

Clinical Review
Leonard Peter Kapcala, M.D.
NDA 21479
Zydis selegiline/Zelapar

Table 21 Schedule of Study procedures and Safety Assessments

| | Days -28 - -8 | Day -7 | Day -6 | Day -5 | Days -4 to -1 | Days 1-10 | Days 1-10 | Day 8 | Day 9 | Day 10 | Days 11-16 | Day 17 |
|------------------------------------|------------------|---------------------|-------------------|--------------------------------|--|--|--------------------|-------------------|-------------------------|---|---------------|-----------|
| | Screen | Study Admittance | Orthostatic BP | Baseline Tyramine Challenge | Selegiline Dosing to Steady State | NARDIL Dosing to Steady State | Trough Sampling | Orthostatic BP | PK Sample Collection | Tyramine Challenge at Steady State | Discharge | |
| Informed Consent | X | | | | | | | | | | | |
| Med History | X | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | | | | | | |
| Physical Exam | X | | | | | | | | | X ^a | | |
| Vital Signs | X | X ^b | X ^c | X ^d | X ^b | X ^b | X ^b | X ^c | X ^b | X ^d | | |
| Safety ECG | X | X | | | | | | | | X ^a | | |
| Exercise Stress ECG (treadmill) | X | | | | | | | | | | | |
| Clinical Lab Tests | X | X | | | | | | | | X ^a | | |
| HIV, Hepatitis B/C | X | | | | | | | | | | | |
| Urine alcohol and drug screen | X | X | | | | | | | | X ^a | | |
| Pregnancy Test (hCG) | X | X | | | | | | | | X ^a | | |
| Overnight stay | | X | X | X | X | X | X | X | X | X | X | |
| Orthostatic BP | | | X | X ^e | | | | X | X ^e | | | |
| Randomization | | | | | X | | | | | | | |
| Administer Study Drug | | | | | X | X ^f | X | X | X | X | X | |

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| | Days -28 - -8 | Day -7 | Day -6 | Day -5 | Days -4 to -1 | Days 1-10 | Days 1-10 | Day 8 | Day 9 | Day 10 | Days 11-16 | Day 17 |
|-----------------------------|------------------|-----------|-----------|-----------|--------------------------------|--|--|--------------------|-------------------|-------------------------|---|-----------|
| Screen | | | | | Baseline Tyramine Challenge | Selegiline Dosing to Steady State | NARDIL Dosing to Steady State | Trough Sampling | Orthostatic BP | PK Sample Collection | Tyramine Challenge at Steady State | Discharge |
| Tyramine Challenge | | | | X | X | | | | | | X | |
| Trough PK Sampling | | | | | | | | X | X | | | |
| Pharmacokinetic Sampling | | | | | | | | | | Xg | | |
| Adverse Events | | | X | X | X | X | X | X | X | X | X ^a | |
| Con Meds | X | X | X | X | X | X | X | X | X | X | X ^a | |

- a Day 16 only, following completion of tyramine challenge measures.
- b Daily Vital Signs including blood pressure, heart rate, temperature, and respiratory rate were measured in this order 10 minutes prior to morning dosing in a semi-supine position.
- c Daily blood pressure and heart rate were taken as the initial semi-supine measures from the orthostatic blood pressure measure obtained 15 minutes prior to the morning dosing.
- d Prior to the administration of tyramine, 3 pre-dose semi-supine BP and heart rate measures (approximately 5 minutes apart) were taken, the average of which was used as the normal blood pressure measure for that day. Following these 3 blood pressure measures the subjects took oral tyramine in gelatin capsules at the prescribed daily dose. Subjects were maintained in a semi-supine position and measurements of heart rate and BP were made at 10 minute intervals for the next 120 minutes. BP measurements continued to be taken every 15 minutes for the next hour (for a total of 3 hours of BP and heart rate measurements following tyramine challenge). If a subject had a BP response that did not subside within the 3 hour time period, BP and heart rate measurements continued every 15 minutes until values returned to normal range as defined by the 3 pre-dose BP measures taken that day.
- e 24 hour orthostatic BP taken at 8:00 AM
- f The NARDIL group received 15 mg once daily (morning) plus placebo (evening) for 3 days, then beginning on Study Day 4 a dose of 30 mg NARDIL (15 mg BID) daily.
- g 12 samples were collected at the following times: pre-dose (0), and post-dosing at 5, 10, 15, and 30 minutes and, 1, 2, 3, 4, 6, 8, 12 hours (24h sample taken on Day 11).

Tyramine Challenges

Baseline Oral Tyramine Challenge

Beginning on Study Day -5, a series of daily tyramine challenge tests was performed to determine the baseline pressor response to tyramine. Tyramine was given 10 minutes prior to the time scheduled for administration of the morning dose of study medication later in the study. The appropriate number of tyramine capsules was taken with 240 mL of water. The dose of tyramine was escalated by a factor of 2 each day until a predefined response was observed. The doses of tyramine used to establish the baseline pressor response were scheduled as follows:

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

Prior to the administration of tyramine, three semi-supine BP and HR measurements were taken approximately 10 minutes apart. The mean of these three pre-dose measurements was used as the baseline for determining the magnitude of the pressor response. After completion of the three pre-dose BP and HR measurements, the subjects received their prescribed daily dose of oral tyramine in gelatin capsules. The subjects remained in a semi-supine position and HR and BP measurements were taken at 10-minute intervals for the next 120 minutes and at 15 minute intervals for the next hour (for a total of 3 hours of monitoring following each tyramine challenge). All BP and HR measurements were taken using a validated automatic blood pressure machine [Welch-Allyn Vital Signs Monitor] at the brachial artery. Any subject exhibiting a significant hypertensive response to tyramine (SBP ≥ 180 mmHg and/or DBP ≥ 115 mmHg) was considered a responder and randomized to receive study medication. Subjects that exhibited a significant hypertensive response to tyramine were not subjected to tyramine challenge with the next higher dose. If a subject had a hypertensive response that had not subsided within the 3-hour time period, BP and HR measurements were continued for every 15 minutes until values returned to normal range as defined by the 3 predose BP measures taken that day. Subjects that showed an increase of ≥ 15 mmHg in SBP for three consecutive measurements (taken 10 minutes apart) were also considered responders and randomized to receive study medication. Any subjects that did not exhibit the minimum increase in systolic blood pressure of ≥ 15 mmHg for three consecutive measurements in response to any dose of tyramine were considered non-responders and were removed from the study prior to randomization. Subjects that had a pressor

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response in SBP of 15-30 mmHg were not precluded from advancing to the next dose of tyramine unless they had also achieved one of the defined maximum BP thresholds (SBP \geq 180 mmHg and/or DBP \geq 115 mmHg). Tyramine dose escalation could also be stopped at the discretion of the investigator for safety reasons based on adverse events or the subject's level of discomfort.

Steady-State Tyramine Challenge

The tyramine challenge tests were repeated at selegiline steady-state beginning on Day 11 and continuing up to Day 16 depending on individual response to a given tyramine dose. Subjects continued to receive the randomized study medication throughout the second series (steady-state) of tyramine challenge assessments. The doses of tyramine used in the steady state tyramine challenge were the same as those administered during the baseline assessment with the addition of one additional lower dose (12.5 mg) according to the following schedule.

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

Any subject that exhibited a hypertensive response (SBP \geq 180 mmHg and/or DBP \geq 115 mmHg) during the steady-state tyramine challenge was considered a completer and was not advanced to the next higher dose of tyramine nor continued receiving doubleblind study drug. Subjects that demonstrated a pressor response of an increase from baseline (pre-tyramine dose) SBP \geq 30 mmHg were considered completers, but were not precluded from advancing to the next dose of tyramine unless they also experienced a defined maximum hypertensive response or adverse events that caused concern on the part of the investigator. Subjects that received all of the steady-state tyramine doses through 400 mg without exhibiting a hypertensive response or an increase from baseline SBP \geq 30 mmHg were also considered as completers for the purpose of analysis. Subjects could potentially undergo a total of 11 tyramine challenge tests (5 at baseline and 6 on-treatment) if they were advanced through the end of each series of escalations (400 mg tyramine).

Daily Schedule of Tyramine Dosing and Relationship to Meals

The approximate timing of dosing and meals during the tyramine challenge days (Days 11-16) was as follows.

Appears This Way
On Original

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| | |
|---------|---|
| 07:20 h | Start BP/HR monitor |
| 07:50 h | Administer tyramine with 240 mL water |
| 08:01 h | Administer ZELAPAR and corresponding placebo as appropriate |
| 08:06 h | Administer NARDIL capsule or placebo as appropriate |
| 10:50 h | Completion of tyramine test (3h BP monitoring) |
| 11:00 h | Lunch |
| 15:20 h | Snack |
| 18:00 h | Dinner |
| 20:06 h | Administer NARDIL capsule or placebo as appropriate |
| 21:00 h | Snack |
| 23:30 h | Begin fast (except water) for 8 hours prior to each tyramine dose |

Orthostatic Blood Pressure Evaluations

On Study Day-6 through Study Day-5 and on Study Day 9 through Study Day 10, SBP, DBP, and HR were recorded at rest after the subject had been supine for 5 minutes and then again after the subject had been standing at rest for 2 minutes. The measurements were performed using a validated automatic blood pressure machine (Vital Signs Monitor) at the brachial artery. The orthostatic BP and HR were recorded pre-dose (0), and at 0.5, 1, 2, 4, 6, 8, 10 and 24 hours after the morning dose of study medication. The 'predose' time point on Day -6 corresponded to the time that study medication would be administered during the treatment phase. Blood pressure measurements were performed on the same arm for each subject throughout the study.

b(4)

Clinical Laboratory Tests

Clinical laboratory tests (hematology, serum chemistry, and urinalysis) were performed at screening (Days -28 to -8), upon admittance to the clinical facility (Day -7), and prior to discharge (Day 16 or following completion of the tyramine challenge tests). Samples were obtained for the following standard tests after a 12-hour fast beginning at 7:00 pm the previous evening :

Hematology : hematocrit, hemoglobin, red blood cell count, white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and platelet count.

Serum Chemistry : albumin, alkaline phosphatase, BUN, creatinine, glucose, total cholesterol, triglycerides, potassium, CPK, ALT, AST, sodium, chloride, total bilirubin, total protein, uric acid, calcium, phosphorus, LDH, bicarbonate

Urinalysis : glucose, ketones, leukocytes, occult blood, pH, protein, specific gravity
 Hepatitis B and C, and HIV (performed at screening only)

Drugs of Abuse: urine alcohol and barbiturates cocaine metabolites, opiates, benzodiazepines, and cannabinoids (performed at screening, Day -7 and discharge)

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Pregnancy Test: Serum α -HCG test for women of child-bearing potential (performed at screening, Day -7 and discharge)

Safety ECGs

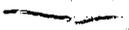
Standard 12 lead digital ECGs were recorded at screening, Day -7, and at discharge. The parameters obtained from the safety ECGs, including QRS, PR, QT, and QTc, were available for immediate review by the investigator for the purposes of safety assessment and determining subject eligibility for the study.

Exercise Stress ECG

All subjects completed an exercise stress ECG prior to enrollment (screening) to rule out the possibility of non-diagnosed coronary artery disease (CAD).

Daily Vital Signs

On Study Day -6 and Study Day 9, blood pressure measurements were taken for assessment of orthostatic blood pressure as described in Section 9.5.3. The BP and HR measurements taken in a semi-supine position 15 minutes before administration of study medication as part of the orthostatic BP assessment were considered to be the values for the daily vital signs. All vital sign measurements were completed approximately 15 minutes prior to any other procedure (eg, clinical laboratory sampling, administration of tyramine or study medication). During the tyramine challenge days (Study Day -5 through Study Day -1 and Study Day 11 through Study Day 16) a series of blood pressure and heart rate measurements were obtained. The average of the three pre-tyramine dose measurements was considered to be the daily vital sign value. These measurements were obtained approximately 5 minutes apart starting 30 minutes prior to dosing.

On all other study days vital signs were obtained 15 minutes before administration of study medication. Measurements were taken in a semi-supine position in the following order: HR, BP, oral body temperature, and respiratory rate. The actual time of vital signs measurements were recorded. All blood pressure and heart rate measurements were taken using a validated automatic blood pressure machine [ Vital Signs Monitor] at the brachial artery.

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Drug Concentration Measurements

Serial blood samples were obtained for the determination of selegiline plasma concentrations at specified time points over a 24-hour period commencing immediately prior to administration of the morning dose of study medication on Day 10. The timing of the blood sample collection was designed to measure the peak plasma concentration profile of selegiline to determine if any effect on the tyramine pressor response was related to the plasma levels of selegiline. The time points for the steady-state blood sample collection on Day 10 were :

Pre-dose (0), 5, 10, 15, and 30 minutes and 1, 2, 3, 4, 6, 8, 12, and 24 hours post dose. In addition to the blood samples obtained at steady state, one sample was taken 10 minutes prior to administration of the morning dose on Day 8 and Day 9 for assessment of trough plasma selegiline levels.

Statistical Methods Planned and Determination of Sample Size

Statistical and Analytical Plans

All statistical analyses were performed according to the Statistical Analysis Plan (SAP), and using Statistical Analysis System (SAS®) Version 8.2 or higher. All statistical tests were 2-sided at the 0.05 significance level unless otherwise specified. Continuous variables were summarized by treatment using the following descriptive statistics: N, mean, standard deviation, median, minimum, and maximum. Categorical variables were tabulated by treatment using the number and percentage of subjects by category. No statistical tests were performed for the routine safety analyses (adverse events, laboratory tests, vital signs).

Subject Data Sets to be Analyzed

Safety: The Randomized Safety Population included all subjects who received at least one dose of double-blind study medication. This definition of the safety population represents a change from the SAP, which described the safety analysis population as all subjects who received at least one dose of tyramine during the baseline challenge. The definition of the safety population was revised to allow for evaluation of the safety profile of the double-blind study medication that might otherwise be obscured against the background of untoward effects associated with tyramine in screen failures. Adverse events experienced by subjects in the randomized safety population prior to administration of double-blind study medication as well as AEs experienced by subjects who were screen failures.

Intent-to-treat (ITT): The ITT Population included all subjects who were randomized, received at least one dose of double-blind study medication, and who received at least one tyramine dose during steady-state treatment.

Per Protocol (PP): The Per Protocol Population included all subjects in the ITT Population who also met both of the following criteria:

- a) did not receive any concomitant MAO inhibitors
- b) completed the steady-state tyramine challenge.

Subjects were considered to have completed the steady-state tyramine challenge if they experienced a hypertensive response (SBP \geq 180 mmHg or DBP \geq 115 mmHg), reached a threshold response of an increase in SBP \geq 30 mmHg over the baseline (pre-dose tyramine), or received all six steady-state doses of tyramine without exhibiting a threshold SBP response \geq 30 mmHg.

Screen failures were defined as subjects who did not receive any randomized double-blind treatment; these subjects were not included in any data analyses. This group included subjects that did not demonstrate a minimum increase in SBP of \geq 15 mmHg for three consecutive measurements at any dose of tyramine during the baseline tyramine challenge (nonresponders). A listing of all screen failures was prepared, which included the subject number and the reason that the subject was not eligible to enter the study.

Primary Effect Analyses

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Three primary analyses were conducted, including two analyses of pharmacodynamic effect and one primary safety analysis.

Primary Effect Analysis No. 1: Change from baseline in systolic blood pressure (SBP) at the highest tyramine dose on treatment

The first primary effect analysis was conducted to determine whether ZELAPAR potentiates the effect of tyramine on SBP. The analysis was conducted on the ITT population. The peak systolic blood pressure response (E_{max}) was defined as the highest increase in SBP (change from pre-dose, where the pre-dose value is the average of the three pre-dose SBP measurements) following administration of the highest tyramine dose. For this analysis the response measure, change from baseline in peak SBP response, was the difference between the E_{max} for the largest dose of tyramine during steady-state and the E_{max} for the corresponding dose of tyramine during baseline.

For each subject, the change from baseline calculation was made within the same tyramine dosage level (fixed as the highest tyramine dose received during randomized treatment). For example, if the highest tyramine dose received during randomized treatment was 200 mg, the change from baseline calculation was the E_{max} value at 200 mg during randomized treatment minus the E_{max} value for the 200 mg dose during the baseline period.

A one-way classification statistical model was applied. Each of the active treatments was compared to placebo using a contrast statement in SAS proc glm

Primary Effect Analysis No. 2: Log tyramine dose at threshold response

The second primary effect analysis was conducted to estimate the relative difference in the tyramine threshold dose. The tyramine threshold dose was defined as the lowest dose of tyramine observed to produce a ≥ 30 mmHg increase in SBP.

Following log-transformation (natural log) the log-tyramine threshold doses observed during randomized treatment were compared using the two, one-sided test procedure. The analysis was conducted on the ITT population. The exponent of the average between-treatment difference (ratio) and 90% confidence limits around the ratio were presented. The statistical model for this response was the one-way classification model using SAS proc glm. Each dose of ZELAPAR (T or test treatment) was compared with NARDIL or placebo (R or reference treatment). A ratio of the test to reference (T/R) log-tyramine threshold doses significantly >1.00 indicated that the dose of tyramine required to produce the threshold response was significantly higher following treatment with ZELAPAR than following treatment with NARDIL. The inverse of the point estimate for the T/R ratio was an estimate of the relative potency of ZELAPAR to NARDIL.

Primary Safety Analysis: Effect of ZELAPAR on Orthostatic Blood Pressure

A series of orthostatic blood pressure and heart rate measurements were obtained for each subject over a 24-hour period at pre-treatment baseline (Day -6) and toward the end of dosing

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to steady state (Day 9). Systolic and diastolic BP measurements both supine and after standing for 2 minutes were recorded and the change in SBP and DBP after standing for 2 minutes (orthostatic blood pressure) was calculated. The difference between the Day 9 values and the Day -6 values was the response variable for this analysis. The one-way classification model was assumed for the orthostatic change in SBP, DBP, and HR. Each active treatment group was compared to placebo at each time point.

The proportion of subjects exhibiting clinically significant orthostatic hypotension (decrease in SBP ≥ 20 mmHg or DBP ≥ 10 mmHg) was calculated. This analysis was conducted on the Safety population. Each of the active treatment groups was compared to placebo with respect to orthostatic hypotension using Fisher's exact test.

Secondary Analyses of Pharmacodynamic Effects

Secondary pharmacodynamic analyses included the following :

Threshold Dose Ratios : This analysis examined the effect data using the "classical approach". A threshold tyramine dose (lowest dose which produces a "sustained" ≥ 30 mmHg increase in SBP) was calculated for each subject at baseline and on randomized treatment. For the purpose of this analysis a "sustained" response was defined as an increase in SBP ≥ 15 mmHg at two consecutive time points (taken 10 minutes apart) where one of the increases was ≥ 30 mmHg. The ratio of the baseline threshold dose to the on-treatment threshold dose was computed for each subject. These ratios were compared between the active treatment groups and also to placebo. Only those subjects that meet the response criteria at baseline and on-treatment were included in the analysis. The statistical model for this response was the one way classification model using SAS proc glm.

Effect of Tyramine Threshold Dose Definition : The second primary effect analysis (log tyramine dose at threshold response) was repeated using two alternative definitions of the tyramine threshold dose: a) the lowest tyramine dose producing an increase in SBP ≥ 15 mmHg at two consecutive time points taken 10 minutes apart where one of the increases was ≥ 30 mmHg; or b) the lowest tyramine dose producing an increase in SBP ≥ 30 mmHg at two consecutive time points taken 10 minutes apart. The analysis, model and presentation of results were the same as that outlined for the second primary effect analysis.

Correlation of blood pressure response to tyramine challenge with the peak blood concentrations of selegiline : On Study Day 10, eleven blood samples were taken from each subject for the analysis of selegiline concentration. The peak effect on SBP (E_{max}) at the highest tyramine dose on-treatment was correlated with the selegiline C_{max} value. The linear correlation coefficient of these responses was calculated across subjects.

Change from baseline in peak SBP at each tyramine dose on treatment : The change from baseline in peak SBP response (E_{max}) was calculated for each subject at each tyramine dose level. Each of the active treatments was compared to placebo at each tyramine dose level using the analysis methods described for the first primary effect analysis (change from baseline SBP at

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the highest tyramine dose on treatment). An analysis was conducted on observed cases (including only those subjects with data at a given dose level); and a second analysis was conducted using the last-observation-carried-forward (LOCF) method to impute results for any tyramine doses not received while on treatment.

Change from baseline in peak DBP and pulse rate : Change from baseline in peak DBP, mean DBP, and pulse rate was calculated for each subject at the highest tyramine dose on treatment. All active treatments were compared to placebo separately for each of these measures. The one-way classification model is assumed.

Summary of Safety Data

All subjects who received at least one dose of double-blind study medication were included in the evaluation of safety.

Vital signs and clinical laboratory test results were summarized by treatment using descriptive statistics and changes from baseline values.

The frequency of AEs, SAEs, treatment-emergent, and treatment-related AEs, as well as AEs by maximum severity, were summarized using MedDRA® 6.0 by system organ class, preferred term, and treatment. Treatment-emergent AEs were defined as any events reported on or after Day 1 following administration of randomized study medication. AEs that occurred during the baseline orthostatic hypotension or tyramine challenge assessments prior to receipt of double-blind study medication were also summarized for those subjects in the randomized safety population. AEs occurring in screen failures were not summarized but were included in the data listings.

Selegiline Plasma Concentration Analysis

Plasma concentrations of selegiline and pharmacokinetic parameters were summarized by treatment group using descriptive statistics. Plasma concentrations as a function of time were presented for individual subjects in data listings. Concentrations below the limit of quantification (BLQ) were treated as zero for descriptive statistics. Mean concentrations that were BLQ were presented as BLQ, and the SD and CV% were reported as not applicable (NA).

The plasma concentration data was used to correlate the maximum tyramine pressor response (Emax) to selegiline Cmax.

Determination of Sample Size

The sample size for this trial was estimated based on the following assumptions :

- the primary variable was change from baseline in peak SPB at the threshold tyramine dose
- a clinically relevant mean between-treatment difference of 10 mmHg (active versus placebo) was observed

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- a common standard deviation of 8.0.

