross-over trial (Z/SEL/94/026; enrolling 148 patients), an open-label extension trial (Z/SEL/97/027) for the placebo-controlled

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trials, and another open-label extension trial (Z/SEL/95/008E) for the active control trial. Studies Z/SEL/94/026 and Z/SEL/95/008) are referred to as "other randomized studies," studies Z/SEL/97/027 and Z/SEL/95/008E are referred to as "extension studies," and studies Z/SEL/97/025, Z/SEL/97/026, Z/SEL/95/008 and Z/SEL/94/026 are collectively known as "short-term studies" or "randomized studies." Studies Z/SEL/94/026, Z/SEL/95/008, and Z/SEL/95/008E were conducted by Scherer alone and studies Z/SEL/97/025, Z/SEL/97/026, and Z/SEL/97/027 were initiated by Scherer and were completed by Elan (2/99 assumed ownership of ZS). The clinical section (#8) contains final study reports for all these trials except study Z/SEL/94/026. Table 28 shows a summary of patients included in all the clinical studies.

Table 28 Summary of Patients : All Clinical Studies

Study Grouping	Ever Received Zydys Selegiline	Ever Received Placebo	Never Received Zydys Selegiline	Ever Received Any Study Drug
Pivotal Double-Blind, Placebo-Controlled, Multicenter Randomized Trial	135	48	7	142
Supportive Double-Blind, Placebo-Controlled, Multicenter Randomized Trial	142	50	8	150
Supportive Open-Label, Active-Controlled, Multicenter Randomized Trial	127	0	45	198
Open-Label, One-Year Extension Study	77	0	0	77
Open-Label, Multi-Year Extension Study	254	0	0	254
Clinical Pharmacology Open-Label, Single-Dose Placebo-Controlled Crossover Study	148	148	0	148

13. INTEGRATED SUMMARY OF EFFICACY (ISE)

13.1. Brief Summary of Efficacy and Efficacy Conclusions

Zydis selegiline (ZS) is effective as an adjunctive treatment to levodopa/L-DOPA (LD) in Parkinson's disease patients who exhibit deterioration to LD therapy. The ZS dose of 2.5 mg/d was effective by virtue of being statistically superior to placebo ($p = 0.0007$) when studied after 12 weeks of treatment with ZS or placebo when the primary efficacy endpoint data (i.e. percent change from baseline in average "OFF" time during waking hours) were collected at 10 and 12 weeks following treatment. The single, positive, pivotal, randomized, placebo-controlled double-blind study (Z/SEL/97/026) is an adequately controlled study that provides substantial evidence for efficacy of ZS. I conclude that ZS demonstrates efficacy based upon the statistical analysis (conducted by Dr. F. Kong, DNDP statistical reviewer) for the primary efficacy

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endpoint using the intent to treat (ITT), last observation carried forward (LOCF) dataset in study Z/SEL/97/026. This analysis shows efficacy similarly as did the various other efficacy analyses of the primary and secondary endpoints presented by the sponsor. The sponsor's other analyses of the primary efficacy endpoint were not considered the appropriate analysis that DNDP had wanted and expected the sponsor to perform. Results from study Z/SEL/97/025 did not show that ZS was statistically superior ($p = 0.127$) to placebo for the same primary efficacy endpoint evaluated in study Z/SEL/97/026. These results were not statistically significant because of a "large" placebo "response" in study Z/SEL/97/025. However, because the response of patients treated with ZS were similar to those observed in Z/SEL/97/026, I conclude that the results of study Z/SEL/97/025 support my conclusion that there is substantial evidence for efficacy of ZS.

For study Z/SEL/97/026 and study Z/SEL/97/025, the sponsor was asked to submit : 1) a separate analysis of the primary efficacy endpoint for each study using the ITT LOCF dataset (based upon requests by DNDP); 2) a separate analysis of secondary efficacy endpoints for each study using this same dataset; 3) SAS codes to enable the statistical reviewer (Dr. F. Kong) to conduct the same analyses as the sponsor using the sponsor's datasets; and 4) separate analyses of the primary and secondary efficacy endpoints for each study using the completer dataset. A descriptive presentation and summary of these analyses have also been requested. As of 1/3/03, these analyses and presentations have not yet been received.

13.2. Reviewer's General Approach to Review of the Efficacy of the Drug

I reviewed the ISE and final study reports for the identical studies (Z/SEL/97/026 and Z/SEL/97/025) to assess the evidence of efficacy for ZS as adjunctive treatment to LD in Parkinson's disease patients who exhibit deterioration to LD therapy. I also reviewed the statistical analyses of the statistical reviewer (Dr. F Kong) for the primary efficacy endpoint using the ITT LOCF dataset.