Based on these assumptions, a sample size of 12 completed subjects per treatment arm was calculated to provide a power of 0.84 and a two sided Type I error rate of 0.05. An enrollment of approximately 16 subjects per treatment arm was planned allow for attrition and complete approximately 12 subjects per treatment arm. Although there were no plans to stratify the analysis for gender, the randomization was conducted to enroll an approximately equal number of men and women.

Changes in the Conduct of the Study or Planned Analyses

Changes in the Conduct of the Study

Two amendments were made to the original protocol dated 24 June 2004. A summary of the major changes to the protocol are provided below.

Amendment No. 1 6 August 2004

- Established criteria for determining the daily baseline BP measurement for the tyramine challenge. The baseline was defined as the mean of 3 BP measurements taken approximately 10 minutes apart prior to administration of tyramine.
- Clarified that nonresponders to tyramine would be discontinued from the study prior to randomization.
- Clarified the criteria for not escalating a subject to the next higher dose of tyramine. Subjects were not to be escalated if they exhibited a clinically significant hypertensive response (SBP ≥ 180 mmHg and/or DBP ≥ 115 mmHg) or if the investigator was concerned for the subject's safety based on AEs associated with elevations in BP.
- Clarified that subjects exhibiting an SBP increase higher than 15-30 mmHg were not precluded from escalation to the next higher dose of tyramine unless they achieved the threshold definition of a hypertensive response (SBP ≥ 180 mmHg and/or DBP ≥ 115 mmHg) or were discontinued from the tyramine challenge at the discretion of the investigator out of concern for safety.

Amendment No. 2 20 August 2004

- Added two additional time points on Day 10 (5 and 10 min post-dose) for the collection of blood samples for analysis of selegiline plasma concentrations.
- Correction made to state that the CRO rather than the sponsor would maintain the randomization code.

Changes to the Analyses

The definition of the safety analysis population was revised from the original definition of all subjects who received at least one administration of tyramine during the baseline tyramine

challenge to include only those subjects who had received at least one dose of double-blind study medication.

Additional statistical comparisons were performed for the two primary effect analyses. In the analysis of the peak SBP response (E_{max}), each ZELAPAR treatment was compared to NARDIL using a one-way classification model, in addition to the comparison of each active treatment to placebo as detailed in the SAP. In the analysis of the tyramine threshold dose, the active treatments were compared to placebo, in addition to the comparison of each ZELAPAR dose to NARDIL as described in the SAP. These additional comparisons were conducted using the primary definition of the tyramine threshold dose as the lowest dose of tyramine that produced an SBP increase ≥ 30 mmHg, as well as the definitions of threshold dose applied in the secondary analyses.

The tyramine threshold dose ratio was calculated in the conventional manner as the ratio of the baseline threshold dose (numerator) to the on-treatment threshold dose (denominator). The SAP defined the threshold dose as the ratio of the on-treatment threshold dose to the baseline threshold dose. The relative potency of the study drugs was expressed as the difference between the tyramine threshold dose ratios obtained for each treatment rather than as a ratio of the response ratios thus obtained.

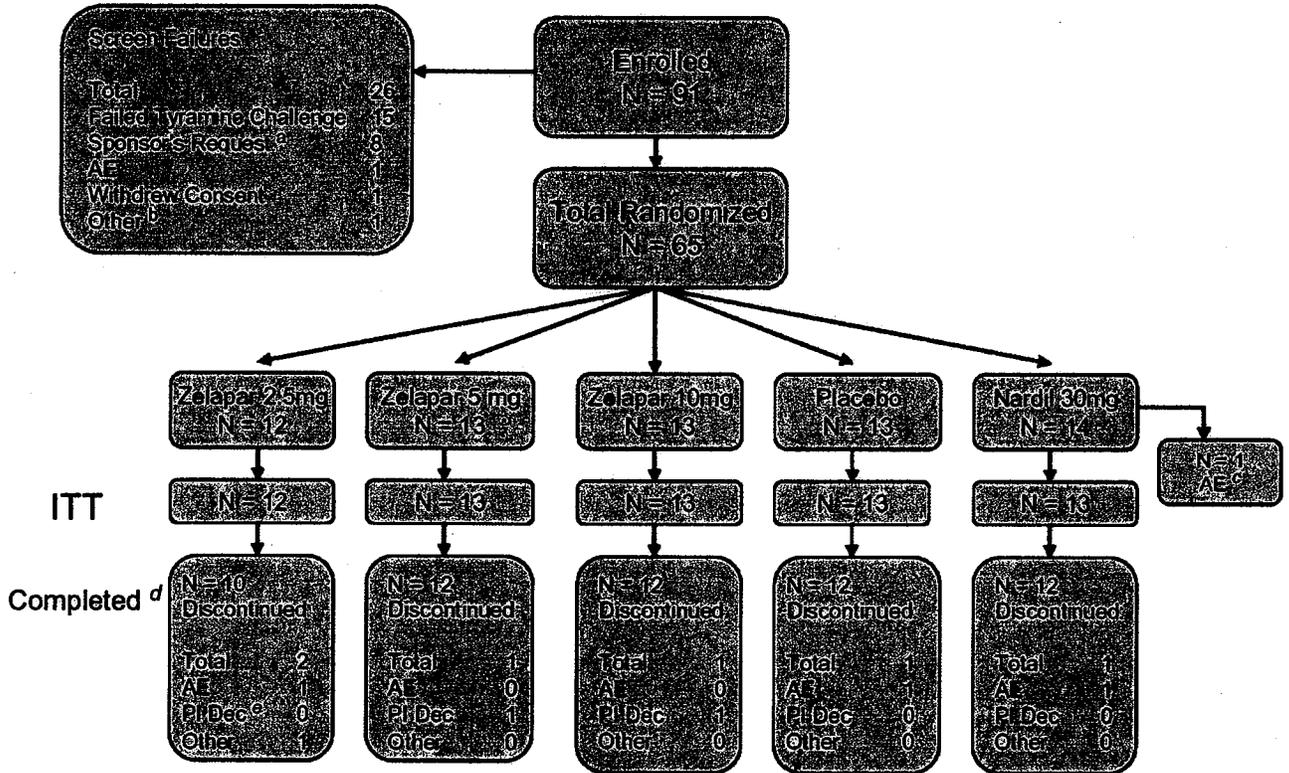
Sponsor's Description of Study Results

Disposition of Subjects

A total of 91 subjects were initially enrolled into the study. A summary of subject disposition is shown in Figure 11. Among these, 26 were identified as screen failures and were not randomized to double-blind study medication. The majority (15 subjects) of the non-randomized subjects failed to meet the minimum tyramine response criteria during the baseline tyramine challenge. Eight (8) subjects were not randomized at Sponsor's request since the objectives for the number of subjects enrolled and completed had been met. The remaining three subjects were not randomized as the result of an AE (1 subject; hypertension, 225/105), withdrawal of consent (1 subject), or other reasons (1 subject; high blood pressure at 50 mg tyramine, 155/75). A total of 65 subjects were randomized, with 12, 13, 13, 13, and 14 subjects in the ZELAPAR 2.5 mg, ZELAPAR 5 mg, ZELAPAR 10 mg, Placebo, and NARDIL 30 mg groups, respectively.

One subject (Subject No. 021) randomized to the NARDIL group discontinued on Day 6 after having received double-blind study medication for 4 days, but prior to receiving at least one tyramine dose after reaching steady state with the double-blind study medication. Consequently, the ITT analysis population consisted of 64 subjects. Since Subject No. 021 did receive study medication, he was included in the randomized safety population ($N = 65$).

Figure 11 Schematic of Study Subject Disposition



- a Subjects not randomized at Sponsor's request since enrollment objectives had been met
- b Subject experienced high blood pressure and discontinued at the discretion of the investigator
- c Subject No. 021 discontinued as a result of an AE after receiving randomized study treatment for 4 days. The subject was not included in the ITT population since he did not receive at least one dose of tyramine while on study treatment.
- d Subjects identified as having completed on CRF ENDSTUDY page. Some subjects may not have achieved a threshold response during the on-treatment tyramine challenge
- e Principal Investigator decision to discontinue based on high blood pressure

Protocol Deviations

No protocol deviations were identified with respect to eligibility criteria, study drug administration times, blood sampling times during the steady-state plasma concentration profiling, or for unauthorized concomitant medications. Subjects identified as screen failures were not considered protocol violators since the protocol provided for a baseline tyramine challenge to assess eligibility for randomization.

PHARMACODYNAMIC EFFECTS

Data Sets Analyzed

The analyses of pharmacodynamic effects were performed for the 64 subjects in the ITT population, which included all subjects who were randomized, received at least one dose of double blind study medication, and who received at least one tyramine dose during steady state treatment.

Demographic and Other Baseline Characteristics

Demographic characteristics are summarized in Table 22 and showed that they were generally similar across all treatment groups.

Table 22 Summary of Demographic Characteristics By Treatment Group

| Demographic Characteristic | ZELAPAR 2.5 mg (N = 12) | ZELAPAR 5 mg (N = 13) | ZELAPAR 10 mg (N = 13) | Placebo (N = 13) | NARDIL 15/30 mg (N = 14) ^a |
|----------------------------|-------------------------------|-----------------------------|------------------------------|--------------------------|---|
| Age (years) | | | | | |
| Mean [SD] (Min - Max) | 50.0 [8.52] (40 - 64) | 49.6 [6.23] (40 - 60) | 51.2 [4.71] (43 - 58) | 50.5 [7.32] (42 - 69) | 50.6 [7.50] (41 - 68) |
| Gender | | | | | |
| Male (%) | 6 (50.0%) | 7 (53.8%) | 7 (53.8%) | 6 (46.2%) | 7 (50.0%) |
| Female (%) | 6 (50.0%) | 6 (46.2%) | 6 (46.2%) | 7 (53.8%) | 7 (50.0%) |
| Race | | | | | |
| Hispanic (%) | 9 (75.0%) | 12 (92.3%) | 11 (84.6%) | 11 (84.6%) | 11 (78.6%) |
| Caucasian (%) | 2 (16.7%) | 1 (7.7%) | 2 (15.4%) | 2 (15.4%) | 2 (14.3%) |
| Black (%) | 1 (8.3%) | 0 | 0 | 0 | 1 (7.1%) |

^a Includes Subject No. 021 who discontinued because of an adverse event on Day 6 after having received study medication for 4 days

SD = Standard Deviation

Data Source: Section 15, Supplemental Table 1.1; Appendix 16.2, Listing 1

Selegiline Plasma Concentration and Pharmacokinetic Results

Plasma Concentration Results

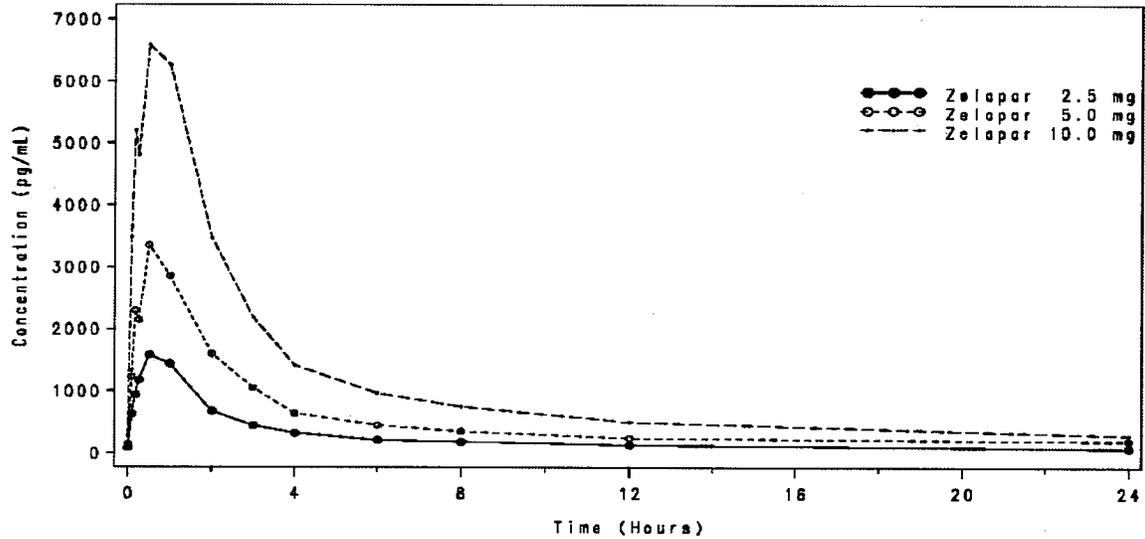
Blood samples were obtained at steady state from all subjects over a 24-hour period on Day 10 in association with administration of the 10th dose of randomized study medication. Blood samples were obtained at the following time points to identify the peak concentration of selegiline for individual subjects for use in the correlation of maximum pressor effect to selegiline C_{max}.

0 (pre-dose), and at 5, 10, 15, and 30 minutes, and 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing

Mean plasma selegiline (steady state on day 10) at each sampling time for reach ZS treatment is shown in Figure 12.

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Figure 12 Mean Plasma Concentrations of Selegiline (pg/mL) at Steady-State (Day 10) from Pre-Dose to 24 Hours



Data Source: Supplemental Figure 1; Supplemental Table 22

Pharmacokinetic Results

Mean PK parameters for selegiline (steady state) are summarized by ZELAPAR dose group in Table 23.

Table 23 Mean (SD) Steady-State Selegiline Pharmacokinetic Parameters by Zydis Selegiline Dose

| Parameter | ZELAPAR 2.5 mg N = 12 | ZELAPAR 5 mg N = 13 | ZELAPAR 10 mg N = 13 |
|------------------------------------|--------------------------|------------------------|-------------------------|
| C _{max} (pg/mL) | 1813.4 (858.1) | 3554.3 (1350.6) | 7921.3 (3356.7) |
| T _{max} (hr) ^a | 0.50 (0.17 – 1.00) | 0.50 (0.17 – 1.00) | 0.50 (0.17 – 1.00) |
| AUC _{ss} (pg • hr/mL) | 5040.0 (3287.1) | 12518.6 (5523.2) | 26125.4 (12949.4) |
| t _{1/2} (hr) | 7.1 (5.1) | 11.7 (3.3) | 10.9 (2.3) |

^a Median (range)

Data Source: Supplemental Table 21

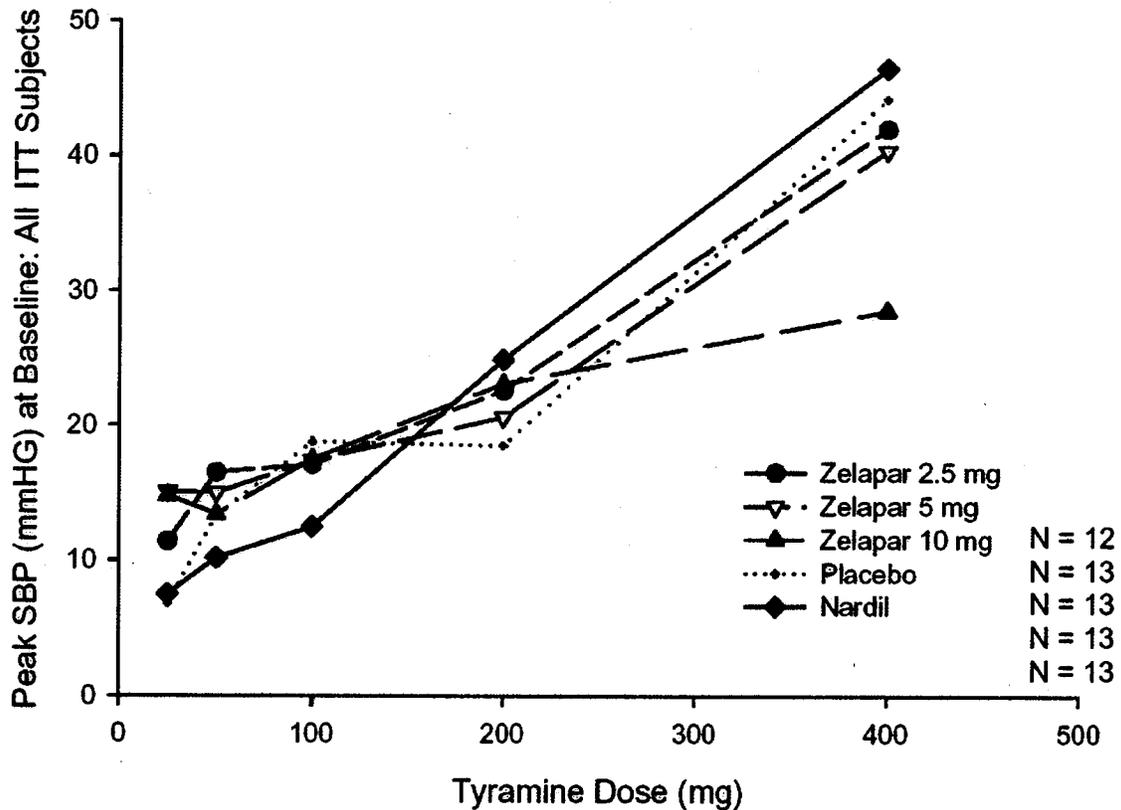
Median T_{max} was 30 minutes (range 10 to 60 minutes) for all doses, which coincided with the time of the tyramine pressor response. The observed C_{max} and AUC_{ss} for selegiline at steady state appeared to be dose proportional for the ZELAPAR doses of 2.5 to 10 mg.

Primary Analyses of Pharmacodynamic Effects

Baseline Tyramine Pressor Response

A total of 64 subjects in the ITT population completed the baseline tyramine challenge (each subject received all dosage levels through 400 mg). Prior to randomization, the peak baseline pressor response was defined for each subject at each dose of tyramine as the maximum change in SBP observed following administration of a given dose of tyramine relative to the baseline SBP (mean of three SBP measurements obtained over a 30-minute period) prior to administration of that dose of tyramine. The mean peak baseline SBP response is displayed graphically in Figure 4.

Figure 13 Mean Peak Systolic Blood Pressure Response to Tyramine : All ITT Subjects (N = 64)



Data Source: Supplemental Table 16.1; Appendix 16.2, Listing 16.1 and Listing 16.4

As expected, the magnitude of the mean peak SBP response (Emax) was clearly associated with the dose of tyramine. By observation, the Emax for SBP increased in a roughly linear

fashion across the tyramine dose range of 25 to 400 mg. Individual results were more variable, but most subjects demonstrated an increase in the Emax for SBP in response to increasing doses of tyramine. The baseline peak SBP response was similar for all treatment groups over the tyramine dose range of 25 mg to 200 mg extending from a response of 7 - 15 mmHg for the 25 mg dose of tyramine up to a response of 19 – 25 mmHg for the 200 mg dose of tyramine. At the 400 mg dose of tyramine, the mean pressor response exhibited by subjects in the 2.5 mg and 5 mg ZELAPAR groups and the placebo and NARDIL groups was similar, ranging from 42 – 47 mmHg. While continuing to demonstrate a dose-dependent increase in the pressor response, the 10 mg ZELAPAR group exhibited a notably lower mean peak response of 28.5 mmHg. The lower mean value for the 10 mg Zelapar group is the result of atypically low peak responses (i.e. 13, 16, and 3 mmHg) in three of the 13 subjects at the 400 mg tyramine dose.

Systolic Blood Pressure Emax at Highest Tyramine Dose

All 64 subjects in the ITT analysis population escalated to at least the second tyramine dose, 25 mg, while receiving randomized study drug. As the tyramine dose escalation progressed, some subjects discontinued after having demonstrated a threshold pressor response, experienced an AE, or were discontinued at the discretion of the investigator out of concern for a potential hypertensive response. Table 24 presents the maximum dose of tyramine administered to subjects in each treatment group.

Table 24 Maximal Tyramine Dose Administered During Randomized Treatment According to Treatment

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

Data Source: Appendix 16.2, Listing 16.4

A notably lower number of subjects progressed beyond the 50 mg tyramine dose in the NARDIL group than in the ZELAPAR or placebo treatments. The number of subjects that continued to participate in the tyramine challenge continued to decrease with higher doses until by the time the final 400 mg dose of tyramine was administered only two subjects remained in the NARDIL group and 3 subjects remained in the 10 mg ZELAPAR group. In contrast, the number of subjects remaining in the 2.5 mg (8 subjects) and 10 mg (7 subjects) ZELAPAR groups was similar to placebo (9 subjects). The drop-off in the number subjects available for analysis at the higher doses of tyramine introduced variability into the analysis of threshold dose; however, the

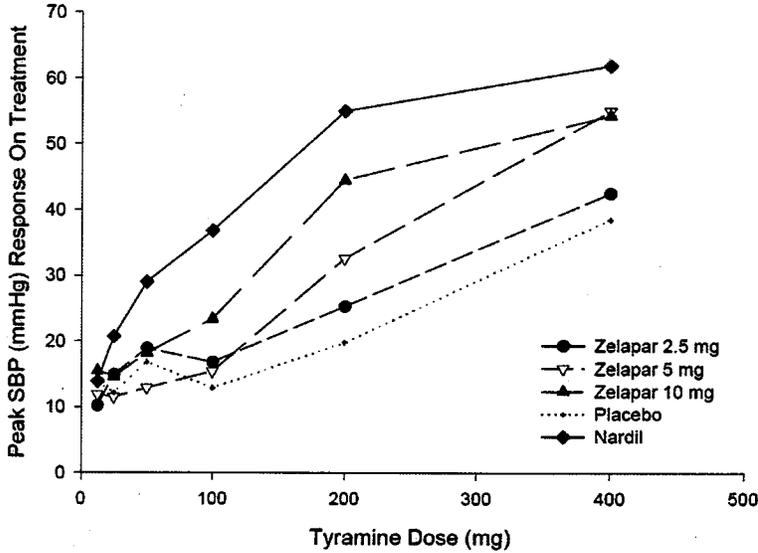
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disproportionately lower numbers of subjects remaining in the 10 mg ZELAPAR and NARDIL groups provides an indication of the ability of those treatments to enhance the tyramine pressor effect, since subjects in these groups experience a response and discontinue at lower doses of tyramine than the lower ZELAPAR doses or placebo groups.

The relationship between the tyramine dose and peak SBP response (E_{max}) during randomized treatment is depicted in Figure 14. **In this figure, the response observed at the highest tyramine dose administered was carried-forward for those subjects who stopped the tyramine dose escalation prior to reaching the 400 mg level.**

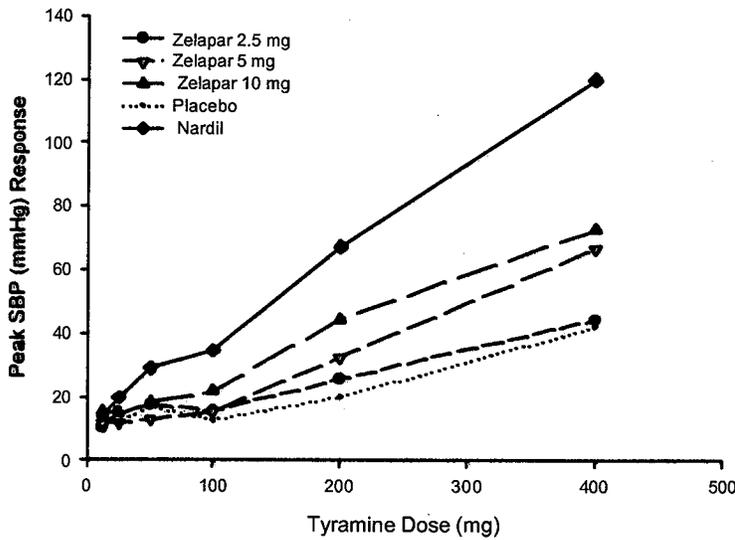
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Figure 14 Mean Peak Systolic Blood Pressure Response to Increasing Tyramine Dose Challenges on Treatment (LOCF) : All ITT Subjects (N = 64)



Data Source: Supplemental Table 16.2; Appendix 16.2, Listing 16.1 and Listing 16.4

Figure 15 Mean Peak SBP Response to Tyramine on Treatment^a (Observed)



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As noted in Figure 14, the mean Emax increased in relationship to the tyramine dose. However, unlike the baseline results, there was a separation in the magnitude of the SBP response between the active treatment groups; where the response to NARDIL 30 mg > ZELAPAR 10 mg > ZELAPAR 5 mg > ZELAPAR 2.5 mg.

The effect of ZELAPAR on the peak SBP response to the highest dose of tyramine administered (Emax) is summarized in Table 25.

In the first primary effect analysis, the change from baseline represents the difference between the peak SBP response at the highest dose of tyramine administered while on randomized treatment (Days 11-16) and the peak SBP response at the corresponding tyramine dose at baseline (Days -5 to -1). No subjects in the ITT analysis population discontinued the on-treatment tyramine challenge before receiving the 25 mg dose of tyramine on Day 12; therefore, all ITT subjects had a pre-randomization tyramine baseline measurement corresponding to 25 mg tyramine and were included in this analysis.

Table 25 Mean Change in Peak Systolic Blood Pressure Response/Increment (Emax) from Baseline at the Highest Tyramine Dose on Treatment

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

SD = Standard Deviation

a p-value for ANOVA comparing active treatments to placebo

b p-value for ANOVA comparing ZELAPAR to NARDIL (positive control)

Data Source: Supplemental Table 11.1; Appendix 16.2, Listing 16.4

The NARDIL positive control group demonstrated a mean increase in SBP pressor response to tyramine of approximately 45 mmHg over baseline, which represented a statistically significant difference from placebo (p <0.001). Administration of ZELAPAR resulted in an increase in the SPB response to tyramine of 10 mmHg, 25 mmHg, and 35 mmHg for the ZELAPAR 2.5 mg, 5 mg, and 10 mg doses, respectively. The 5 mg and 10 mg dose of ZELAPAR exhibited an effect on the peak tyramine pressor response that was clinically significant (=20 mmHg) and statistically significantly different from placebo. The effect of ZELAPAR 2.5 mg on the peak tyramine pressor response was neither clinically significant nor statistically significant from placebo.

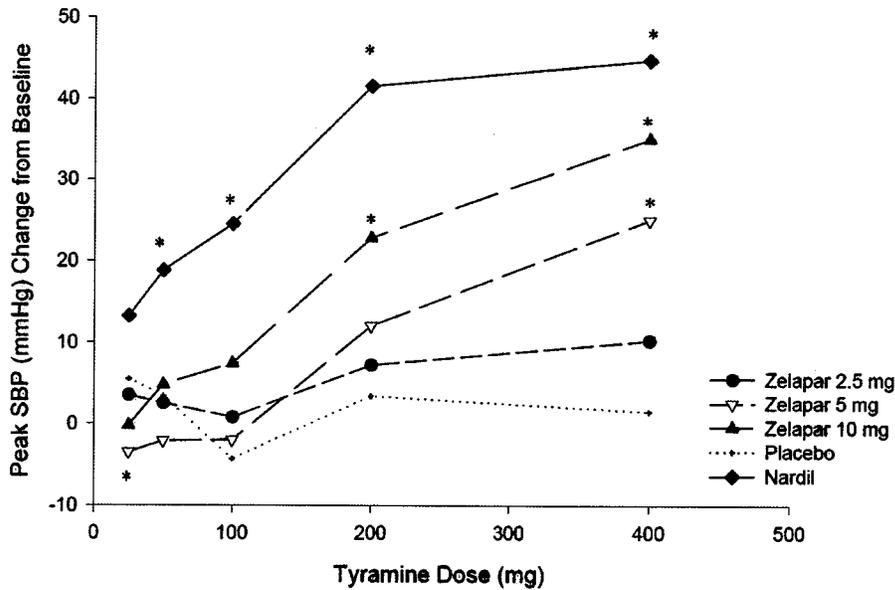
Comparison of ZELAPAR to NARDIL showed that the effect of the 2.5 mg and 5 mg doses of ZELAPAR on the maximum tyramine pressor response was significantly lower than NARDIL,

while the effect of the suprathreshold 10 mg dose of ZELAPAR was not significantly different from NARDIL.

The primary analysis of Emax at the highest administered dose of tyramine (Table 25) was confirmed and extended by exploring the maximum SBP change from baseline produced by the active treatments at each dose of tyramine.

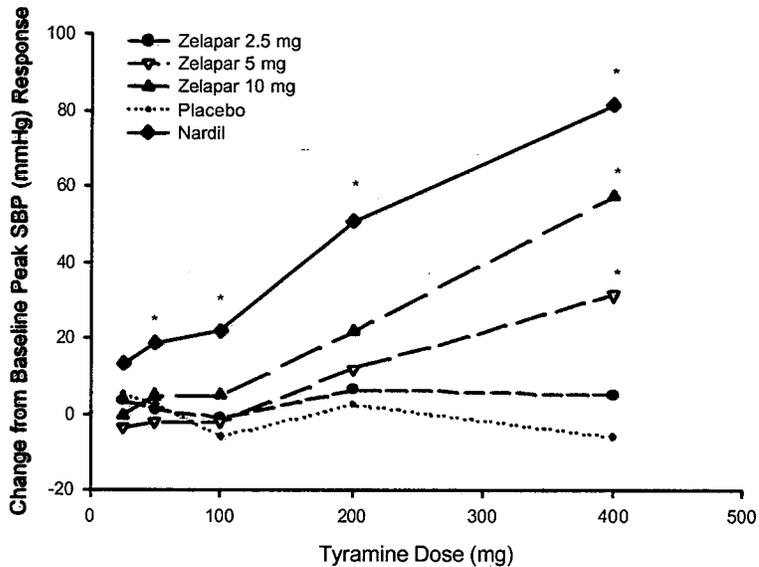
An LOCF analysis of the mean peak SBP change from baseline at each on-treatment tyramine dose is summarized displayed graphically in Figure 14. This analysis was performed in a manner analogous to that of the primary analysis. For each subject, the change from baseline represents the difference between the observed peak SBP response and the SBP response at the corresponding baseline dose, up to the highest tyramine dose administered on treatment. If a subject did not progress beyond a given dose of tyramine during randomized treatment, the change from baseline for the highest dose of tyramine was carried forward to calculate the mean change at higher dosage levels. The results of this secondary analysis showed that progressively higher doses of ZELAPAR were clearly associated with potentiation of the pressor response to a fixed dose of tyramine.

Figure 16 Mean Peak Systolic Blood Pressure Change from Baseline by Treatment for each Dose of Tyramine (LOCF)



* statistically significant difference from placebo at 0.05 level
 Data Source: Supplemental Table 16.2; Appendix 16.2, Listing 16.1 and Listing 16.4

Figure 17 Mean Change from Peak Baseline SBP Response to Tyramine (Observed)



None of the active treatments had a significant positive effect on the pressor response at the lowest dose of tyramine tested for which an on-treatment and baseline comparison was possible (25 mg). The ZELAPAR 2.5 mg dose did not show a significant difference from placebo at any dose of tyramine during the on-treatment tyramine challenge. The peak SBP change from baseline increased in a tyramine-dose-dependent manner for the 5 mg and 10 mg doses of ZELAPAR. The difference in response relative to placebo achieved statistical significance at the 400 mg tyramine dose for ZELAPAR 5 mg, at the 200 mg and 400 mg tyramine doses for ZELAPAR 10 mg, and at the 50 mg, 100 mg, 200 mg, and 400 mg tyramine doses for NARDIL 30 mg. A dose-dependent increase in the peak SBP response to tyramine was also clearly evident for NARDIL and the difference was significantly different from placebo at the 50 mg, 100 mg, 200 mg, and 400 mg doses of tyramine.

Analysis of the peak SBP change from baseline at each tyramine dose for the observed cases (Figure 17) yielded results consistent with the LOCF analysis (Figure 16).

Tyramine Threshold Dose

The tyramine dose-response data for individual subjects could not be reliably fit to a logistic or sigmoidal Emax model. The goodness-of-fit statistics were very poor and the parameter results were highly correlated. As a result, the alternative definition of threshold dose noted in the statistical plan was utilized. The relative potency of ZELAPAR and NARDIL was compared by evaluating the effect of each treatment on the dose of tyramine required to produce a predefined increase in SBP over baseline (pre-treatment with tyramine). For the primary analysis, the tyramine threshold dose was defined as the lowest dose of tyramine observed to elicit a = 30 mmHg increase in SBP.

Secondary analyses of effect were performed using two alternate definitions of the tyramine threshold dose: a) the lowest dose of tyramine that produced an increase in SBP = 15 mmHg at two consecutive time points (10 minutes apart) where one of the two qualified measurements was = 30 mmHg, or b) the lowest dose of tyramine producing an increase in SBP = 30 mmHg at two consecutive time points (10 minutes apart).

Table 26 summarizes the analysis of the tyramine threshold dose for the initial observation of an increase in SBP = 30 mmHg (at least one increment) from the pre-treatment baseline.

Table 26 Tyramine Threshold Dose Producing at Least One Increment (\geq 30 mm Hg) in Systolic Blood Pressure (Emax) During Randomized Treatment

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

LS = Least Squares
T = Test
R = Reference
Data Source: Supplemental Table 12.1; Appendix 16.2, Listing 16.4

The adjusted least squares (LS) mean threshold dose of tyramine necessary to elicit at least a single = 30 mmHg increase in SBP when administered concomitantly with ZELAPAR was approximately 141, 200, and 168 mg tyramine for the 2.5 mg, 5 mg, and 10 mg doses of ZELAPAR, respectively. In comparison, the dose of tyramine required to produce the same effect in the control groups was approximately 67 mg for NARDIL and 272 mg for placebo. The tyramine threshold dose for ZELAPAR 2.5 mg was approximately 2-fold higher than that of NARDIL. The tyramine threshold dose for ZELAPAR 5 mg and 10 mg was 3-fold and 2.5-fold higher, respectively, than that of NARDIL. The 90% CIs constructed for the tyramine threshold dose ratios indicate that the three doses of ZELAPAR could not be distinguished from placebo with regard to their effect on the tyramine threshold dose required to produce a = 30 mmHg increase in the SBP response. In contrast, treatment with NARDIL reduced the threshold dose by 4-fold from placebo (T/R = 0.2452; 90% CI = 0.1268, 0.4741). Evaluation of the tyramine threshold dose (30 mmHg) was influenced by a number of subjects with isolated and possibly spurious elevations in blood pressure. For example, Subject 074 in the ZELAPAR 2.5 mg group was identified as having an on-treatment tyramine threshold dose (= 30 mmHg) of 50 mg based on a peak SBP response of 36 mmHg after treatment with 50 mg tyramine; however, the subject did

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not show any increase in SBP in response to 100 mg or 200 mg tyramine. Similarly, Subject 054 in the ZELAPAR 5 mg group was considered to have reached a threshold dose (= 30 mmHg) at 12.5 mg tyramine based on a SBP response of 35 mmHg; however, the successive doses of 25 mg and 50 mg tyramine failed to produce a threshold pressor response = 30 mmHg. This intra-individual variability in tyramine sensitivity has been observed in previous studies utilizing the tyramine challenge method (Z/SEL/95/007, Z/SEL/96/014, and AN17933-101).

Comparison of the relative potency of ZELAPAR and NARDIL to increase the pressor response to tyramine was also performed using the alternate definitions of the threshold tyramine response. The results of these analyses are displayed in Table 27.

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Table 27 Tyramine Threshold Dose A Sustained Increase in Systolic Blood Pressure During Steady State on Study Treatment

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

LS = Least Squares

T = Test

R = Reference

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

b Lowest dose of tyramine producing an increase in SBP ≥ 30 mmHg at two consecutive time points (10 minutes apart)

Data Source: Supplemental Tables 12.2 and 12.3; Appendix 16.2, Listing 16.4

When the threshold response was defined as the lowest dose of tyramine producing an increase in SBP = 15 mmHg at two consecutive time points (10 minutes apart), where one of the two measurements was = 30 mg ("15-30"), the results of the comparative analysis were essentially the same as for the primary analysis definition of threshold dose (at least single increment ≥ 30 mmHg), since the redefined threshold dose only changed for one subject (Subject No. 029 in the 2.5 mg ZELAPAR group).

Definition of the threshold dose as a sustained response of an increase in SBP = 30 mmHg for two consecutive measurements taken 10 minutes apart ("30-30") revealed a more pronounced difference between the two lower doses of ZELAPAR and NARDIL than was apparent in the

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primary analysis. The LS mean threshold dose (30-30) for ZELAPAR was 336 mg, 317 mg, and 213 mg tyramine for the ZELAPAR 2.5, 5 mg, and 10 mg groups, respectively, corresponding to a difference from the NARDIL mean threshold dose (79 mg tyramine) of 4.2-, 4-, and 2.7-fold, respectively. The 90% confidence limits around the relative potency estimates all excluded 1.0, indicating that all three doses of ZELAPAR were significantly less potent than NARDIL. Under the alternate threshold dose definition (30-30), all three doses of ZELAPAR were more similar to placebo than was demonstrated for the less stringent primary analysis definition of threshold dose (≥ 30 mmHg).

Secondary Analyses of Pharmacodynamic Effects

Tyramine Threshold Dose Ratios for Sustained Response

The ratio of the baseline tyramine threshold dose to the on-treatment threshold dose was determined for each treatment using the two previously described alternate definitions of sustained threshold response (SBP 15-30 mmHg and 30-30 mmHg). The threshold dose ratios thus obtained for each active treatment were compared to placebo, and the threshold dose ratios for each ZELAPAR dose were compared to NARDIL. The results of these analyses are presented in Table 28 represents the traditional approach to the evaluation of relative potency of MAO inhibitors in increasing the pressor response to tyramine. In this analysis, a threshold dose ratio of "1" would indicate that the treatment had no effect on the tyramine pressor response. A threshold dose ratio >1 indicated that the treatment interacts with tyramine in a positive manner and potentiates the pressor effect.

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Table 28 Comparison of Tyramine Threshold Dose Ratios for Sustained Systolic Blood Pressure Response

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

T = Test

R = Reference

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

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

Data Source: Supplemental Tables 15.1 and 15.2; Appendix 16.2, Listing 16.4, Listing 20

When the threshold tyramine dose was defined as the lowest dose of tyramine producing an increase in SBP = 15 mmHg at two consecutive time points (taken 10 minutes apart), where one of the measurements was = 30 mmHg, the threshold dose ratios for the ZELAPAR treatments were approximately 2.3, 1.3 and 1 for the 2.5 mg, 5 mg, and 10 mg doses, respectively. The threshold dose ratios for NARDIL and placebo were 7 and 1.75, respectively.

Using the threshold dose definition as the lowest dose of tyramine that produced an increase in SBP = 30 mmHg at two successive time points resulted in threshold dose ratios of 1.3, 1, and 1.5 for the 2.5 mg, 5 mg, and 10 mg doses of ZELAPAR, respectively. The corresponding threshold dose ratios were 5.6 and 0.8 for NARDIL and placebo, respectively. Application of the upper and lower limits of the 90% CIs for the differences in the threshold ratios between

treatments indicated that none of the ZELAPAR treatments were different from placebo, whereas the threshold dose ratio obtained for NARDIL was significantly greater than that of placebo for both definitions of the threshold dose for sustained pressor response. All three doses of ZELAPAR exhibited significantly lower threshold dose ratios than NARDIL. A number of issues complicate the interpretation of the threshold dose ratio comparison. The high (>1) ratio obtained for placebo using the "15-30" definition of threshold dose illustrates the effect on the mean ratio by individual subjects with spurious results. A number of subjects in the placebo group and in all three ZELAPAR groups required a higher dose of tyramine while on treatment than at baseline to elicit the same predefined pressor response (individual subject threshold dose data and threshold dose ratios are not presented here). Given the small number of subjects available for this analysis (i.e. exhibited a threshold response on treatment and at baseline), the impact of a few subjects with inversed threshold dose ratios is substantial. For several of these subjects, the inversed ratios derive from instances where an isolated increase in SBP was identified early during the on-treatment tyramine challenge, even though subsequent higher doses of tyramine might not have produced a threshold response.

The inherent variability of the tyramine threshold dose ratio method of comparing the potency of MAOIs is clearly evident from the results obtained for the placebo group included in this study. A baseline/on-treatment ratio with a value close to "1" would be expected for placebo; however, the placebo group actually demonstrated a threshold ratio of 1.75 for a sustained "15-30" mmHg response, which was higher than that obtained for the ZELAPAR 5 mg (1.30) and ZELAPAR 10 mg (0.95) groups. One subject (No. 027) in the placebo group exhibited a 400 mg threshold dose for the 15-30 mmHg response at baseline and 50 mg during the on-treatment tyramine challenge, representing an apparent 8-fold increase in sensitivity to tyramine. The variability is somewhat reduced when a more sustained pressor response (30-30 mmHg) is used as the criterion for defining the threshold dose, but still contributes to uncertainty in the interpretation of the results. To date, the majority of published studies evaluating the potency of MAOIs on the tyramine response have not included a placebo group that would signal the degree to which a few subjects with inconsistent or spurious results can influence the value of the threshold ratios. The effect of this variability is perpetuated and amplified when the "ratio of ratios" method is applied to evaluate the relative potency of MAOIs on the threshold dose.

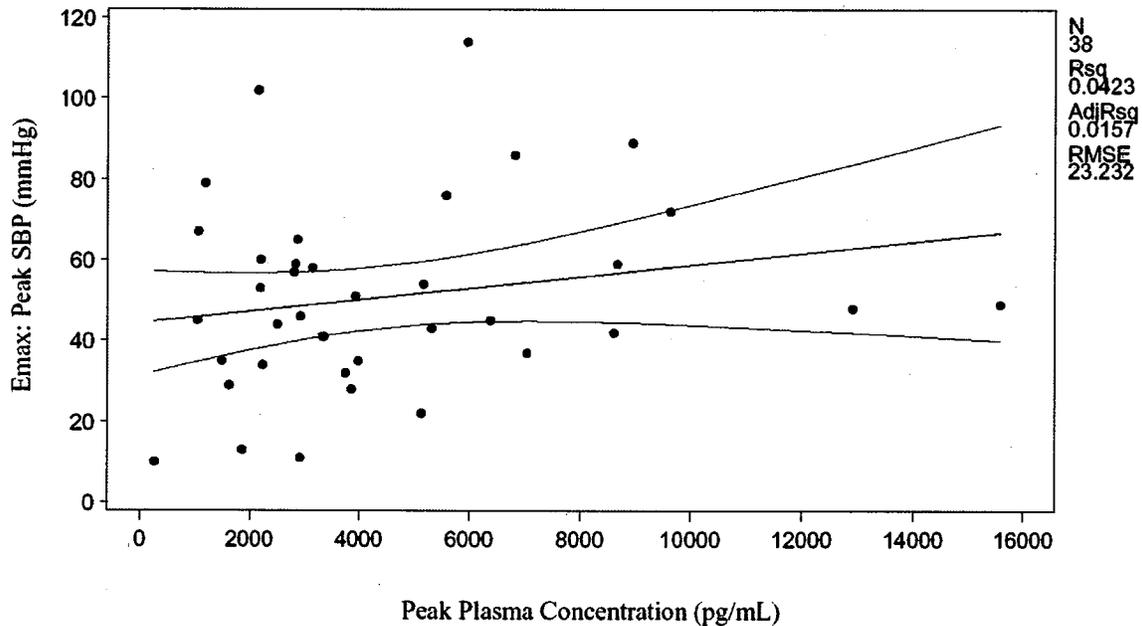
The threshold dose was subject to considerable variability within dose groups as a result of the small number of subjects, which was reflected in the relatively large standard deviations around the mean values and the wide 90% CI surrounding the differences in the mean threshold ratios between treatment groups.

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

A simple linear regression analysis was performed to correlate the peak SBP response (E_{max}) at the highest dose of tyramine on treatment to the observed peak plasma concentrations (C_{max}) and total exposure (AUC) to selegiline at steady-state. Figure 18 displays the plot of SBP E_{max} values versus the corresponding peak plasma concentrations of selegiline for the 38 subjects in

the ITT population that received ZELAPAR. The correlation statistics are provided to the right of the figure.