Detailed Review of Trials Showing Efficacy or Supporting Efficacy

13.3. Study Z/SEL/97/026 (Study Showing Efficacy)

13.3.1. Description of Protocol Z/SEL/97/026 (Study Showing Efficacy)

Title of Study :

A Randomized, Double-Blind, Parallel-Group Study to Compare the Safety and Efficacy of Zydys selegiline 1.25 to 2.5 mg Q.D. with Placebo as an Adjunct in the Management of

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Parkinsonian Patients Being Treated With Levodopa Who Exhibit Deterioration in the Quality of Their Response to This Therapy

Study initiation date : 12/18/97

Study completion date : 10/15/99

Protocol Description (Synopsis/Summary) Amendment No. 5 (3/5/99)

Objectives :

To compare the efficacy and safety of Zydis Selegiline (ZS) 1.25 to 2.5 mg q.d. with placebo as an adjunct in the management of Parkinsonian patients being treated with levodopa (LD) who exhibit deterioration in the quality of their response to this therapy.

STUDY DESIGN and SCHEDULE :

This study was to be conducted in the U.S. and was to be a multicenter, double-blind, randomized, placebo-controlled, parallel-group comparison of two treatments (ZS 1.25 to 2.5mg q.d.) in 135 Parkinsonian patients receiving levodopa (LD) therapy, with or without a DOPA-decarboxylase inhibitor (DDCI). Although the protocol did not specify that it was necessary to use a DDCI along with LD, it appears that all patients did use a DDCI (e.g. carbidopa). Two-thirds of patients were to be randomized to ZS q.d. and one-third to Zydis Placebo q.d. In total, it was anticipated that 155 patients would be recruited into the study to allow for patients who withdraw. These patients were to be recruited from up to 18 centers in the U.S. It was intended that each investigator would recruit approximately 12 - 36 patients.

Throughout the study, symptoms of Parkinson's disease (PD) would be rated using patient/caregiver completed diary cards to record "ON" and "OFF" times, the Clinical Global Impression Scale (CGI), the Patient's Global Impression Scale (PGI) and the Motor and Activities of Daily Living sub-scales of the Unified Parkinson's Disease Rating Scale (UPDRS). At each investigator site, the CGI and UPDRS ratings were to be made by an appropriately qualified assessor who would be independent from all other aspects of the study conduct and patients were to be instructed not to volunteer any information to this assessor (e.g. adverse events) that might compromise the blinded nature of these ratings. For consistency and reproducibility, the same assessor was supposed rate a patient throughout the entire study. The patient was instructed how to rate "ON" (i.e. improved function of parkinsonian symptoms) and "OFF" (i.e. deteriorated function of parkinsonian symptoms).

The study would be composed of 2 periods and patients would be permitted to attend for scheduled visits within ± 3 days of the stated, scheduled Visit days. See Figure 8 for schematic diagram of study.

Period 1: Period 1 would last for 2 weeks (Visits 1, 2 and 3 occurring on Days -14, -7 and 0 relative to the start of study medication respectively). In Period 1 patients would continue to take

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their existing antiparkinsonian therapy and their eligibility for randomization at Visit 3 (minimum average of 3 hours "OFF" time per day) would be assessed by diary card completion.

Period 2: Period 2 would last for 12 weeks (Visits 4, 5, 6, 7, 8, 9 and 10 occurring on Days 7, 14, 28, 42, 56, 70 and 84 of study treatment respectively). During Period 2, patients would initially be randomized to receive either ZS 1.25 mg q.d. or Zydis Placebo q.d. (i.e. 1 tablet q.d.). Patients were instructed to take ZS without eating or drinking for at least 5 minutes prior to and after taking ZS which was also to be taken upon awakening in the morning before breakfast. After 6 weeks of study treatment, a patient's daily dose of ZS would be increased to 2.5 mg q.d. (or Zydis Placebo equivalent; i.e. 2 tablets q.d.). This treatment regimen would then be maintained for the remainder of the study.

During Period 2, if a patient showed evidence of dopamine overactivity (e.g. dyskinesia, confusion, nausea, orthostatic hypotension, dystonia and hallucinations) the treating physician was to consider reducing the total daily dose of LD to restore optimum control of the patient's symptoms. Dose reduction could be performed at one of the scheduled visits or in-between visits by telephone contact with the patient/caregiver. Patients were not supposed to be switched from immediate release formulations of LD to controlled release formulations of LD in order to achieve optimal symptom control. Also, after reducing a patient's total daily dose of LD during Period 2, the treating physician was not subsequently supposed to increase the total daily dose to beyond the total daily dose taken during Period 1, nor was any other therapy to be introduced in an attempt to control the patient's symptoms. However, if a patient had been receiving a fixed daily dose of a dopamine agonist since study entry (i.e. Visit 1) in addition to LD, the daily dose could also be reduced during Period 2, but was not supposed to be increased beyond the daily dose taken during Period 1.

If patients were taking anticholinergic drugs, the dose was to remain stable during the study.

Safety and tolerability of treatment was to be assessed throughout the study by oropharyngeal examinations, measurement of vital signs, routine blood and urine laboratory analyses and monitoring of adverse events.

Blood samples for population pharmacokinetic purposes were to be taken from all patients during Visit 6 and Visit 10 (i.e. after 1 month and 3 months' study drug treatment respectively). In addition, when possible, blood samples for pharmacokinetic (PK) analysis were to be taken from any patients who experienced serious adverse events requiring hospitalization or treatment in order to provide an adequate assessment of causality.