Figure 18 Correlation of Peak Systolic Blood Pressure Tyramine Response on Treatment to Selegiline Cmax at Steady State (95% CI)

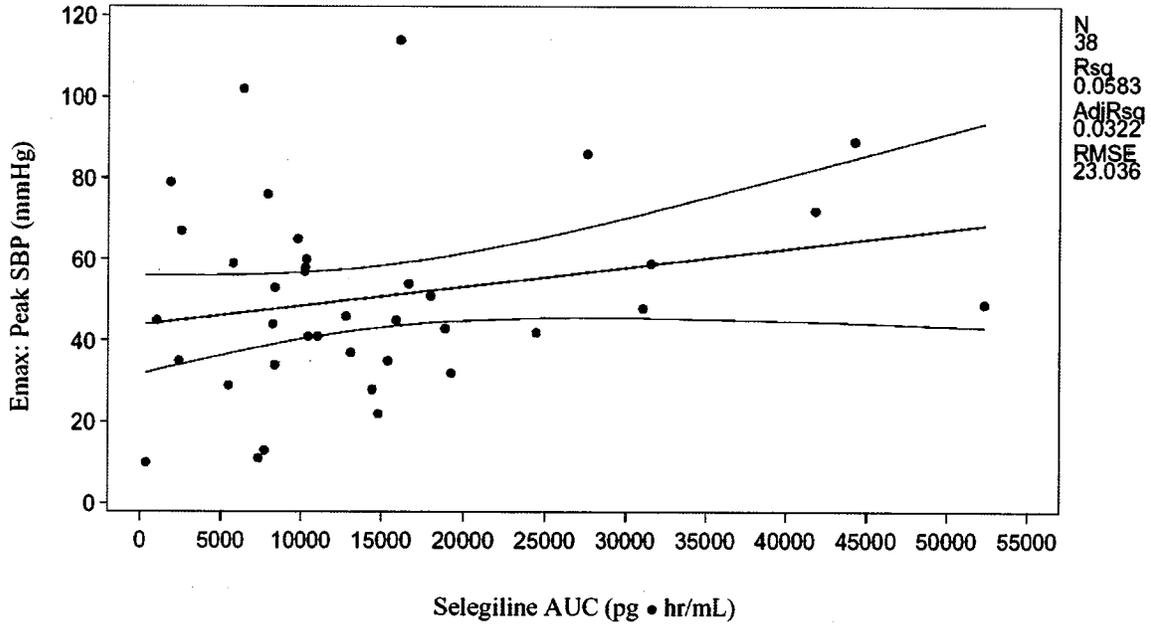


Data Source: Supplemental Figure 2

The slope of the Emax-Cmax regression line was 0.0014, indicating the lack of any relationship between peak plasma levels of selegiline and the peak on-treatment SBP response to tyramine. The plasma concentration and SBP Emax data were highly variable as evidenced by the low r^2 value for the linear regression (0.0423). In order to further explore the possible relationship of Emax to levels of selegiline, a correlation analysis was performed for Emax and total exposure to the drug at steady state (AUC). The results of the analysis and associated regression statistics are displayed in Figure 19. The slope of the Emax-AUC regression line was 0.0005, and the r^2 was low (0.0583), indicating a high degree of variation and the lack of any relationship between total exposure to selegiline and the peak on-treatment SBP response to tyramine.

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Figure 19 Correlation of Peak Systolic Blood Pressure Tyramine Response on Treatment to Selegiline AUC at Steady State (95% CI)



Data Source: Supplemental Figure 2

As was seen for the regression analyses for the combined ZELAPAR dose groups, no meaningful correlation of Emax to selegiline Cmax or AUC at steady state was demonstrated for any of the ZELAPAR dose groups when examined individually.

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Change in Peak and Mean Diastolic Blood Pressure (DBP) and Heart Rate (HR)

The change in the peak DBP response from baseline (pre-randomization) compared to post-treatment was calculated. This calculation was based upon the difference of the change from baseline between the peak DBP response to tyramine (relative to the mean DBP measurements obtained prior to tyramine administration) at the highest dose of tyramine administered while on study treatment (Days 11-16) and the peak DBP response to tyramine at the corresponding dose of tyramine administered during the pre-randomization challenge (Days -5 to -1).

The change in the peak DBP response from baseline (pre-randomization) was 1.3 mmHg, 9.2 mmHg, and 6.3 mmHg for the 2.5 mg, 5 mg, and 10 mg doses of ZELAPAR, respectively. None of the ZELAPAR treatment groups demonstrated a change in peak DBP from baseline that was significantly different from that observed in the placebo group (1.2 mmHg). In contrast, the NARDIL control group demonstrated an 18.4 mmHg change from baseline DBP at the highest tyramine dose, which was significantly different from placebo ($p < 0.001$). The magnitude of the increase in DBP response over baseline was smaller for all three ZELAPAR doses than for NARDIL, and the relative difference attained statistical significance for the 2.5 mg ($p < 0.001$) and 10 mg ($p = 0.0136$) ZELAPAR groups.

The effect of ZELAPAR on the maximum decrease in HR in response to tyramine was similarly analyzed in comparison to placebo and NARDIL. Treatment with ZELAPAR resulted in further peak HR decreases from the baseline response of -4.7 bpm, -6.4 bpm, and -9 bpm for the 2.5 mg, 5 mg, and 10 mg doses of ZELAPAR, respectively. Only the ZELAPAR 10 mg group showed an effect on the HR response that was significantly different ($p = 0.0236$) from the placebo change from baseline response of -1.4 bpm. The effect of NARDIL on the HR response was -5.5 bpm ($p = 0.2098$). Comparison of the ZELAPAR on-treatment change from baseline peak HR response to that of NARDIL did not demonstrate any significant differences.

Comparison of the treatment effect on the mean DBP response at the maximum on-treatment tyramine dose to the corresponding response at baseline did not reveal any significant differences between the active treatments and placebo nor between the 5 mg and 10 mg ZELAPAR treatments and NARDIL. The 5 mg and 10 mg ZELAPAR groups demonstrated increases from baseline in the maximum DBP response of 3.6 mmHg and 3.1 mmHg, respectively, and the placebo and Nardil groups demonstrated increases of 2.1 mmHg and 6.6 mmHg, respectively. The 2.5 mg ZELAPAR group actually showed a small decrease in the mean DBP response (-0.3 mmHg) from baseline that was significantly different from placebo ($p = 0.0107$). No significant differences in the maximum mean HR response from baseline were evident between the active treatment groups and placebo, nor between the ZELAPAR treatment groups and NARDIL.

Statistical/Analytical Issues

Adjustments for Covariates

No adjustments for covariates were made.

Handling of Dropouts or Missing Data

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Subjects that discontinued were not replaced.

If there were insufficient data to compute a response variable for a given subject, that subject was not included in the analysis. The analysis of change from baseline orthostatic hypotension included only those subjects with a baseline measurement at each time point. Similarly, the comparative analyses of on-treatment/baseline tyramine threshold dose ratios included only those subjects with baseline data corresponding to the on-treatment tyramine dose. The analyses of the change from baseline in peak SBP, DBP, and HR at each tyramine dose were conducted both for observed cases only and LOCF for all subjects in the ITT population.

Multicenter Studies

This study was conducted at two sites but no analysis of center effects was performed.

Multiple Comparisons/Multiplicity

No statistical adjustments were made for multiple comparisons.

Examination of Subgroups

No subgroup analyses were performed.

Pharmacodynamic Analysis Summary and Conclusions

The peak SBP response (E_{max}) increased with tyramine dose in a relatively linear fashion both during baseline and steady-state tyramine challenge testing for all 5 treatment groups. The mean (SD) E_{max} change from baseline at the highest tyramine dose during randomized treatment was 10.2 (18.85), 25.1 (23.11), 35.0 (30.68), 44.7 (23.16), and 1.5 (16.28) mmHg for the ZELAPAR 2.5 mg, ZELAPAR 5 mg, ZELAPAR 10 mg, NARDIL 30 mg and placebo treatment groups respectively. There was no clinically or statistically significant difference from placebo on peak SBP for the recommended dose of ZELAPAR (2.5 mg daily). The E_{max} results were statistically significantly higher than placebo in subjects receiving ZELAPAR 5 mg ($p = 0.0113$), ZELAPAR 10 mg ($p < 0.001$), and NARDIL 30 mg ($p < 0.001$). The effect of NARDIL 30 mg on peak SBP was significantly higher than the effect of ZELAPAR 2.5 mg ($p < 0.001$) and ZELAPAR 5 mg ($p = 0.0338$). The effect of the suprathreshold 10 mg dose of ZELAPAR was not significantly different from NARDIL ($p = 0.2872$).

In subjects treated with NARDIL 30 mg, the mean peak change from baseline in SBP was significantly higher than placebo following tyramine doses of 50, 100, 200, and 400 mg. Statistically significant differences from placebo were observed following the 200 and 400 mg tyramine doses in subjects receiving ZELAPAR 5 mg and following the 400 mg tyramine dose in subjects receiving ZELAPAR 10 mg. There were no statistically significant differences from placebo for peak change from baseline in SBP at any tyramine dosage level in subjects receiving ZELAPAR 2.5 mg.

Several analyses examined the relative potency of the three ZELAPAR doses and the active control. While all of these analyses suffered from various shortcomings, all demonstrated that ZELAPAR, at all three dosage levels, was in the range of 2- to 4- fold less potent than NARDIL 30

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mg in potentiation of the tyramine pressor response. Inclusion of a placebo group in this study demonstrated the considerable effect of intra-subject variability on the interpretation TPR as an indicator of the relative potency of MAOIs. Application of the conventional method of computing the tyramine threshold dose ratio resulted in a TPR of 5.57 – 7.00 for NARDIL 30 mg, which was consistent with published TPR values of 4.0 and 10 for NARDIL 30 mg and 45 mg, respectively.

No correlation was demonstrated between the peak SBP tyramine response (E_{max}) and peak plasma levels (C_{max}) of selegiline at steady-state nor between E_{max} and the AUC for selegiline at steady state.

With respect to effect on mean DBP at the maximum on-treatment tyramine dose to the corresponding response at baseline did not reveal any significant differences between the active treatments and placebo nor between the 5 mg and 10 mg ZELAPAR treatments and NARDIL. The 2.5 mg ZELAPAR group actually showed a small decrease in the mean DBP response (-0.3 mmHg) from baseline that was significantly different from placebo. There were no significant differences in the maximum mean HR response from baseline between placebo and ZELAPAR treatment groups nor between ZELAPAR treatment groups and NARDIL. Regardless of the analysis approach utilized, as the primary SBP E_{max} at a defined dose or alternatively, calculation of the threshold dose, or even use of the more traditional TPR ratio analysis method, the results demonstrate that the clinical therapeutic dose of ZELAPAR 2.5 mg is similar to placebo with regard to any potential effect on the tyramine pressor response at steady state. The 5 mg (2x recommended therapeutic) and 10 mg (4x recommended therapeutic) doses of ZELAPAR appear to potentiate the tyramine pressor response; however all doses of ZELAPAR have a lower effect on the response than did 30 mg of NARDIL.

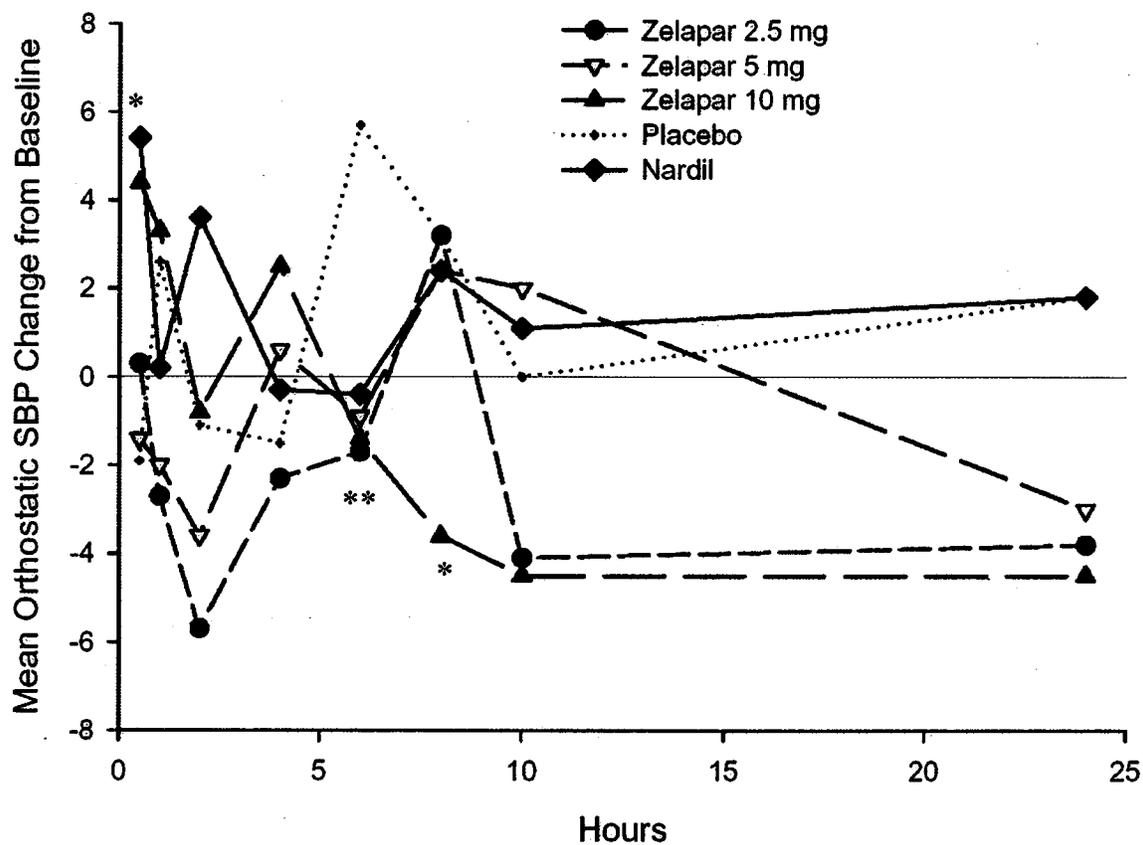
SAFETY EVALUATION

Orthostatic Hypotension

The mean change in orthostatic SBP from baseline is illustrated graphically in Figure 20. The summary of effect of each treatment on orthostatic SBP, DBP, and HR by time is shown in Table 29, Table 30, and Table 31 respectively.

The change in orthostatic SBP on treatment relative to the pre-randomization baseline was variable and no trends were apparent between treatment groups or within treatment groups with respect to time after dosing. The mean change from baseline orthostatic SBP at scheduled time points over the 24-hour post-dose assessment period ranged from -5.7 to 3.2 mmHg for 2.5 mg ZELAPAR, from -3.6 to 2.4 mmHg for 5 mg ZELAPAR, and from -4.5 to 4.4 mmHg for the 10 mg ZELAPAR dose, with no discernable pattern to the values. All three ZELAPAR groups demonstrated a statistically significant difference from placebo in the magnitude of the change from baseline orthostatic SBP at the 6-hour time point; the magnitude of the difference from placebo was -7.4 mmHg ($p = 0.025$), -6.6 mmHg ($p = 0.039$), and -7.1 mmHg ($p = 0.028$) for the 2.5 mg, 5 mg, and 10 mg ZELAPAR dose

Figure 20 Mean Change of from Baseline Orthostatic Systolic Blood Pressure



* Significantly different from placebo (<0.05)
** All active treatments significantly different from placebo (<0.05)
Data Source: Supplemental Table 13.1, Appendix 16.2, Listing 18

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Table 29 Summary of Effect of Treatment on Orthostatic Systolic Blood Pressure Post-Treatment by Time

Parameter: Change in Systolic Blood Pressure (Standing - Supine)

| Time Post Dose | Zelapar 2.5 mg (N=12) | | | Zelapar 5 mg (N=13) | | | Zelapar 10 mg (N=13) | | |
|--------------------------------|-----------------------|--------------|--------------|---------------------|--------------|--------------|----------------------|--------------|--------------|
| | Baseline | On Treatment | Change | Baseline | On Treatment | Change | Baseline | On Treatment | Change |
| Descriptive Statistics | | | | | | | | | |
| Mean (SD) | | | | | | | | | |
| 0.5 Hr | 5.7 (8.47) | 5.9 (5.92) | 0.3 (10.58) | 6.6 (5.16) | 5.2 (7.50) | -1.4 (6.24) | 1.7 (7.62) | 6.1 (5.94) | 4.4 (9.24) |
| 1.0 Hr | 2.9 (5.53) | 0.3 (5.88) | -2.7 (8.85) | 4.5 (5.94) | 2.5 (5.39) | -2.0 (8.23) | 2.4 (8.28) | 5.7 (12.47) | 3.3 (12.18) |
| 2.0 Hr | 5.4 (4.34) | -0.3 (10.37) | -5.7 (10.38) | 7.4 (7.01) | 3.8 (8.17) | -3.6 (5.42) | 3.4 (8.57) | 2.6 (8.83) | -0.8 (10.71) |
| 4.0 Hr | 3.2 (7.21) | 0.9 (5.84) | -2.3 (7.39) | 6.1 (6.06) | 6.7 (6.76) | 0.6 (8.03) | 3.6 (7.91) | 6.2 (6.77) | 2.5 (10.96) |
| 6.0 Hr | 4.8 (7.15) | 3.1 (6.43) | -1.7 (9.87) | 6.2 (5.30) | 5.2 (6.62) | -0.9 (7.65) | 2.4 (5.50) | 1.0 (6.01) | -1.4 (7.89) |
| 8.0 Hr | 2.8 (7.79) | 5.9 (6.32) | 3.2 (8.19) | 5.5 (6.35) | 7.8 (10.37) | 2.4 (8.70) | 1.8 (9.20) | -1.8 (8.88) | -3.6 (11.67) |
| 10.0 Hr | 6.1 (8.68) | 2.0 (7.94) | -4.1 (13.88) | 1.5 (9.19) | 3.5 (6.21) | 2.0 (12.95) | 2.8 (9.44) | -1.7 (8.09) | -4.5 (11.36) |
| 24.0 Hr | 3.9 (5.79) | 0.2 (8.43) | -3.8 (7.81) | 6.7 (6.02) | 3.7 (8.64) | -3.0 (8.52) | 5.2 (11.92) | 0.7 (7.58) | -4.5 (13.13) |
| Difference from Placebo | | | | | | | | | |
| LSMean (p-value) | | | | | | | | | |
| 0.5 Hr | - | - | 2.2 (0.536) | - | - | 0.5 (0.875) | - | - | 6.3 (0.070) |
| 1.0 Hr | - | - | -5.3 (0.147) | - | - | -4.6 (0.195) | - | - | 0.7 (0.845) |
| 2.0 Hr | - | - | -4.6 (0.193) | - | - | -2.5 (0.461) | - | - | 0.3 (0.929) |
| 4.0 Hr | - | - | -0.8 (0.827) | - | - | 2.1 (0.557) | - | - | 4.0 (0.260) |
| 6.0 Hr | - | - | -7.4 (0.025) | - | - | -6.6 (0.039) | - | - | -7.1 (0.028) |
| 8.0 Hr | - | - | -0.1 (0.985) | - | - | -0.8 (0.805) | - | - | -6.8 (0.049) |
| 10.0 Hr | - | - | -4.1 (0.362) | - | - | 2.0 (0.648) | - | - | -4.5 (0.310) |
| 24.0 Hr | - | - | -5.5 (0.128) | - | - | -4.8 (0.179) | - | - | -6.2 (0.081) |

| Time Post Dose | Placebo (N=13) | | | Nardil 30 mg (N=13) | | |
|--------------------------------|----------------|--------------|--------------|---------------------|--------------|--------------|
| | Baseline | On Treatment | Change | Baseline | On Treatment | Change |
| Descriptive Statistics | | | | | | |
| Mean (SD) | | | | | | |
| 0.5 Hr | 6.2 (9.37) | 4.2 (9.67) | -1.9 (8.60) | -0.8 (6.27) | 4.6 (6.67) | 5.4 (8.50) |
| 1.0 Hr | 2.0 (5.49) | 4.6 (9.37) | 2.6 (7.33) | 1.7 (7.31) | 1.8 (6.97) | 0.2 (7.44) |
| 2.0 Hr | 8.2 (7.96) | 7.2 (8.54) | -1.1 (10.06) | 0.2 (5.95) | 3.8 (6.28) | 3.6 (5.39) |
| 4.0 Hr | 9.1 (8.04) | 7.6 (5.75) | -1.5 (9.66) | 4.5 (5.68) | 4.2 (7.15) | -0.3 (8.19) |
| 6.0 Hr | 3.5 (7.55) | 9.2 (8.30) | 5.7 (7.74) | 2.5 (5.55) | 2.1 (6.54) | -0.4 (6.63) |
| 8.0 Hr | 4.2 (6.77) | 7.4 (6.67) | 3.2 (7.57) | 1.6 (6.58) | 5.0 (6.32) | 2.4 (6.14) |
| 10.0 Hr | 1.9 (5.22) | 1.9 (9.54) | 0.0 (5.80) | 2.1 (6.56) | 4.2 (8.38) | 1.1 (9.84) |
| 24.0 Hr | 3.9 (9.88) | 5.7 (8.64) | 1.8 (6.61) | 1.7 (8.07) | 2.8 (6.81) | 1.8 (6.76) |
| Difference from Placebo | | | | | | |
| LSMean (p-value) | | | | | | |
| 0.5 Hr | - | - | - | - | - | 7.3 (0.037) |
| 1.0 Hr | - | - | - | - | - | -2.5 (0.488) |
| 2.0 Hr | - | - | - | - | - | 4.7 (0.175) |
| 4.0 Hr | - | - | - | - | - | 1.2 (0.744) |
| 6.0 Hr | - | - | - | - | - | -6.1 (0.057) |
| 8.0 Hr | - | - | - | - | - | -0.8 (0.816) |
| 10.0 Hr | - | - | - | - | - | 1.1 (0.808) |
| 24.0 Hr | - | - | - | - | - | -0.0 (0.996) |

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Table 30 Summary of Effect of Treatment on Orthostatic Diastolic Blood Pressure Post-Treatment by Time

Parameter: Change in Diastolic Blood Pressure (Standing - Supine)

| Time Post Dose | Zelapar 2.5 mg (N=12) | | | Zelapar 5 mg (N=13) | | | Zelapar 10 mg (N=13) | | |
|--------------------------------|-----------------------|--------------|--------------|---------------------|--------------|--------------|----------------------|--------------|--------------|
| | Baseline | On Treatment | Change | Baseline | On Treatment | Change | Baseline | On Treatment | Change |
| Descriptive Statistics | | | | | | | | | |
| Mean (SD) | | | | | | | | | |
| 0.5 Hr | 7.9 (6.40) | 7.3 (4.70) | -0.6 (7.75) | 9.4 (6.63) | 5.5 (5.24) | -3.9 (5.47) | 6.2 (2.74) | 5.8 (5.00) | -0.5 (4.81) |
| 1.0 Hr | 7.8 (4.33) | 2.7 (3.45) | -5.1 (5.28) | 6.8 (5.18) | 7.6 (5.64) | 0.8 (5.97) | 6.8 (4.81) | 5.4 (6.91) | -1.5 (7.11) |
| 2.0 Hr | 7.3 (4.59) | 2.5 (6.37) | -4.8 (7.24) | 9.2 (6.88) | 6.0 (5.31) | -3.2 (7.95) | 6.5 (5.46) | 6.3 (6.05) | -0.2 (7.47) |
| 4.0 Hr | 7.3 (3.73) | 5.8 (3.59) | -1.5 (3.00) | 7.5 (3.13) | 5.1 (5.07) | -2.4 (4.70) | 7.7 (4.42) | 5.9 (9.53) | -1.8 (10.21) |
| 6.0 Hr | 7.6 (3.96) | 5.7 (5.35) | -1.9 (4.64) | 7.9 (6.69) | 8.1 (3.97) | 0.2 (6.79) | 5.2 (4.87) | 6.2 (5.67) | 0.9 (6.26) |
| 8.0 Hr | 7.0 (6.06) | 4.6 (4.81) | -2.4 (6.49) | 6.6 (5.41) | 7.3 (6.34) | 0.7 (5.42) | 6.5 (4.89) | 3.5 (4.93) | -3.0 (7.11) |
| 10.0 Hr | 7.2 (4.88) | 5.3 (4.83) | -1.8 (7.55) | 5.7 (5.50) | 7.8 (4.73) | 2.1 (6.36) | 5.7 (5.38) | 2.9 (6.33) | -2.8 (8.77) |
| 24.0 Hr | 6.6 (5.37) | 3.8 (3.44) | -2.8 (6.12) | 7.6 (4.81) | 5.0 (7.54) | -2.6 (9.12) | 5.7 (7.45) | 4.6 (3.57) | -1.1 (8.80) |
| Difference from Placebo | | | | | | | | | |
| LSMean (p-value) | | | | | | | | | |
| 0.5 Hr | - | - | 2.6 (0.274) | - | - | -0.8 (0.737) | - | - | 2.7 (0.243) |
| 1.0 Hr | - | - | -4.8 (0.063) | - | - | 1.1 (0.665) | - | - | -1.2 (0.642) |
| 2.0 Hr | - | - | -3.1 (0.342) | - | - | -1.5 (0.642) | - | - | 1.5 (0.642) |
| 4.0 Hr | - | - | 1.8 (0.521) | - | - | 0.9 (0.738) | - | - | 1.5 (0.577) |
| 6.0 Hr | - | - | -2.5 (0.306) | - | - | -0.4 (0.869) | - | - | 0.4 (0.869) |
| 8.0 Hr | - | - | -3.3 (0.202) | - | - | -0.2 (0.951) | - | - | -3.8 (0.126) |
| 10.0 Hr | - | - | -2.5 (0.369) | - | - | 1.4 (0.615) | - | - | -3.5 (0.211) |
| 24.0 Hr | - | - | 1.2 (0.702) | - | - | 1.4 (0.643) | - | - | 2.9 (0.329) |

| Time Post Dose | Placebo (N=13) | | | Nardil 30 mg (N=13) | | |
|--------------------------------|----------------|--------------|--------------|---------------------|--------------|--------------|
| | Baseline | On Treatment | Change | Baseline | On Treatment | Change |
| Descriptive Statistics | | | | | | |
| Mean (SD) | | | | | | |
| 0.5 Hr | 8.8 (5.42) | 5.6 (7.51) | -3.2 (4.16) | 4.8 (4.59) | 6.5 (5.59) | 1.7 (6.40) |
| 1.0 Hr | 6.6 (4.61) | 6.3 (6.01) | -0.3 (6.90) | 6.7 (4.99) | 3.5 (4.05) | -3.2 (5.97) |
| 2.0 Hr | 9.0 (4.43) | 7.3 (8.34) | -1.7 (8.32) | 5.2 (6.14) | 6.2 (5.27) | 0.9 (8.70) |
| 4.0 Hr | 10.2 (4.91) | 6.8 (6.91) | -3.3 (6.05) | 6.5 (6.41) | 6.1 (6.79) | -0.5 (8.33) |
| 6.0 Hr | 7.2 (5.77) | 7.7 (5.85) | 0.5 (5.30) | 3.5 (4.39) | 6.8 (3.63) | 3.2 (6.34) |
| 8.0 Hr | 7.5 (6.04) | 8.3 (4.57) | 0.8 (5.91) | 3.6 (5.79) | 5.9 (4.09) | 1.7 (6.54) |
| 10.0 Hr | 6.2 (6.80) | 6.9 (6.74) | 0.7 (6.68) | 3.7 (4.92) | 5.6 (3.88) | 1.6 (4.76) |
| 24.0 Hr | 10.2 (7.20) | 6.2 (4.96) | -4.0 (5.86) | 4.2 (3.51) | 4.3 (5.76) | 0.1 (7.23) |
| Difference from Placebo | | | | | | |
| LSMean (p-value) | | | | | | |
| 0.5 Hr | - | - | - | - | - | 4.8 (0.038) |
| 1.0 Hr | - | - | - | - | - | -2.9 (0.242) |
| 2.0 Hr | - | - | - | - | - | 2.6 (0.406) |
| 4.0 Hr | - | - | - | - | - | 2.8 (0.304) |
| 6.0 Hr | - | - | - | - | - | 2.7 (0.252) |
| 8.0 Hr | - | - | - | - | - | 0.8 (0.747) |
| 10.0 Hr | - | - | - | - | - | 0.9 (0.751) |
| 24.0 Hr | - | - | - | - | - | 4.1 (0.183) |

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Table 31 Summary of Effect of Treatment on Orthostatic Pulse Post-Treatment by Time

Parameter: Change in Heart Rate (Standing - Supine)

| Time Post Dose | Zelapar 2.5 mg (N=12) | | | Zelapar 5 mg (N=13) | | | Zelapar 10 mg (N=13) | | |
|---|-----------------------|--------------|--------------|---------------------|--------------|--------------|----------------------|--------------|--------------|
| | Baseline | On Treatment | Change | Baseline | On Treatment | Change | Baseline | On Treatment | Change |
| Descriptive Statistics | | | | | | | | | |
| Mean (SD) | | | | | | | | | |
| 0.5 Hr | 5.9 (8.76) | 5.3 (6.25) | -0.7 (9.09) | 7.6 (12.53) | 9.0 (8.05) | 1.4 (9.40) | 11.8 (9.14) | 5.5 (8.10) | -6.3 (11.50) |
| 1.0 Hr | 9.1 (7.51) | 6.3 (4.96) | -2.8 (7.32) | 9.0 (10.06) | 12.0 (12.19) | 3.0 (15.53) | 14.7 (8.44) | 9.8 (7.68) | -4.8 (9.22) |
| 2.0 Hr | 13.1 (10.28) | 7.1 (6.43) | -6.0 (10.84) | 8.4 (6.76) | 13.0 (11.42) | 4.6 (9.75) | 16.0 (10.42) | 12.1 (5.98) | -3.9 (8.39) |
| 4.0 Hr | 11.8 (13.45) | 12.3 (11.08) | 0.4 (14.55) | 11.2 (7.05) | 15.3 (11.13) | 4.1 (7.80) | 15.6 (9.00) | 15.2 (9.08) | -0.4 (12.24) |
| 6.0 Hr | 13.5 (11.88) | 12.3 (9.46) | -1.2 (9.70) | 8.8 (9.91) | 16.8 (10.86) | 8.1 (10.41) | 15.5 (7.33) | 13.8 (5.95) | -1.8 (7.14) |
| 8.0 Hr | 7.6 (7.28) | 7.2 (6.70) | -0.4 (10.83) | 11.8 (10.35) | 6.0 (6.27) | -5.8 (10.07) | 8.6 (7.35) | 8.5 (6.27) | -0.1 (7.41) |
| 10.0 Hr | 7.3 (8.01) | 7.4 (4.06) | 0.2 (8.41) | 9.5 (9.77) | 8.8 (4.83) | -0.8 (10.80) | 9.8 (9.34) | 8.2 (8.86) | -1.7 (12.07) |
| 24.0 Hr | 6.8 (10.13) | 9.5 (5.62) | 2.8 (11.25) | 9.0 (8.65) | 11.0 (10.82) | 3.7 (8.61) | 10.9 (6.46) | 9.4 (7.04) | -1.5 (5.52) |
| Difference from Placebo LSMean (p-value) | | | | | | | | | |
| 0.5 Hr | - | - | 0.9 (0.792) | - | - | 3.0 (0.396) | - | - | -4.7 (0.186) |
| 1.0 Hr | - | - | 0.0 (0.998) | - | - | 5.8 (0.204) | - | - | -2.0 (0.662) |
| 2.0 Hr | - | - | -2.9 (0.457) | - | - | 7.7 (0.049) | - | - | -0.8 (0.826) |
| 4.0 Hr | - | - | 3.7 (0.453) | - | - | 7.4 (0.132) | - | - | 2.9 (0.548) |
| 6.0 Hr | - | - | -1.6 (0.664) | - | - | 7.6 (0.041) | - | - | -2.2 (0.544) |
| 8.0 Hr | - | - | -0.2 (0.959) | - | - | -5.5 (0.118) | - | - | 0.2 (0.965) |
| 10.0 Hr | - | - | 1.9 (0.615) | - | - | 1.0 (0.791) | - | - | 0.1 (0.984) |
| 24.0 Hr | - | - | 3.4 (0.358) | - | - | 4.3 (0.243) | - | - | -0.9 (0.796) |

| Time Post Dose | Placebo (N=13) | | | Nardil 30 mg (N=13) | | |
|---|----------------|--------------|--------------|---------------------|--------------|--------------|
| | Baseline | On Treatment | Change | Baseline | On Treatment | Change |
| Descriptive Statistics | | | | | | |
| Mean (SD) | | | | | | |
| 0.5 Hr | 11.2 (10.18) | 9.6 (8.50) | -1.6 (7.57) | 9.6 (5.38) | 7.7 (3.86) | -1.9 (6.34) |
| 1.0 Hr | 11.8 (7.61) | 8.9 (5.72) | -2.8 (8.91) | 13.5 (10.49) | 7.0 (5.66) | -6.5 (14.44) |
| 2.0 Hr | 11.5 (9.60) | 8.4 (9.42) | -3.1 (7.87) | 10.8 (9.65) | 10.4 (4.93) | -0.5 (11.50) |
| 4.0 Hr | 10.2 (6.61) | 6.8 (7.55) | -3.3 (10.10) | 13.7 (12.68) | 6.5 (7.17) | -7.2 (15.47) |
| 6.0 Hr | 11.4 (13.78) | 11.8 (9.38) | 0.5 (11.03) | 11.4 (8.54) | 9.8 (8.72) | -1.6 (7.68) |
| 8.0 Hr | 10.2 (13.27) | 9.9 (10.39) | -0.2 (7.11) | 11.8 (7.20) | 11.1 (5.94) | -1.3 (8.66) |
| 10.0 Hr | 9.6 (7.79) | 7.8 (10.47) | -1.8 (8.32) | 10.8 (6.84) | 11.2 (5.34) | 0.1 (7.12) |
| 24.0 Hr | 9.8 (8.83) | 9.2 (7.13) | -0.6 (11.33) | 6.8 (4.94) | 9.1 (6.49) | 1.6 (7.27) |
| Difference from Placebo LSMean (p-value) | | | | | | |
| 0.5 Hr | - | - | - | - | - | -0.3 (0.930) |
| 1.0 Hr | - | - | - | - | - | -3.6 (0.431) |
| 2.0 Hr | - | - | - | - | - | 2.6 (0.497) |
| 4.0 Hr | - | - | - | - | - | -3.8 (0.429) |
| 6.0 Hr | - | - | - | - | - | -2.1 (0.572) |
| 8.0 Hr | - | - | - | - | - | -1.1 (0.758) |
| 10.0 Hr | - | - | - | - | - | 1.9 (0.631) |
| 24.0 Hr | - | - | - | - | - | 2.2 (0.547) |

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groups, respectively. This apparent significant difference from placebo is likely a reflection of the comparatively large positive change from baseline (5.7 mmHg) in the placebo group at the 6-hour time point relative to the values for the other time points in the placebo group. The 10 mg ZELAPAR group also demonstrated a nominally significant difference of -6.8 mmHg ($p = 0.049$) from placebo at 8 hours. No significant differences in orthostatic SBP from placebo were evident for NARDIL at any time point.

As with orthostatic SBP, the orthostatic DBP and HR measurements were also variable at baseline and on-treatment, which translated into considerable variability in the change from baseline at each time point. No apparent trends in orthostatic DBP or HR were evident as a result of treatment with ZELAPAR.

The proportion of subjects exhibiting clinically significant on-treatment orthostatic hypotension, defined as a decrease in SBP ≥ 20 mmHg or DBP ≥ 10 mmHg from pretreatment measurements was compared to placebo. The number of subjects with clinically significant hypotension (i.e. decrease in SBP ≥ 20 or DBP ≥ 10 mm Hg) on Day 9 was highly variable over the series of time points within each treatment group and is shown in Table 32.

Table 32 Proportion of ITT Subjects (N=64) Exhibiting Clinical Significant Orthostatic Hypotension

| Time Post Dose (hours) | ZELAPAR 2.5 mg N = 12 n (%) | ZELAPAR 5 mg N = 13 n (%) | ZELAPAR 10 mg N = 13 n (%) | Placebo N = 13 n (%) | NARDIL 30 mg N = 13 n (%) |
|------------------------|-----------------------------------|---------------------------------|----------------------------------|----------------------------|---------------------------------|
| 0.5 | 1 (8.3%) | 2 (15.3%) | 0 | 1 (7.6%) | 1 (7.6%) |
| 1 | 3 (25.0%) | 1 (7.6%) | 2 (15.3%) | 1 (7.6%) | 1 (7.6%) |
| 2 | 4 (33.3%) | 2 (15.3%) | 2 (15.3%) | 2 (15.3%) | 0 |
| 4 | 0 | 1 (7.6%) | 3 (23.0%) | 3 (23.0%) | 3 (23.0%) |
| 6 | 1 (8.3%) | 1 (7.6%) | 1 (7.6%) | 0 | 0 |
| 8 | 2 (16.6%) | 0 | 3 (23.0%) | 0 | 0 |
| 10 | 3 (25.0%) | 1 (7.6%) | 2 (15.3%) | 1 (7.6%) | 0 |
| 24 | 2 (16.6%) | 2 (15.3) | 2 (15.3%) | 2 (15.3%) | 0 |

SD = Standard Deviation

Note: Clinically significant orthostatic hypotension is defined as a decrease in SBP ≥ 20 mmHg or DBP ≥ 10 mmHg from baseline.

Data Source: Supplemental Table 14.1; Appendix 16.2, Listing 18

Over one half (36/64) of the subjects experienced orthostatic hypotension at some time point on Day 9, and the majority of these met the criteria for orthostatic hypotension by exhibiting a single observation of a drop in DBP ≥ 10 mmHg. No trends in the incidence of orthostatic hypotension were evident with respect to dose of ZELAPAR or time after administration of study treatment. No significant differences from placebo were demonstrated for any active treatment at any time point.

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Clinical Laboratory Evaluation, Adverse Events, Discontinuations from Study

I did not present clinical laboratory evaluations, adverse events, discontinuations from study because I did not find them to be remarkable and worthy of presentation considering what is known from the safety profile of my previous review.

Vital Signs, Physical Findings, and Other Observations Related to Safety Vital Signs

Specific measurements of SBP, DBP, and HR were obtained at baseline and on-treatment as variables for the primary and secondary analyses of the pharmacodynamic effects of ZELAPAR in this study. A small trend toward increasing mean pulse rate from baseline was noted across all treatment groups beginning around Day 13 or 14. Over the period extending from Day 13 through Day 16, change in mean pulse rate from baseline ranged from 4.1 – 10.7 bpm for the 2.5 mg ZELAPAR group, 0.6 – 4.1 bpm for the 5 mg ZELAPAR group, 0.9 – 2.0 bpm for the 10 mg ZELAPAR group, 0 - 3.8 bpm for placebo, and 1.8 to 3.9 bpm for the NARDIL group. A speculative explanation for this phenomenon might be apprehension on the part of the subjects toward an intensification of the symptoms of the tyramine pressor response beyond those already experienced at lower doses.

All of the active treatment groups displayed an increase in mean SBP at discharge relative to baseline. An increase of 8.1 mmHg, 2.2 mmHg, and 6.2 mmHg was observed for the 2.5 mg, 5 mg, and 10 mg ZELAPAR groups, respectively, and 1.8 mmHg and 5.4 mmHg for placebo and NARDIL, respectively. Whether this increase in SBP at discharge represents a real effect is unclear, since with the exception of the 2.5 mg ZELAPAR (7.4 mmHg) and NARDIL (4.4 mmHg) groups on Day 16, notable increases in the routine (pre-study treatment) SBP from baseline were not observed for any groups during the on-treatment tyramine challenge. No mean changes from baseline were observed for respiration rate or temperature for any treatment group.

Routine vital sign measurements for individual subjects showed considerable inter- and intrasubject variability, with sporadic abnormalities in SBP, DBP, and HR. No trends in the individual abnormalities were evident with respect to treatment or study day.

Sponsor's Safety Conclusions

Safety was assessed in all subjects who received at least one dose of randomized study medication (N = 65). All of the most frequently reported treatment-related AEs (headache, palpitations, nausea, and dizziness) occurred during the on-treatment tyramine challenge and are consistent with the signs and symptoms of the well characterized tyramine pressor response. In general, there were no distinctions between treatment groups overall, although there were some reported differences.

No clinically meaningful changes were observed for laboratory test results or routine vital signs. Mean increases from baseline in cholesterol and triglycerides were observed upon discharge. The significance of the change in serum lipids is unclear since the changes were seen in all treatment groups, including placebo, and the mean baseline values were relatively high, which was possibly related to the demographic of the subject population (i.e. older adult

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and predominantly Hispanic). Samples for the discharge clinical laboratory tests were obtained for the majority of subjects following a 12-hour fast as specified in the protocol. Alterations in diet as a result of the standard meals provided during confinement to the clinical research facility may possibly have contributed to the observed changes in serum lipid levels.

Neither ZELAPAR (2.5 mg, 5 mg, 10 mg) nor NARDIL demonstrated any ability to induce orthostatic hypotension in this study compared to placebo.

Sponsor's Discussion and Overall Conclusions

This study was designed as a definitive trial to evaluate the effect of ZELAPAR (ZYDIS selegiline HCl) on the tyramine pressor response. Previous studies have yielded variable and conflicting results with regard to the interaction of ZELAPAR with tyramine. Studies conducted to date with ZELAPAR and other MAOIs have employed a similar design that compares the relative potency of the investigational agents in the degree to which they decrease the dose of tyramine necessary to elicit a predefined pressor response. This has been accomplished by determining the ratio of the on-treatment tyramine threshold dose to the baseline tyramine threshold dose; where the threshold dose is the lowest dose associated with a sustained (for 10 – 15 minutes) increase in SBP \geq 30 mmHg. This approach, like any classical relative potency comparison, inherently assumes that the comparison of doses is being conducted at a fixed level of response. However, the increase in SBP at "threshold" doses is often quite dissimilar between groups. In addition, since this trial employs a placebo control group it is not necessary to compare ratios of doses; rather, this design allows for a straightforward comparison of change from baseline in tyramine pressor response between treatment groups.

Examination of mean peak SBP (E_{max}) across the tyramine doses at baseline indicated that tyramine produced a clear dose-dependent pressor response in the absence of any MAOI influence. A similar pattern of increasing peak SBP is observed during randomized treatment, but unlike the baseline results, there is a separation in the level of SBP response between the active treatment groups; where the response to NARDIL 30 mg > ZELAPAR 10 mg > ZELAPAR 5 mg > ZELAPAR 2.5 mg.

This first primary analysis of effect in this study compared the effect of ZELAPAR and control treatments on the maximum pressor response at the highest dose of tyramine administered (E_{max}). The mean (SD) E_{max} change from baseline at the highest tyramine dose during randomized treatment was 10.2 (18.85), 25.1 (23.11), 35.0 (30.68), 44.7 (23.16), and 1.5 (16.28) mmHg for the ZELAPAR 2.5 mg, ZELAPAR 5 mg, ZELAPAR 10 mg, NARDIL 30 mg and placebo treatment groups respectively. There was no clinically or statistically significant difference from placebo for peak SBP at the recommended dose of ZELAPAR (2.5 mg daily). The E_{max} results were statistically significantly higher than placebo in subjects receiving ZELAPAR 5 mg ($p = 0.0113$), ZELAPAR 10 mg ($p < 0.001$), and NARDIL 30 mg ($p < 0.001$). The effect of NARDIL 30 mg on peak SBP was significantly higher than the effect of ZELAPAR 2.5 mg ($p < 0.001$) and ZELAPAR 5 mg ($p = 0.0338$). The effect of the suprathreshold 10 mg dose of ZELAPAR was not

significantly different from NARDIL ($p = 0.2872$). This analysis represents a robust assessment of whether any interaction exists between ZELAPAR and placebo, which doses produced a significant interaction, and how the level of effect associated with ZELAPAR compares to the active control.