Patients who completed Visits 3 to 10 (Period 2) would be deemed to have successfully completed the study. Patients could, if they wished, then continue with study treatment by entering an extension study (protocol Z/SEL/97/027).

For those patients who did not enter the extension study, a follow-up examination was to be conducted 2 weeks after Visit 10.

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Key Inclusion Criteria :

- Male or female patients over 30 years of age with an affirmed diagnosis of idiopathic Parkinson's disease which responds to LD therapy.
- Patients who were receiving immediate and/or controlled release LD, with or without a DDCI and take a maximum of 6 doses per 24 hours at a minimal interval of 3 hours. If, in addition to LD, a patient is receiving a fixed daily dose of a dopamine agonist, e.g. Parlodel (bromocriptine), Permax (pergolide), Mirapex (pramipexole), Requip (ropinirole), Cabaser (carbergoline), this would be considered acceptable.
- Patients who were experiencing end of LD dose deterioration (the "wearing off" phenomenon) with predictable, mild to moderate "on-off" fluctuations. To be eligible for randomization to study treatment at Visit 3, potential patients must exhibit a minimum average of 3 hours "OFF" time per day, as assessed by diary card completion during the 2 week screening phase (between Visits 1 and 3).
- Females of childbearing potential who were using an accepted method of birth control. Acceptable birth control measures were: abstinence, hormonal contraceptive (oral and implant), barrier contraceptives (condoms, diaphragm with spermicide), surgical (hysterectomy, tubal ligation), IUD.

Key Exclusion Criteria :

- Patients who had taken selegiline within the 3 months prior to Visit 1.
- Patients who were taking or had taken the following medications within the 6 weeks prior to Visit 1 :
 - Any COMT inhibitor: e.g. Tasmar (tolcapone), Comtan (entacapone).
 - Any monoamine oxidase inhibitor: e.g. Nardil (phenelzine), Painate (tranylcypromine).
 - Opioid analgesics: e.g. Demerol (meperidine and other trade names).
 - Any selective serotonin re-uptake inhibitor (SSRI): e.g. Prozac (fluoxetine), Paxil (paroxetine), Zoloft (sertraline), Serzone (nefazodone), Effexor (venlafaxine), Luvox (fluvoxamine).
 - Any antidepressant drug, except when taken at a low dose and only at night for the purpose of effective sleep.
 - Treatment with anticholinergics would be permitted providing that the dose remained stable throughout the study.
 - Treatment with Hormone Replacement Therapy (HRT) would be permitted providing that the dose remained stable throughout the study.
- Patients who had received any other investigational drug within the 2 months prior to Visit 1.

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- Patients with impaired cognitive function, defined as a score of less than 24 points on a Mini-Mental State examination conducted at Visit 1.
- Patients with severe depression or psychosis.
- Patients who had undergone any neurosurgery for Parkinson's disease within the last 10 years.
- Patients who had experienced LD-induced hallucinations within the 6 months prior to Visit 1.

See Table 29 for schedule of assessments/events for efficacy, safety, and pharmacokinetic parameters.

Efficacy Variables

The primary efficacy variable/endpoint was defined as the reduction in percentage "OFF" time during waking hours (derived from patient/caregiver completed diary cards collected immediately prior to weeks 10 and 12) compared to percentage "OFF" during waking hours at baseline (derived from patient/caregiver completed diary cards collected over each of the 2 weeks prior to randomization). Although the last amended protocol specified that the primary efficacy analysis would be conducted on the intent-to-treat (ITT) population, the protocol did not clearly specify which of several datasets (e.g. last observation carried forward-LOCF dataset, visit-wise dataset, the completer dataset, per protocol dataset) would comprise the primary efficacy analysis. The ITT was defined as patients who were randomized to a treatment, received at least 1 dose of study medication, had baseline percent "OFF" time data during waking hours, and had at least one set of "OFF" time data during waking hours during treatment. Amendment # 2 (2/4/98) noted that the primary efficacy analysis was changed to analyze the ITT population instead of the LOCF dataset for the ITT population. However, the Statistical Analysis Plan (12/9/99) noted that the primary efficacy analysis would be performed on the ITT population and refers to the reader to "(see LOCF ITT population definition below)."

Diaries (24 hour) completed by the patient/caregiver were to be collected during 2 different days between Visits 1 and 2 and between Visits 2 and 3 in period 1 (i.e. screening/baseline). Diaries were to collect data of the patient's state at 1/2 hour intervals over 24 hours from midnight until the next midnight. When there were missing data entries, averages of available data would be used to compute average data. The diary categories of the patient's predominant state at each half hour interval included "OFF", "ON", "ON with dyskinesias", and "asleep." An assessor reviewed "OFF" with each patient to achieve a consensus definition/rating. When possible, a diary was to be collected on a day during the middle of the week and on a weekend day, avoiding a day before a visit when a UPDRS assessment was scheduled. Diary results indicating percentage "OFF" during waking hours at baseline and at post-treatment (from diary entries for the week preceding the week 10 Visit and the week preceding the week 12 Visit) were to be used