The conclusions from the primary Emax analysis were supported by the results from the assessment of Emax at each dose of tyramine. In subjects treated with NARDIL 30 mg, the mean peak change from baseline in SBP was significantly higher than placebo following tyramine doses of 50, 100, 200, and 400 mg. Statistically significant differences from placebo were observed following the 200 and 400 mg tyramine doses in subjects receiving ZELAPAR 5 mg and following the 400 mg tyramine dose in subjects receiving ZELAPAR 10 mg. There were no statistically significant differences from placebo for peak change from baseline in SBP at any tyramine dosage level in subjects receiving ZELAPAR 2.5 mg. The second primary analysis, the evaluation of tyramine threshold dose, represented a comparison of the relative potency of ZELAPAR and NARDIL on a defined pharmacodynamic endpoint, rather than a definitive analysis of the presence of an effect relative to a positive control. None of the ZELAPAR doses were shown to be different from placebo in this analysis, and all showed significantly lower potency than NARDIL; however, interpretation of these results should take into consideration a number of potentially confounding factors. In contrast to the dose response evident in the analysis of SBP Emax, the analysis of the threshold dose ratios (TPR or TSF) for the 15-30 mmHg response appeared to show an inverse relationship between ZELAPAR dose and potentiation of the tyramine response. These inconsistent results reflect the considerable variability in identification of the threshold dose for individual subjects, and the impact of a few subjects with spurious results on the mean values obtained for a small sample population. A number of subjects exhibited an inverse threshold dose ratio suggesting an inhibitory effect of the treatment on the tyramine pressor response. This obviously invalid conclusion was actually an artifact resulting in part from isolated elevations in SBP early in the series of tyramine challenges at baseline, as well as difficulty in the ability to discriminate a defined threshold dose along a discontinuous scale. For example, a tyramine threshold dose of 400 mg would be identified for a subject exhibiting an initial 30 mmHg response (eg, Subject No 025) and a subject exhibiting a 62 mmHg response (e.g. Subject No. 015), when in fact a considerable difference exists between the two threshold SBP responses. The sample size available for the comparison of tyramine threshold ratios was small as a result of a number of subjects that did not reach a threshold response during the baseline tyramine challenge. Although the threshold dose may have eventually been reached if the tyramine doses had been escalated beyond 400 mg, safety considerations precluded increasing the dose in the study population of older adults. Pharmacodynamic modeling of the threshold dose might have increased the resolution of the threshold dose, allowing for a more precise comparison of potency; however, insufficient data points (the dose of tyramine was not pushed high enough to achieve a true Emax) and individual variability did not allow the data to be fit to a meaningful model. In the classical design, a threshold dose would require an observation of a sustained (10-15 minute) increase in SBP ≥ 30 mmHg. Comparison of threshold doses using a similar definition (2 consecutive measurements taken 10 minutes apart showing an increase in SBP ≥ 30 mmHg) resulted in a relative potency estimate that was consistent with the observed effect on SBP in the primary analysis. However, this analysis is

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limited by the fact that only a small number of subjects in each treatment group achieved the threshold response criteria. More frequent monitoring of blood pressure and pushing the tyramine dose in small increments to higher dosage levels would also have improved the estimate of threshold doses.

No correlation was demonstrated between the peak SBP tyramine response (E_{max}) and peak plasma levels (C_{max}) of selegiline at steady state nor between E_{max} and the AUC for selegiline at steady state.

With respect to effect on mean DBP at the maximum on-treatment tyramine dose to the corresponding response at baseline did not reveal any significant differences between the active treatments and placebo nor between the 5 mg and 10 mg ZELAPAR treatments and NARDIL. The 2.5 mg ZELAPAR group actually showed a small decrease in the mean DBP response (-0.3 mmHg) from baseline that was significantly different from placebo. There were no significant differences in the maximum mean HR response from baseline between placebo and ZELAPAR treatment groups nor between ZELAPAR treatment groups and NARDIL. Nearly all of the AEs occurred during the on-treatment tyramine challenge and were characteristic of the known signs and symptoms of the tyramine pressor effect (eg, headache, palpitations, nausea, dizziness, and anxiety). No signals of any new safety concerns with ZELAPAR were evident from the AEs, laboratory test results, or routine vital signs. The potential for ZELAPAR to induce orthostatic hypotension was studied while subjects were receiving steady-state administration. There was no evidence that ZELAPAR was associated with clinically relevant orthostasis at any dosage level.

In conclusion, this study was a robust evaluation of the potential for ZELAPAR to interact with tyramine. The results demonstrate that the clinically recommended dose of ZELAPAR 2.5 mg is similar to placebo with regard to its effect on the tyramine pressor response at steady state. The active control drug (NARDIL 30 mg) demonstrated a clear positive effect on tyramine pressor response that was comparable to the published results, and this effect was substantially higher than that observed with the clinically recommended 2.5 mg ZELAPAR dose. ZELAPAR, at an intermediate dose of 5 mg and at a suprathreshold dose of 10 mg daily, was shown to enhance the tyramine pressor effect, but the level of effect observed following the 5 mg dose was clinically and statistically significantly lower than that observed with NARDIL 30 mg.

Reviewer Comments

- Overall, I agree with the sponsor's major interpretations and conclusions drawn from this study.
 - Treatment with ZS 2.5 mg daily is not associated with an increase in tyramine sensitivity for increased blood pressure responses.
 - Although treatment with "high" doses of ZS (5 and 10 mg daily) is dose-dependently associated with increased tyramine sensitivity for increased blood

pressure responses, this increased sensitivity is of limited clinical significance and the risk for these higher doses appears to be less than that associated with treatment with a non-selective MAO inhibitor, phenelzine (30 mg daily).

- This study supports the safety of the approval of treatment with ZS 2.5 mg daily with respect to risk of tyramine-induced hypertensive “cheese” reaction.

There are several other noteworthy comments.

- There are some remarkable positive and negative aspects related to this study. The sponsor followed DNDP recommendations and conducted a randomized, double-blind, placebo-controlled study with a positive control that yielded data capable of addressing the main question about whether there is increased tyramine sensitivity associated with ZS treatment. The placebo group served as a highly desired reference for showing responses unrelated to drug treatment and the positive control group treated with phenelzine (Nardil) facilitated assay sensitivity.

The main negatives were that the sponsor did not study higher doses of tyramine to characterize a full tyramine dose-response curve and allow one to characterize TSFs (TPRs) more comprehensively in most if not all of the subjects. Another noteworthy shortcoming was that the sponsor did not study a comparator group treated with conventional, swallowed selegiline at the FDA recommended dose (5 mg BID) to permit a comparison of ZS results.

- The sponsor had presented tabular data (Table 28) showing the mean TSF (i.e. TPR) for each treatment groups based upon the 2 different threshold criteria (2 consecutive threshold SBP increments - one ≥ 15 mm Hg AND one ≥ 30 mm Hg; 2 consecutive threshold SBP increments ≥ 30 mm Hg) that comprised the secondary analyses of the log dose-response curve but had not presented mean TSF or TPR for the criterion (at least single ≥ 30 mm Hg SBP increment) used for the primary analysis. Although the sponsor had provided mean tyramine threshold doses for these various criteria, the mean TSF for a treatment group must be calculated by computing the TSF for each individual based upon the threshold criterion used first and then computing the average of these TSFs to determine the mean TSF for the respective treatment group. In response to DNDP request, the sponsor provided the mean TSF for each treatment group using the primary analysis criterion (at least single ≥ 30 mm Hg SBP increment) and I constructed a table (Table 33) comparing results based upon each of the 3 different tyramine threshold criteria.

Table 33 shows that the applying the criterion of a single increment in SBP of ≥ 30 mm Hg compared to immediately prior to tyramine dosing showed increased (i.e. > 1) TSF for the 2.5 and 5 mg daily doses (2.67 and 4.29 respectively) but a normal TSF (i.e. ~ 1) for the highest ZS dose (10 mg daily). Applying this criterion also suggested that there was not only an expected, moderately increased TSF (7.0) for the positive control group

but that the placebo group was associated with a mildly increased TSF (1.78). Results derived from applying a somewhat more stringent criterion (e.g. 2 consecutive threshold SBP increments - one ≥ 15 mm Hg AND one ≥ 30 mm Hg) were generally similar to requiring a single SBP increment (≥ 30 mm Hg) with the exception that the mean TSF for the 5 mg ZS groups was nearly normal (1.30). In contrast, the most stringent criterion (2 consecutive threshold SBP increments ≥ 30 mm Hg) appeared to provide the most reliable results. The mean TSF for the lowest ZS dose groups (2.5 and 5 mg daily) were essentially normal (i.e. ~ 1) and the mean TSF for the highest dose group was mildly increased at 1.50. In this set of results, the mean TSF for placebo was essentially normal (i.e. ~ 1) and the mean TSF for the phenelzine positive control group was 5.7, similar to the expected increased tyramine sensitivity.

The geometric mean tyramine threshold dose based upon this most stringent tyramine threshold criterion similarly reflected results suggested from analyses of mean TSFs. The mean tyramine threshold dose for 2.5 and 5 mg daily ZS groups (336 and 317 mg respectively) were similar to that for placebo (303 mg). The mean tyramine threshold dose for the highest doses ZS group (10 mg) was mild-moderately decreased relative to placebo and that mean dose for phenelzine (79 mg) was markedly lower than that of placebo, indicating significantly increased tyramine sensitivity.

These analyses also supported DNDP's concern (and recommendation) that application of a more stringent criterion (e.g. requiring at least 2 or even 3 consecutive increments in SBP ≥ 30 mm Hg) would more likely indicate true positive tyramine-induced increments and decrease the chances of observing, spurious false positive increments and thereby assigning inappropriate tyramine threshold doses that tend to overestimate tyramine sensitivity and suggest false impressions. I had thought that requiring 3 consecutive SBP increments ≥ 30 mm Hg collect at 5 minute intervals would be ideal. The sponsor's approach seemed to provide similar information in that the 2 consecutive SBP increments occurred at 10 minute intervals. Both approaches required a sustained SBP > 30 mm Hg over 10 minutes. These results also indicated that the puzzling results obtained in the previous "definitive" tyramine challenge study (101) were spurious and likely erroneous because a not very stringent criterion (single SBP increment > 30 mm Hg) had been utilized.

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Table 33 Comparison of Mean TSFs (TPRs) Using Different Tyramine Threshold Criteria for Characterizing Tyramine Threshold Dose Across Treatment Groups

| Treatment (N) | At Least Single ≥ 30 mm Hg SBP Increment (N) | 2 Consecutive Threshold SBP Increments (one ≥ 15 mm Hg and one ≥ 30 mm Hg) (N) | 2 Consecutive Threshold SBP Increments (≥ 30 mm Hg) (N) |
|-------------------|---|--|---|
| ZS 2.5 mg (11) | 2.67 (6) | 2.33 (6) | 1.33 (3) |
| ZS 5 mg (12) | 4.29 (10) | 1.30 (8) | 1.06 (4) |
| ZS 10 mg (13) | 0.95 (7) | 0.95 (7) | 1.50 (3) |
| Placebo (10) | 1.78 (8) | 1.75 (7) | 0.83 (3) |
| Nardil 30 mg (13) | 7.00 (11) | 7.00 (11) | 5.57 (7) |

- Various analyses suggested that there was a dose-dependent increased sensitivity to tyramine for the 5 and 10 mg daily ZS treatments based upon characterizing tyramine dose response curves. However, when the mean TSF was assessed there was no clear increased tyramine sensitivity for any of the ZS treatments ranging from 2.5 to 10 mg daily. Considering these observations, it appears that characterizing the tyramine-induced dose response curve may be a more sensitive approach for assessing increased tyramine sensitivity.

There is one note of caution with respect to these data upon which the dose-response curves were based. The tyramine threshold criteria used to determine the highest tyramine dose to be administered and to construct these curves were based upon demonstrating at least a single increment in SBP ≥ 30 mm Hg. What the shape of these curves would look like if one applied the more stringent tyramine threshold criteria of requiring 2 consecutive SBP increments ≥ 30 mm Hg is not known. One could argue that these dose-response data may not be reliable for the same reason that Table 33 suggested that application of single threshold SBP increment may be spurious in suggesting a true threshold was achieved. It would be of interest to explore these data to see if one could construct curves based upon showing peak SBP responses to the various tyramine doses that achieved a threshold response consisting of 2 consecutive SBP increments ≥ 30 mm Hg. Nevertheless, the fact that the mean TSF for the highest ZS dose (10 mg) was 1 (based upon a single SBP threshold increment) in the face of dose-response curves indicating increased tyramine sensitivity leads me to suspect that a tyramine dose-response curve may be a more sensitive for demonstrating increased tyramine sensitivity than characterizing the mean TSF (TPR).

In view of these data, I would suggest that it would be ideal to conduct tyramine testing challenges (using a stringent, sustained SBP increment as a threshold criterion) across a full range of doses as conducted by the sponsor with the exception that it would be

desirable and safer to include higher doses (i.e. 500, 600, 700, and 800 mg) and also a 300 mg tyramine dose group. The 300 mg group is strongly recommended because subjects who exhibit a tyramine-induced pressor response just below the threshold criterion at 100 mg could exhibit a markedly increased hypertensive response if they were challenged with this large increment jumping from 200 mg to 400 mg instead of 100 mg increments). This approach would then allow one to characterize not only a comprehensive/complete tyramine dose response curve but also a comprehensive assessment of TSF. The sponsor's stopping at a highest challenge dose of 400 mg did not permit characterization of TSF in a considerable percentage of subjects but only in a minority of subjects (Table 33) because the mean tyramine threshold dose of untreated subjects probably ranges between 400 and 500 mg (based upon our experience with tyramine testing and that in the published literature).

- The tyramine dose-response data (Figure 15 and Figure 17) suggested that the "high" doses of ZS treatment (5 and 10) were associated with increased tyramine sensitivity. Consequently, the question arises as how to assess the clinical significance of this apparent increased sensitivity to drug treatment. Although the characterization of mean TSF based upon a minority of subjects suggested that there is no significantly increased tyramine sensitivity (i.e. > 2 fold), this characterization was limited in that it was based upon results of a relatively small number/percentage (i.e. 3-4 subject/each ZS group; ~ 30 % of subjects across all ZS groups) of subjects tested and using the most stringent (and seemingly best) tyramine threshold criterion (2 consecutive threshold SBP increments \geq 30 mm Hg).

A "high" tyramine content oral challenge from food and/or drink is considered to be probably in the range of 40-50 mg tyramine. In addition, administration of a tyramine challenge added to food can be associated with decreased bioavailability of tyramine (including decrease C_{max}, AUC and delayed T_{max}) and decreased pressor responses depending on various conditions. Given that the fasting tyramine study challenge would appear to represent a tyramine challenge under a worst case scenario that could be experienced by eating and/or drinking food or liquid containing up to 100 mg of readily bioavailable tyramine, I constructed a table (Table 34) showing the percentage of subjects showing tyramine threshold response to tyramine challenge doses up to 100 mg administered under fasting conditions for each treatment group for the least stringent tyramine threshold criterion and for the most stringent tyramine threshold criterion.

None of the ZS doses (2.5, 5, or 10 mg daily) seemed capable of producing a sustained threshold pressor response (\geq 30 mm increase systolic blood pressure) after challenge with increasing tyramine doses up to 100 mg under fasting conditions more frequently than placebo-treated subjects. In contrast, a substantial percentage of subjects (15 % challenged with 25 mg tyramine and 62 % challenged with 100 mg tyramine) treated with the positive control (phenelzine, non-selective MAO inhibitor) showed sustained threshold pressor responses (2 consecutive \geq 30 mm increment of systolic

blood pressure) after challenge with increasing tyramine doses up to 100 mg under fasting conditions more frequently than placebo-treated subjects (0 %).

I interpret these results as suggesting that none of the daily ZS treatments (2.5, 5, or 10 mg) likely appear to be associated with a significant risk for a tyramine-induced hypertensive “cheese” reaction. The ZS dose to be approved would be 2.5 mg. Of seeming relevance, the fact that none of the higher doses of ZS (5 and 10 mg daily) appeared to be capable of inducing sustained pressor responses (based upon the most stringent tyramine threshold criterion and expecting a dose-dependent ZS response more frequently than placebo) suggests a reasonable margin of safety with respect to a hypertensive risk for patients who might experience a significantly increased pharmacokinetic (PK) exposure (up to an equivalent dose of 10 mg daily) for some reason.

- I had asked the sponsor to provide additional figures showing the peak SBP response on treatment and the change from baseline for peak SBP response based upon actual, observed data. The sponsor had provided figures showing these responses based upon the LOCF principle in which the maximal response to the highest tyramine dose administered was illustrated. These figures (Figure 14 and Figure 16) showed that ZS responses for the high doses (5 and 10 mg) appeared to flatten out at higher doses rather than progressively increase as might have been expected. These requested figures showed that responses that were based upon decreasing numbers of subjects in each dose group as the tyramine dose increased because tyramine challenge testing ceased when a subject experienced a tyramine threshold response. Indeed, as suspected these requested figures (Figure 15 and Figure 17) showed that ZS responses for the 5 and 10 daily treatments progressively increased when actual observed data were used.

There is one note of caution with respect to these data upon which the dose-response curves were based. The tyramine threshold criteria used to determine the highest tyramine dose to be administered and to construct these curves were based upon demonstrating at least a single increment in SBP ≥ 30 mm Hg. What the shape of these curves would look like if one applied the more stringent tyramine threshold criteria of requiring 2 consecutive SBP increments ≥ 30 mm Hg is not known.

- I agree with the sponsor’s interpretation of the orthostatic (supine to standing) VS data that ZS did not appear to be associated with any clear alteration in orthostatic VS when compared to results of the placebo group. In particular there was no clear dose-dependent ZS induced orthostatic hypotension, the change that was of major interest. Figure 20 illustrates that there was no clear effect of ZS treatment. Of note, all active treatments showed a slight mean decrease of mean orthostatic SBP change from baseline relative to the modest mean increase in orthostatic SBP change from baseline. However, there was no difference in the ZS results across a 4 fold increase in dose. In addition, the highest ZS dose (10 mg) was associated with a “statistically significant” mean decrease in SBP change from baseline vs placebo but this nominal p value ($p = 0.049$) was borderline

statistically significant. Of significant potential relevance, there were no statistical adjustments made for multiple comparisons of possible changes in orthostatic VS that had been assessed by comparing each active treatment with placebo using Fisher's exact test. I question whether there is any realistic basis for interpreting this apparent change as being real based upon several considerations. First, there were no statistical adjustments for making multiple statistical comparisons of several treatments at several times relative to placebo. Second there was no pattern of orthostatic VS responses of ZS treatments comparing all 3 doses to placebo that suggested that this was a real effect. Finally, this apparently isolated change at 8 hours would not be expected based upon any known nor suspected pharmacokinetic-pharmacodynamic relationship.

In addition, the percentage of ZS treated patients showing orthostatic hypotension (SBP decrease ≥ 20 mm Hg and/or DBP decrease of ≥ 10 mm Hg) did not suggest a dose-dependent increased frequency relative to placebo at any of the multiple timepoints assessed after dosing.

Altogether, the sponsor's analyses based upon the multiple assessments of orthostatic VS after 11 days treatment in this randomized, double-blind, placebo-controlled study did not suggest any clear effect of ZS treatment on mean changes of SBP or DBP from baseline nor on the incidence of orthostatic systolic or diastolic hypotension. Thus, the questionable results observed in the previous uncontrolled study (101; without placebo group) did not appear to be real.

- In response to my request, the sponsor conducted and submitted separate analyses of supine, standing, and orthostatic (change from supine to standing) systolic and diastolic blood pressure for categorical increments in blood pressure (SBP ≥ 20 mm Hg, and/or DB) ≥ 10 mm Hg). The previous, uncontrolled study had suggested that ZS increases blood pressure compared to conventional, swallowed selegiline. Compared to placebo, there was no clear suggestion of a hypertensive effect of ZS. These analyses were interpreted by looking for a more frequent incidence (compared to placebo) of a categorical increment in blood pressure related to ZS and when this was assessed, consideration of whether this possible increment was also consistently observed at higher doses at the same frequency or at greater frequency suggesting a dose-response. These analyses did not support the suspicion raised in the original NDA review that ZS might increase blood pressure at particular times after dosing.

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Table 34 "Low" Fasting Tyramine Challenge Doses (≤ 100 mg) Achieving Different Systolic Blood Pressure Tyramine Threshold Criteria at Baseline and Post-Treatment by Randomized Treatment Group

| Tyramine Threshold Dose (mg) At least one \geq 30 mm Hg SBP Increment | Baseline (Randomized Treatment Group) | | | | Post-Treatment (Randomized Treatment Group) | | | | | |
|---|---------------------------------------|-------------------|--------------------|-------------------|---|---------------------|-------------------|--------------------|-------------------|-------------------------------------|
| | ZS 2.5 mg N = 12 | ZS 5 mg N = 13 | ZS 10 mg N = 13 | Placebo N = 13 | Phenelzine (Nardil) 30 mg N = 13 | ZS 2.5 mg N = 12 | ZS 5 mg N = 13 | ZS 10 mg N = 13 | Placebo N = 13 | Phenelzine (Nardil) 30 mg N = 13 |
| 12.5 | NT | NT | NT | NT | NT | 0 | 1 (8%) | 0 | 0 | 2 (15%) |
| 25 | 0 | 0 | 1 (8%) | 0 | 0 | 1 (8%) | 0 | 0 | 0 | 1 (8%) |
| 50 | 0 | 1 (8%) | 1 (8%) | 0 | 0 | 1 (8%) | 0 | 2 (15%) | 1 (8%) | 3 (23%) |
| 100 | 1 (8%) | 2 (15%) | 1 (8%) | 1 (8%) | 0 | 1 (8%) | 1 (8%) | 1 (8%) | 0 | 2 (15%) |
| Cumulative | 1 (8%) | 3 (23%) | 3 (23%) | 1 (8%) | 0 | 3 (25%) | 2 (15%) | 3 (15%) | 1 (8%) | 8 (62%) |
| Tyramine Threshold Dose (mg) 2 successive \geq 30 mm Hg SBP Increments | | | | | | | | | | |
| 12.5 | NT | NT | NT | NT | NT | 0 | 0 | 0 | 0 | 0 |
| 25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (15%) |
| 50 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (8%) | 0 | 4 (31%) |
| 100 | 0 | 2 (15%) | 1 (8%) | 1 (8%) | 0 | 0 | 0 | 0 | 0 | 2 (15%) |
| Cumulative | 0 | 2 (15%) | 1 (8%) | 1 (8%) | 0 | 0 | 0 | 1 (8%) | 0 | 8 (62%) |

NT = Not Tested

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- The sponsor had assessed whether there is a correlation of peak SBP tyramine response on treatment to plasma selegiline Cmax at steady state (95% CI) and to plasma selegiline AUC at steady state (95% CI). The correlation was weak for all ZS treatments but was higher for AUC ($r^2 = 0.0583$; adjusted $r^2 = 0.0322$) than for Cmax ($r^2 = 0.0423$; adjusted $r^2 = 0.0157$).

Based upon correlation of TSF with plasma Cmax and AUC from the study of ZS treatment and data from another study of transdermal selegiline treatment, I suggest that the level of selegiline AUC seems most likely associated with the loss of MAO-B selectivity and increased tyramine sensitivity. ZS. There is no significant/substantive increased tyramine sensitivity associated with "high dose ZS treatment (5 or 10 mg daily) based upon TSF despite the fact that Cmax is higher for ZS treatment than with high dose transdermal selegiline treatment (40 mg). However, there is an approximate 10 fold increase in tyramine sensitivity as reflected by increased TSF of ~ 10 related to high dose transdermal selegiline treatment (40mg) in association with a much higher in selegiline AUC compared to AUC associated with 10 mg daily ZS treatment.

- The sponsor had described changes in some laboratory parameters including increments in serum cholesterol and triglycerides and decrements in CPK. I do not attach much significance to these changes from baseline across all treatment groups because there was no suggestion that they were related to ZS treatment nor were dose-dependent for the various ZS treatment groups.
- My original review had suggested high dose ZS (10 mg) was associated with mild mean increments in BUN and creatinine from baseline and in the frequency of outliers with categorical shifts from normal to increased from baseline to the end of the randomized, double-blind, placebo-controlled studies. The fact that these apparent increments in BUN and/or creatinine were not observed in this study nor in the QTc study suggests that either longer treatment is required to observe these changes with high dose 10 mg treatment or that they may not have suggested a real effect.

7. SUMMARY OF NEW SAFETY DATA (SAFETY UPDATE-SU)

This Safety Update (SU) shows the safety experience of all patients treated with Zydis selegiline in all clinical trials (including any clinical trials other than Study Z/SEL/97/027) after the last 120-day Safety Update cutoff date (31 December 2001). The additional safety information discussed in this Update includes the following :

1. Study Z/SEL/97/027 was ongoing at the time of the previous 120-day Safety Update data cutoff date of 31 December 2001. The study completed and data are now included in this Update

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for the 106 patients who had been categorized as ongoing, based on those who had not completed the final visit (92 as reported previously) and 14 other patients with study data still outstanding at the time of the data cutoff.

2. Two new Phase 1 pharmacology studies in healthy volunteers (Studies RNA600301-101 and RNA-ZEL-B21-102) were initiated and completed after 120-day Safety Update was filed on 08 November 2002. Subjects All summary safety information reported for healthy volunteers has been revised, as applicable. The final study reports for the Phase 1 pharmacology studies contained detailed safety information/data. This SU summarizes important safety information from these studies.

3. In response to a request from the Division of Neuropharmacological Drug Products of the FDA, the oropharyngeal data were reanalyzed in an attempt to simplify the interpretation of the results. These data were also provided in this SU.

4. Withdrawal information for 7 patients was reconciled in the database after the previous data cutoff date of 31 December 2001. Data for withdrawal for 5 patients were recoded in the database for Protocol Z/SEL/97/027 to accurately reflect the data query resolutions questioning the exact reasons for withdrawal. Data for AEs that were previously reported as resulting in withdrawal of study drug were queried and updated for 2 patients.

5. Codes for various records of AEs after the data cutoff date of 31 December 2001 were updated

The objectives of this Update were to :

- present a complete assessment of the safety profile of Zydis selegiline hydrochloride in PD patients in all clinical trials including the completed long-term safety extension study, Protocol Z/SEL/97/027;
- present a reanalysis of the oropharyngeal data in an attempt to simplify the interpretation of the results;
- provide additional safety information in healthy volunteers.

This SU provides summary data for all PD patients from all studies, new safety information obtained after the last safety cutoff date of 31 December 2001, and a summary of the new safety data in healthy volunteers.

The new PD patient data compare the most recent safety experience with the experience shown in the previous 120-day Safety Update. All sections from the 120-day Safety Update that were affected by the additional information collected for PD patients were discussed in this SU. New data were presented in in-text tables in **boldface** font and located immediately under the original data from the previous 120-day Safety Update to allow for an immediate comparison between what was presented previously and how the reconciled data appear now. All AE data updated

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since 31 December 2001 were presented side-by-side with the data from the previous 120-day Safety Update. Statistical tables and data listings and other supportive documentation were included in the appendices to this SU.

For the purpose of this Update, data collected from Study Z/SEL/97/027 after 31 December 2001 through 08 January 2003 (completion of the extension study) were entered into the database.

Disposition

The clinical study that contributed new disposition data to this SU is the completed long-term extension study Z/SEL/97/027. Table 35 shows the update disposition data.

Table 35 Disposition – Extension Studies

| | Number of Patients (%) in Extension Studies | | | |
|--|---|------------------------------|------------------------|--------------------|
| | Previous Placebo | Zydis Selegiline 1.25/2.5 mg | Zydis Selegiline 10 mg | Overall |
| Total | 83 | 307 | 24 | 331 |
| Completed Study | 3 (3.6%) | 52 (16.9%) | 19 (79.2%) | 71 (21.5%) |
| | 25 (30.1%) | 131 (42.7%) | | 150 (45.3%) |
| Withdrawn | 51 (61.4%) | 123 (40.1%) | 5 (20.8%) | 128 (38.7%) |
| | 58 (69.9%) | 176 (57.3%) | | 181 (54.7%) |
| Reasons for Withdrawal | | | | |
| Adverse events | 21 (25.3%) | 43 (14.0%) | 2 (8.3%) | 48 (14.5%)* |
| | 27 (32.5%) | 60 (19.5%) | | 62 (18.7%) |
| Protocol deviation | 0 | 6 (2.0%) | 0 | 7 (2.1%) |
| | 1 (1.2%) | 13 (4.2%) | | 13 (3.9%) |
| Lost to follow-up | 1 (1.2%) | 5 (1.6%) | 0 | 5 (1.5%) |
| | 1 (1.2%) | 9 (2.9%) | | 9 (2.7%) |
| Lack of efficacy | 12 (14.5%) | 29 (9.4%) | 0 | 29 (8.8%) |
| | 12 (14.5%) | 41 (13.4%) | | 41 (12.4%) |
| Other | 17 (20.5%) | 40 (13.0%) | 3 (12.3%) | 43 (12.4%) |
| | 16 (19.3%) | 53 (17.3%) | | 56 (16.9%) |
| Data are from Studies Z/SEL/95/008E and Z/SEL/97/027 | | | | |
| Note: "Previous Placebo Patients" refers to patients who were randomly assigned to Zydis placebo in the original studies and started on Zydis selegiline in the extension studies | | | | |
| * Patient Y59 was originally classified as withdrawn due to lack of efficacy, but the updated dataset revealed that the patient was withdrawn due to an AE, which brings the total number of withdrawals due to AEs in the 120-day Safety Update to 49 patients. | | | | |
| Data Source: Appendix 1 End-of-text Table 1.2.2, Appendix 2 End-of-text Listing 1.2 | | | | |

Exposure and Duration of Treatment

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All Studies

The overall extent of exposure for patients who received Zydis selegiline is presented in Table 36. A total of 430 patients were exposed to Zydis selegiline in all studies included in this Update. The overall mean duration of exposure for all studies increased from 482.5 days to 530.9 days. The maximum duration of exposure was 1690 days and 122 (28.4%) patients were exposed to Zydis selegiline for at least 2 years. These results reflect a combination of corrections or errors in treatment start/stop dates and addition of data that were not available for the original ISS datasets and the previous 120-day SU. From a cumulative perspective, the number of patients treated for ≥ 6 months, ≥ 1 year and ≥ 2 years was 274, 232, and 122, respectively.

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Table 36 Overall Duration of Exposure to Zydis Selegiline in All Studies

| Overall (any dose) | |
|---|---|
| Number of Patients | 430 |
| Mean Duration (SD) (days) | 482.5 (411.51) 530.9 (494.59) |
| Median Duration (days) | 372.5 375.5 |
| Minimum, Maximum Number of Days | 2, 1379 2, 1690 |
| Exposure Duration Categories ^a | Number of Patients (%) |
| <90 days | 114 (26.5%) 114 (26.5%) |
| 90 - 179 days | 42 (9.8%) 42 (9.8%) |
| 180 - 269 days | 21 (4.9%) 21 (4.9%) |
| 270 - 364 days | 23 (5.3%) 21 (4.9%) |
| 365 - 729 days | 100 (23.3%) 110 (25.6%) |
| ≥730 days | 130 (30.2%) 122 (28.4%) |
| <p>Note: Data are from multiple-dose Studies Z/SEL/97/025, Z/SEL/97/026, Z/SEL/97/027, Z/SEL/95/008, and Z/SEL/95/008E and exclude Study Z/SEL/94/026 in which 148 patients were exposed to a single dose of Zydis selegiline.</p> <p>Note: Six patients were rolled over from the Z/SEL/95/008E study to the Z/SEL/97/027 study. Their exposure in the Z/SEL/97/027 study was added to the overall exposure.</p> <p>^a Patients were counted in only 1 category based on the total duration of exposure. Data are presented to match source tables and may not reflect numbers presented in the previous 120-day Safety Update.</p> <p>Data Source: Appendix 1 End-of-text Table 3.2</p> | |

Adverse Events – All Studies

Table 37 summarizes the treatment emergent adverse event (TEAE) incidence and numbers of TEAEs, serious AEs (SAEs) and discontinuation for TEAEs for all patients in the 120-day SU and all patients in this SU. In Protocol Z/SEL/97/027, a TEAE was defined as an AE that was not present prior to Day 0 of the study or an AE that had an increase in severity or frequency during the study. Chronic conditions that were part of the patient’s medical history were not considered TEAEs, unless they increased in severity or frequency. The updated database for all PD patients includes 838 new AEs, 53 new serious AEs (SAEs), and 28 new AEs/SAEs leading to withdrawal of 13 additional patients. These represent the additions to the database as well as data query results that were resolved after the 120-day SU cutoff date. While the overall numbers of

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patients with any AE, SAE, or who withdrew due to an AE/SAE are greater in this Update than the numbers presented in the previous 120-day SU, it is not entirely a result of more patients reporting events. Increases in the overall incidence of TEAEs from the previous 120-day SU were small and can be expected with the continued monitoring of safety in this population of Parkinson's Disease patients. Thus, the overall safety conclusions for Zydis selegiline did not change.

Table 37 Overview of Adverse Events in all Multiple-Dose Parkinson's Disease Studies Safety Population

| | Number of Patients (%) ^a | |
|---|-------------------------------------|-------------------------|
| | 120-day Safety Update (N=644) | Current Data (N=644) |
| Patients with any adverse event | 463 (71.9%) | 469 (72.8%) |
| Number of adverse events | 3375 | 4213 |
| Patients with serious adverse events | 93 (14.4%) | 108 (16.8%) |
| Number of serious adverse events | 155 | 208 |
| Patients who withdrew due to adverse events | 74 (11.5%) | 87 (13.5%) |
| Number of adverse events causing withdrawal | 117 | 145 |
| Note: A patient was counted once if he/she reported one or more adverse events at each level of summary. A patient who was in a short-term study and who enrolled in an extension study was counted only once. ^a Percentages were calculated by hand as the number of patients with events divided by total number of patients. Data Source: Appendix 1 End-of-text Tables 4.1.1, 4.4.1, and 4.5.1 | | |

The sponsor presented a table that summarizes the TEAEs by body system/preferred term that occurred in $\geq 5\%$ of patients while receiving study drug in the extension studies. Although the sponsor did not specifically note that the frequency of these TEAEs had changed, my review of this table did not suggest a substantive change in the frequency of a specific TEAE or TEAEs within a body system.

Deaths – Extension Studies

No new deaths in PD patients treated with Zydis selegiline were reported between the end of the previous 120-day SU data collection period and this SU.

Serious Adverse Events – Extension Studies

The updated database includes 53 new SAEs in 33 patients. The types of SAEs reported in this SU are consistent with those reported in the 120-day SU. New SAEs that were not reported in the previous 120-day SU and occurred in more than one patient include, cardiovascular disorder (2 patients), dizziness (2), hallucinations (2), and gastrointestinal hemorrhage (2).

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Withdrawal Due to Adverse Events – Extension Studies

The sponsor presented a table identifying patients who withdrew from the extension study due to TEAEs, since the closure of the 120-day SU database. Six of the 13 patients who withdrew from the extension study due to TEAEs, were associated with SAEs, 4 of which resulted in death [Dizziness and shortness of breath (C-37), Heart arrest (X-25), Respiratory Arrest (X-99), and Hemorrhagic stroke (Y-34)]. The other 2 patients who withdrew due to non-fatal SAEs associated with atrial fibrillation (A-58) and a multitude of events including accidental injury, depression, dysarthria, myasthenia, urinary and fecal incontinence (C-08). The remaining 7 patients withdrew from the study due to nonserious TEAEs, including anxiety, depression, nervousness, abnormal dreams, hallucinations, dyskinesias, dizziness, flatulence, nausea and vomiting, and kidney pains.

Although there were not dramatic changes in the frequency of withdrawal overall, withdrawals due to nervous system adverse events resulted in increases due to depression (3 new patients), dizziness and dyskinesia (2 new patients each).

Abnormal or Significant Clinical Laboratory Values - Extension Studies

Shifts from abnormal (eg, low or high) values in serum chemistry and hematology were observed in the extension studies, but overall, the majority of patients' values were within normal limits between Baseline and Weeks 12 to 39 and even after 40 or more weeks of treatment. Results of the Phase 1 studies (RNA600301-101 and RNA-ZEL-B21-102) suggest that cholesterol and triglyceride values may be affected by short-term treatment with Zydis selegiline. However, in the extension study, most patients had cholesterol and triglyceride values within normal limits at Baseline and few shifted to below or above normal limits even after 40 weeks of treatment.

Thus, it appears that there is no overall detrimental effect on serum chemistry, hematology, or urinalysis values associated with long-term administration of Zydis selegiline.

Vital Signs - Extension Studies

There were not any new findings of VS suggestion a new concern.

Electrocardiography

All patients were previously reported in the ISS or the 120-day SU and there are no new data for this SU.

Reviewer's Conclusions

- I agree that there were no new findings in this most recent SU that changed my assessment of the safety profile of ZS relative to the last 120 day SU.

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8. POSTMARKETING EXPERIENCE

The prior sponsor Elan Pharmaceuticals maintains the license for this product in Europe and is responsible for collecting postmarketing experience information. The current sponsor, Valeant Pharmaceuticals International, does not have the rights to this product in Europe or other safety databases and therefore cannot provide postmarketing experience information, except as that which would be obtained from a review of the published clinical literature.

Although ZS has been approved for Parkinson's Disease in the United Kingdom, Italy, and Portugal, the sponsor is not involved in the ownership nor marketing of these products in these countries.

9. CLINICAL LITERATURE REVIEW

A literature search was performed using National Library of Medicine "PubMed" database, with the search parameters utilizing the terms "selegiline" between 01 July 2002 and 02 March 2005. Initially, no distinction was made between clinical and nonclinical publications. The reference citation search resulted in a list of 203 publications. A review of this list and available abstracts resulted in identifying 13 publications that either addressed the safety of Zydis selegiline in clinical studies or provided safety information on selegiline in nonclinical investigations.

Of the 13 new publications identified as adding new information, 5 publications reported clinical findings :

- the results from clinical studies reported in the NDA, either Phase 1 (Clarke et al, 2003a and 2003b) or Phase 3 (Waters et al, 2004) studies
- a commentary on the new Zydis selegiline formulation (Prescrire International, 2003).
- the results from a study examining the orthostatic hypotensive effects following treatment with selegiline alone, levodopa/carbidopa alone, or the combination of selegiline and levodopa/carbidopa (Bhattacharya et al, 2003).

The remaining 8 new publications reported nonclinical findings from in vivo or in vitro studies of selegiline :

- in vitro drug metabolism findings (Dragoni et al, 2003a and 2003b, Levai et al, 2004, Salonen et al, 2003)
- cardiovascular effects of drug-drug interactions with selegiline (Dodam et al, 2004, Schindler et al, 2003)

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- smooth muscle contraction activity (Yoshimura et al, 2004)
- effect of high-dose selegiline on morphine reinforcement and precipitated withdrawal (Grasing, He, 2005).

Reviewer Comment

I did not find any of these literature references provided by the sponsor to be worthy of comment.

10. COMMENTS TO MEDICAL OFFICER FROM CLINICAL PHARMACOLOGY /BIOPHARMACEUTICAL REVIEW AND REVIEWER COMMENTS

The Clinical Pharmacology/ Biopharmaceutical review (Dr. Andre Jackson reviewer) contained several comments to the medical officer. These comments and recommendations from this review are shown here. I have provided my comments to these comments or recommendations that I have deemed noteworthy or deserving of a particular comment.

Comments to the MO Tyramine Study:

The following are the limitations of the study. The clinical relevance of these limitations needs to be assessed by the Medical Officer :

1. The highest dose of tyramine used in the study was 400 mg. Traditionally tyramine doses up to 800 mg have been evaluated.
2. The primary definition of log tyramine dose to produce a threshold response has been amended from the original protocol. Was this in concurrence with the Medical Officer. (see definitions on page 14, primary definition, and 15, secondary definition, of the review). What would be the appropriate endpoint to base decision.
3. Is there a bias introduced by enrolling only responders (i.e., using an enrichment design) at the baseline assessment.

Reviewer Comment

- None of these comments are serious concerns that alter the way we interpret these data.
- We had recommended using higher doses, which the sponsor did not follow but was able to collect useful information anyway. It is likely that better/more comprehensive data

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would have been collected if the sponsor had studies a full tyramine dose range up to 800 mg as we had recommended.

- Considering that this is a safety study, it is not necessary to have a rigid statistical analysis plan and there is no problem with dropping the log tyramine data threshold assessment that was not feasible with the data collected.
- There is no concern with the sponsor's screening/ enrichment plan that selected responders.

Comments to the MO QT Study:

The results for QTcI (i.e., individual corrected) showed a mean high of 7.85 msec increase at 3 hr for the positive control moxifloxacin treatment which is far below the reported 20 msec level which substantially increases the likelihood of the drug being proarrhythmic. For the treated groups no values was larger than 6 msec. The Medical Officer should decide where to include this information in the label.

Reviewer Comments

- The nearly mean 8 msec largest QTc increment for moxifloxacin corresponded with a nearly mean - 4 msec decrease for the placebo group showing an ~ 12 msec treatment effect increment for moxifloxacin. The ≥ 20 msec figure QTc prolongation referred to is a generally accepted value that stimulates serious concern about QTc prolongation and risk for Torsades des pointes. QTc increments in the range of 10-20 msec are thought to be of indeterminate significance. While I would agree that no ZS treatment in all subjects showed a > 6 msec treatment effect (placebo-corrected), I would note that the upper bound of the 95 % CI (one-sided) was not able to exclude 11 msec for the largest time-matched QTc increment relative to placebo and this observation makes this a "positive" "thorough" QTc study. I would also note that the largest time-matched mean QTc increment in females was ~ 10 msec and was associated with a 95 % CI (one-sided) that was not able to exclude 20 msec.

Comments to the MO Drug Metabolism:

1. In the firm's current proposed label they have conducted a thorough literature search and update the proposed label based upon the available information in the literature related to the CYP enzymes responsible for the metabolism of selegiline.
2. The firm has cited literature IC₅₀ values which range ~700-1000 fold higher than the reported maximum plasma concentrations for selegiline. Therefore, the firm has concluded that selegiline is not likely to inhibit CYP450.

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3. OCPB has requested that the firm investigate the in vitro drug interaction at drug concentrations at or exceeding the enzymes IC_{50} to definitively determine if selegiline has the potential to inhibit CYP3A4 metabolism.

4. OCPB has also requested the firm to look at the in vitro potential for the induction of CYP3A4, CYP1A2, 2A6, 2B6, and 2C8 metabolism by selegiline.

5. Additional drug-drug interaction studies may need to be considered depending on the information gathered on the metabolism of selegiline. However, since the steady-state Zelapar levels are only 2-3 fold greater than Eldepryl and do overlap OCPB believes these studies can be done as Phase IV commitments.

Reviewer Comment

- The emphasis here appears to be what is the potential of selegiline to have drug-drug interactions with other drugs via its potential interactions with CYP enzymes? **It is not clear to me that the sponsor has provided information/data excluding the potential of other drugs to interact with CYP metabolizing enzymes and thus possibly result in significant, many fold elevations of selegiline exposure.** Drug-drug interactions by inhibiting important CYP metabolizing enzyme pathways that could result in several fold exposures (e.g. > 4 fold AUC and/or C_{max} relative to uncomplicated exposure to 2.5 mg daily ZS) could potentially result in significant toxicity (adverse events) particularly significantly increased tyramine sensitivity and hypertensive "cheese" reactions and possibly even significant QTc prolongation resulting in Torsades des pointes if ZS can really increase QTc.
- We already are aware of a drug-drug between oral contraceptives and oral conventional selegiline (Laine et al., Br. J. Clin. Pharmacol., 47, 249-254, 1999) in which the administration of 10 mg selegiline (single dose) was associated with a 22 fold increase in AUC and a 11 fold increase in C_{max} .

Comments to the MO Gender/Age/Race:

1. There appears to be a trend for a lower C_{max} in females, but it was not consistent in all studies (e.g., in QT study RNA 600301 C_{max} increased by 15%). Overall there appears to be no Gender effect for Selegiline. A statement related to gender has been included in the updated label.

2. OCPB has requested that the firm conduct an analysis on their current single dose and multiple dosing data to determine if there is any effect of age/race on the pharmacokinetics of selegiline.

Reviewer Comment

- I agree that this is a reasonable approach/recommendation.

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Comments to the MO Liver and Renal Study:

1. The peak serum concentrations and AUC values were 7- and 18 fold higher in patients with impaired liver function and 15- and 23 fold lower in patients with drug –induced liver function.
2. Patients with impaired kidney function had peak concentrations and AUC values 4-6 fold higher than normals.
3. Child-Pugh scores were not reported by the investigators.
4. OCPB has requested that the firm conduct studies in hepatic and renal patients with selegiline.
5. **OCPB strongly suggests that a caution (WARNING) be placed in the label related to the use of selegiline in patients with either liver or renal insufficiency.**

Reviewer Comment

- I have outlined my concerns previously that if hepatic or renal impairment increases exposure (AUC and/or Cmax) to selegiline exposure many fold (> 4 fold; e.g. AUC possibly up to 18 fold increase for hepatic impairment and AUC possibly up to 6 fold increase for renal impairment), that serious adverse events could result. The adverse events that I am most particularly concerned about relate to an increased tyramine sensitivity resulting in hypertensive “cheese” reactions and significant QTc prolongation resulting in Torsades des pointes if ZS can really increase QTc.

Comments to the MO Food Effects:

1. The reported effect of food on the immediate release and the orally disintegrating formulation are contradictory.
2. OCPB has requested the firm to conduct a food/fasting study as a Phase IV commitment to clarify the current information.

Reviewer Comment

- I agree with conducting a food/fasting study assessing the true effect of food on ZS PK.
- The observation that food alters the exposure to selegiline suggests to me that a significant portion of ZS is swallowed instead of virtually all of it being absorbed buccally.

Summary of Requested Phase IV Commitments:

These items were included in the Approvable letter to the firm of February 7, 2003 but to date have not been addressed by the firm related to:

Drug Metabolism

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1. The firm needs to better characterize the potential for selegiline or its metabolites to inhibit CYP450 enzymes by using in vitro drug concentrations above the IC₅₀ for the enzyme.
2. The firm needs to look at the in vitro potential for the induction of CYP3A4, CYP1A2, 2A6, 2B6, and 2C8 metabolism by selegiline.
3. Additional drug-drug interaction studies may need to be considered depending on the information gathered on the metabolism of selegiline.

Urinary Excretion

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

Food Effect

The firm has agreed to conduct another food study.

Liver and Renal studies

The firm has agreed to conduct these studies.

Age/Race

The firm should analyze their current single and multiple dose data to determine any effects of age/race on the pharmacokinetics of selegiline.

An Additional Phase IV Item has been requested based upon the review of Journal Articles related to the effect of Oral Contraceptives on Selegiline Pharmacokinetics (reference OCPB review of NDA-19334 submission dated July 21, 2003).

Oral Contraceptives

The firm should conduct a three-way cross-over between Premarin 0.625 mg daily and medroxyprogesterone acetate 5 mg, selegiline and ORTHO TRI-CYCLEN. The focus of the study would be to determine the effect of the contraceptive on selegiline pharmacokinetics.

Recommendations

1. The tyramine effect study results indicated no effect of selegiline on SBP in the presence of Tyramine greater than the positive control, however study design considerations must be addressed by the MO before the study can be found to be acceptable.

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2. The thorough QT study showed that there was no increase in the QT interval over the positive control Moxifloxacin, so it can be concluded that selegiline has no impact on cardiac repolarization.

3. Meta analysis of single dose data and multiple dose data from the Tyramine study and the QT studies indicated no effect of gender on the pharmacokinetics of selegiline.

Reviewer Comment

- I have noted my comments about the tyramine challenge study conducted and find that it is acceptable in that it provides reasonable information on effects of ZS treatment (2.5, 5, and 10 mg daily) on tyramine sensitivity.
- I do not consider that we can exclude an effect of high dose ZS (10 mg) treatment on QTc prolongation/cardiac repolarization for the reasons outlined in my comments section of the QTc study.
- I agree that there does not appear to be a significant effect of gender on the PK of selegiline.

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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Leonard Kapcala
9/29/2005 07:03:19 PM
MEDICAL OFFICER

John, Here is my clinical review of the response
to the approavable letter. Please sign and check
with me if any questions. Thanx.. Len

John Feeney
10/2/2005 04:26:27 PM
MEDICAL OFFICER
Concur; see my memo to the file.

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MEMORANDUM

NDA 21-479 Zelapar ODT

FROM: John Feeney, M.D.
Neurology Team Leader

SUBJECT: New NDA for Adjunctive Treatment for the Management of
Parkinson's Disease

DATE: February 7, 2003

Oral selegiline has been approved in the United States for adjunctive treatment **of Parkinson's disease (PD) for over a decade. Additional evidence bearing on** the use of oral selegiline as initial monotherapy in early PD was accrued in the DATATOP study, but that sponsor has never pursued a claim beyond adjunctive treatment. Elan Pharmaceuticals has developed a new formulation of selegiline, an orally disintegrating tablet, which is absorbed across the buccal mucosa. This formulation has obvious advantages for patients with difficulty swallowing, a problem for some patients with PD. Also, it only needs to be taken once daily.

The transmucosal absorption of selegiline bypasses the large first-pass effect seen with the currently marketed oral selegiline. Therefore, a lower total daily dose of the new formulation results in comparable systemic exposure (as measured by AUC of the parent drug) to that seen after swallowing the currently marketed formulation. Likewise, by bypassing first-pass metabolism, there are much lower levels of circulating metabolites with the new formulation.

Because of the vast experience with selegiline over the past 10 years, DNDP notified the sponsor of Zelapar that only one positive efficacy study would be required to support approval. As discussed below, the sponsor actually has performed 2 separate controlled trials, identical in design. Study 26 demonstrated a positive effect in reducing the amount of time spent in the Off state for patients who had demonstrated a deterioration in their response to L-dopa therapy. Study 25 did not demonstrate such an effect and the sponsor has proposed a **greater-than-expected placebo response in the study to explain the "aberrant" results.**

While the systemic exposures as measured by AUC are comparable for Zelapar 2.5mg (the dose proposed for marketing and supported by the results of Study 26) and oral selegiline 5mg bid (the currently approved dose), the C_{max} for Zelapar occurs earlier and is about 2-fold greater. Because of this, DNDP believed one of the primary safety issues with the new formulation would be the demonstration of selectivity for MAO-B. The sponsor has performed 3 tyramine challenge studies to demonstrate the lack of inhibition of MAO-A. The first 2 studies employed as a control group a single daily dose of selegiline 10mg

instead of the currently approved 5mg bid. DNDP had told the sponsor that the higher Cmax with the 10mg dose vs the 5mg bid dosing regimen could have resulted in loss of selectivity for MAO-B and masked differences in selectivity between the new formulation and the marketed selegiline. Therefore, the sponsor performed a third tyramine challenge study comparing marketed selegiline 5mg bid with 3 different daily doses of Zelapar, 1.25mg, 2.5mg, and 5mg. The results of these studies are discussed below.

The primary medical review was conducted by Dr. Leonard Kapcala. He reviewed both the efficacy and safety of Zelapar. Dr. Fanhui Kong performed the statistical review. Dr. Veneeta Tandon wrote the clinical pharmacology/biopharmaceutics review.

The chemistry review was conducted by Dr. Mona Zarifa. The pharmacology/toxicology review was done by Dr. Lois Freed.

Efficacy

Studies 25 and 26 were identical in conduct and design. Both included patients with a diagnosis of idiopathic PD who were currently taking L-dopa and who had begun to experience Off periods. During the 2 weeks prior to randomization, all patients filled out diaries 2 days per week. The diaries divided each 24 hour period into 30 minute increments. Patients were asked to categorized each 30 minute increment as: 1) On, 2) Off, 3) On with dyskinesias, or 4) asleep. Patients had to have an average of 3 hours per day in the Off state in order to be randomized.

Concomitant medications to treat PD were allowed. Patients were required to be taking L-dopa. The dose of L-dopa could be decreased if evidence of dopaminergic side effects emerged. The dose of L-dopa could not be increased. Other drugs allowed were dopamine agonists and anticholinergics. COMT inhibitors were prohibited.

There was a 2-week screening period prior to randomization. The treatment period was 12 weeks long. After 6 weeks of treatment, all patients had their dose increased from 1.25mg to 2.5mg.

The final draft of the statistical analysis plan is dated December 1999. According to this plan, the primary outcome was reduction in average percentage of daily Off time, comparing the average percentage of awake time spent Off for the diaries collected at visits 10 and 12 to the same average percentage for the diaries collected during the 2 week screening period. The difference would be **reported as the absolute difference with "%" as the appellation.**

While the plan outlines an ITT analysis for the primary analysis, it defines 2 possible ITT populations, confusing the common meaning or use of ITT. The plan

states, "When the phrase ITT population is used, it is generally assumed that relevant analyses are performed on the ITT completers." The ITT LOCF population is defined but is not stated to be the primary efficacy population. A Per Protocol (PP) was also to be developed. In summary, the primary analysis plan left ambiguity as to the primacy of the ITT LOCF vs the Completers analysis. An ANCOVA was to be the statistical test if the normality assumptions proved true.

The final study reports for studies 25 and 26 clearly indicate that the ITT LOCF was viewed by the sponsor as a "supportive" analysis, while the OC analysis was considered primary.

Study 26

Both study groups had an average of 7 hours per day Off time at baseline. At the end of 12 weeks, Zelapar-treated patients had 2 hours per day less Off time on average, while placebo-treated patients had 0.5 hours per day less Off time.

The sponsor first presents an OC analysis, implying that they believe this to be the primary analysis. The table below shows the results of this analysis:

Reduction in % Off Time During Waking Hours from Baseline to Weeks 10-12

| | Zelapar n=87 | Placebo n=44 | p-value |
|------------------------------|-----------------|-----------------|------------------|
| Sponsor's OC Analysis | -13.1 | -3.9 | <0.001 |

Nevertheless, the sponsor also performed the ITT LOCF analysis with a resultant p-value < 0.001. Dr. Kong believes the sponsor performed this analysis, carrying forward only the percent Off time from the single last visit, unless both week 10 and week 12 visits occurred. He believes, in keeping with the protocol, that the correct way to perform this ITT LOCF analysis is to carry forward the values for the last 2 visits during the trial, whenever they occurred. He performed such an analysis with a resultant p-value 0.0007. The normality assumption was shown to be correct, so that the ANCOVA was acceptable to Dr. Kong. The table below shows the results with the 2 techniques:

Reduction in % Off Time During Waking Hours from Baseline to Weeks 10-12

| | Zelapar n=94 | Placebo n=46 | p-value |
|----------------------------|-----------------|-----------------|------------------|
| Sponsor's ITT LOCF | -12.4 | -4.0 | <0.001 |
| Dr. Kong's ITT LOCF | -13.9 | -5.1 | <0.001 |

As in other trials in PD, the protocol allowed the dose of concurrent L-dopa to be reduced if dopaminergic side effects emerged. Between group differences on this

maneuver always have the potential to impact the outcome of the trial. In study 26, there was no obvious difference between groups with roughly 80% of patients in both the Zelapar and placebo groups having no change in L-dopa dosing during the trial. For those patients who did reduce their dose, the actual degree of dose reduction is not obvious in the submission and will need to be pursued further for labeling purposes.

Results of the patient-rated and physician-rated global tests, as well as the UPDRS subscales are summarized in the reviews of Drs. Kong and Kapcala.

Study 25

Both study groups had an average of 7 hours per day Off time at baseline. At the end of 12 weeks, Zelapar-treated patients had 2 hours per day less Off time on average, while placebo-treated patients had 1.3 hours per day less Off time.

As in the study 26 final report, the sponsor first presents an OC analysis, implying that they believe this to be the primary analysis. The table below shows the results of this analysis:

Reduction in % Off Time During Waking Hours from Baseline to Weeks 10-12

| | Zelapar n=89 | Placebo n=46 | p-value |
|------------------------------|-----------------|-----------------|-------------|
| Sponsor's OC Analysis | -11.6 | -9.8 | 0.47 |

Again, the sponsor performed an ITT LOCF analysis (dealing with missing data as in study 26) with a resultant p-value 0.80. Dr. Kong repeated the ITT LOCF analysis (dealing with missing data as described above) with a resultant p-value **0.127, considerably better than the sponsor's result. Again, the normality assumption held true.** The table below shows the results with the 2 techniques:

Reduction in % Off Time During Waking Hours from Baseline to Weeks 10-12

| | Zelapar n=98 | Placebo n=50 | p-value |
|----------------------------|-----------------|-----------------|-------------|
| Sponsor's ITT LOCF | -10.3 | -9.5 | 0.80 |
| Dr. Kong's ITT LOCF | -12.1 | -7.4 | 0.13 |

Whatever differences truly exist between the sponsor's approach and Dr. Kong's approach, it is interesting to note the effect those differences have on the between group differences in study 25. It is somewhat concerning that the results

seem so "analysis dependent." I have discussed these issues with Dr. Kong and his team leader, Dr. Kun Jin, and asked them to investigate the results further.

As in study 26, the protocol allowed the dose of concurrent L-dopa to be reduced if dopaminergic side effects emerged. Between group differences on this maneuver have the potential to impact the outcome of the trial and in study 25 there was a difference between groups with 27% of patients in the Zelapar group reducing their dose while only 15% of placebo patients did so. This differential would seem to bias toward the null in study 25. The actual degree of dose reduction is not obvious in the submission and may need to be pursued further for labeling purposes.

Efficacy Conclusions

By all analyses of the primary outcome in study 26, Zelapar was superior to placebo. The most appropriate analysis, the ITT LOCF, showed a statistically significant effect. The observed difference between Zelapar and placebo of 1.5 hours per day would certainly be considered clinically relevant. Because of the long marketing history of oral selegiline in the U.S., DNDP has previously informed the sponsor that a single efficacy study could support the current application. Given the results of study 26, along with the vast body of evidence bearing on the effectiveness of oral selegiline, I believe Zelapar has been shown to be effective as adjunctive therapy with L-dopa for the reduction of Off time.

The results of study 25 deserve comment. This study was identical in design to study 26, but did not demonstrate a difference between Zelapar and placebo. I have commented above on several facets of the study that distinguish it from study 26. First, L-dopa dose reduction in the 2 treatment groups of study 25 was unequal, perhaps driving toward a null result. Second, different analyses (of the same patient populations) which differ only slightly result in a family of p-values from 0.1 to 0.8. This analysis-dependent outcome suggests some unusual pattern to the data and merits further investigation. Third, the change from baseline in Off time for placebo-treated patients was fairly large, 1.3 hours, making a demonstration of a difference more difficult. For all these reason, the results of study 25 do not alter my opinion that Zelapar is effective in PD.

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Safety

Dr. Kapcala has reviewed the safety data for Zelapar.

In the original NDA, there were 578 patients treated in the safety database. From **Dr. Kapcala's review, 148 received only 1 dose so that roughly 430 patients** received more than 1 dose. Roughly 280 patients were treated for 6 months or more. Roughly 230 patients were treated for a year or more. Subsequently, the sponsor submitted a 120-day safety update, but this does not appear to have changed the total number of exposures significantly.

Another 219 healthy volunteers participated in trials. Of these, 108 received single doses and 111 were in multidose studies.

There were 8 deaths in the original NDA (1 of these was taking the marketed selegiline formulation) and 4 more in the safety update. Two patients exposed to Zelapar 10 mg per day for 1-2 months were thought to have had myocardial infarctions. One of these patients had actually discontinued Zelapar 13 days prior to his first MI. The other patient died in his sleep. A third patient was presumed to have died from an MI one month after starting Zelapar 2.5 mg per day. Myocardial infarction is not an unexpected background event in this patient population, however.

One patient died from complications of a sigmoid volvulus after 3 months on Zelapar 2.5 mg per day. There was a hemorrhagic stroke, but this seemed unrelated to study drug in this 80 yo man.

Across the 2 placebo-controlled trials (2:1 randomization), there were 9 patients with serious AEs in the Zelapar group vs 2 placebo patients. Sixty patients in all extension studies experienced serious AEs. The most common serious AEs seen were backpain, accidental injury, chest pain, postural hypotension, and pneumonia. Accidental injury would not be considered unusual in an elderly **population with Parkinson's disease, especially if they became more ambulatory as a result of less "off" time.**

In the placebo-controlled trials, the rate of discontinuation was similar across groups, 9% for Zelapar and 8% for placebo. Discontinuation for AE occurred for 5% of Zelapar patients and 1% of placebo patients. Reasons for discontinuation for the Zelapar patients included depression, weakness, accidental injury, and chest pain.

Common AEs included dizziness, nausea, pain, headache, insomnia, rhinitis, dyskinesia, stomatitis, and dyspepsia.

Dr. Kapcala reports that no patients withdrew from a study because of a laboratory abnormality. He did identify elevations in BUN and creatinine in his

safety review, but these were only reported in patients on Zelapar 10 mg/day, a dose considerably higher than that to be recommended for marketing. This merits mention in labeling.

Vital Signs

Given the higher C_{max} expected with Zelapar 2.5 mg/day compared to the marketed selegiline formulation, Dr. Kapcala has stressed the importance of adequately characterizing changes in blood pressure in relation to dosing, ideally capturing results at T_{max}. Such data were not collected in the controlled trials, but were collected in study 101 (PK and tyramine challenge study).

Unfortunately, the only analyses of the BP data from study 101 are based on mean changes; outlier analyses based on pre-defined clinically important changes would be more informative. Dr. Kapcala and I believe the latter analysis should be requested from the sponsor. Again, unfortunately, although BP data was timed to dose in study 101, there was no placebo arm for comparison; any comparison can only be made to the marketed selegiline arm (under unblinded conditions).

In the controlled trials, where vital signs were not timed in relation to dosing, Dr. Kapcala reports that 6% of Zelapar patients shifted from clinically acceptable **resting systolic BP to a "potentially important" resting systolic BP > 160**; only 1% of placebo patients did so. Further investigation of this finding seems indicated, to include an analysis of proportions of patients in each group with a clinically significant *change* in resting systolic BP.

Because orthostatic BP is a common problem both from the underlying disease, PD, and as a side effect of medications used to treat PD, Dr. Kapcala devoted considerable attention to investigating this finding. Between group differences in orthostatic changes, on going from sitting to standing, were not considerable. But, for going from supine to standing, 21% of Zelapar patients had a clinically significant drop in systolic BP vs 9% of placebo patients.

Importantly, the differences between groups on resting systolic BP and orthostatic changes in systolic BP may possibly be greater if an analysis could be done with data timed toward T_{max}.

Electrocardiograms

As with the vital sign data above, Dr. Kapcala believes it is critical to investigate ECG data timed to dosing. This has not been done in any study to date.

ECG data was provided initially for one controlled trial, study 25, and revealed a 7 msec prolongation of QT interval on Zelapar vs placebo. While not found in the other controlled trial, submitted later, it raised the question of QT prolongation with selegiline. This issue has not been addressed with marketed selegiline and

may be more important with Zelapar, given the higher C_{max}. No cases of torsades are identified in the Zelapar safety database.

Oropharyngeal Exams

In the controlled trials, examination of the oral cavity was conducted by dentists or oral surgeons. The results of these special evaluations were tabulated in this submission and incidence figures provided *by different mouth regions* (i.e. right cheek, left cheek, upper lip, lower lip, etc). Areas of reddening, swelling, and ulceration were noted. Unfortunately, the proportions of *patients* in each treatment group with any of the above lesions, irregardless of mouth region, were not provided. These proportions should be provided by the sponsor. Of particular concern to me are the between group differences in the category "mild ulceration." These always favor placebo for every region checked. If affected patients are represented in all regions, the overall between group difference may not be great, but if affected patients are only represented in single regional groups, there may be a much larger proportion of Zelapar patients with mild ulceration.

Safety Update

Dr. Kapcala has reviewed the safety update and has not reported any new concerns raised by his review.

Tyramine Studies

Because of this NDA, the review team clarified 3 important sources of variability relevant to the conduct of valid tyramine challenge studies with any selegiline product.

First, the NDA review highlighted the need to resolve the food effect on selegiline bioavailability. Current labeling for marketed selegiline reports a 2-3 fold increase in exposure to parent drug when taken with food. This is based on a food effect study which was apparently conducted in 1993. The food effect study submitted with this NDA included a study arm with marketed selegiline. In the current study, food decreased the exposure by 2-3 fold. Given the exposure-dependent nature of MAO-B selectivity, it seems critical to clarify this issue. Currently, the Dosage and Administration section of labeling for marketed selegiline does not dictate the intake of drug in relation to food.

Second, Dr. Tandon has reviewed several biopharm studies which suggest that, beyond the time that steady state would be expected (several days at most), increasing accumulation is experienced after Zelapar. In one study (study 101),

exposure of selegiline at day 10 was 3-4 fold higher based on AUC than at day 1. Additional accumulation was not studied beyond day 10. In a different study (study 96/014), exposure at day 28 was 9-10 fold higher based on AUC than at day 1, without measurements at intervening timepoints. The corresponding Cmax was the same at day 1 and day 10 in the first study, while the Cmax rose 2-3 fold in the second study. While day 10 and day 28 data were not collected in the same study, there is at least a suggestion that exposure increases between day 10 and day 28. If true, this implies that MAO-B selectivity should be studied at day 28 or beyond.

Third, from another recent NDA, transdermal selegiline for depression, this review team learned that there is evidence from previous tyramine challenge studies that tyramine sensitivity, both for transdermal selegiline and currently marketed selegiline, increases over time. This provides direct evidence for a changing MAO-B selectivity. This fact could follow from the second point above, accumulation over time, or it could occur independent of actual exposure.

The 3 tyramine challenge studies in the current NDA are described in detail in Dr. **Kapcala's review**. **Only one compared Zelapar to marketed selegiline given as 5 mg bid**. The other 2 studies provided marketed selegiline as 10 mg once daily. All **studies enrolled 10-20 patients per arm**. **Each subject's threshold dose of tyramine for causing a predefined change in systolic BP was established during a drug-free baseline**. In general, this dose is on the order of 500-600 mg tyramine. Then, after 12 days on study drug (marketed selegiline or Zelapar at different doses), the tyramine threshold is again determined. This was on the order of 25-200 mg tyramine. The ratio of baseline tyramine threshold dose to on-study tyramine threshold dose is then determined for each patient. These are on the order of 1-20.

In study 101, the only study to provide marketed selegiline as 5 mg bid, an anomalous result is reported for marketed selegiline. First, almost half the subjects experienced a tyramine threshold dose of 25-50 mg while on selegiline. Because a tyramine-rich meal might include 25-50 mg tyramine, the implication is **that these patients would be at risk of a "cheese reaction."** **The average tyramine ratio for this group was 6.7, well above a reasonable average of about 2 based on previous experience.**

In study 101, none of the Zelapar groups performed worse than marketed selegiline. The sponsor takes comfort in this fact, given the long marketing experience of selegiline 5 mg bid.

Of note, study 101 was not blinded and did not have either a placebo or active-control arm (a non-selective MAO inhibitor). The tyramine challenges were performed on days 12 through 14. Subjects took medication on days 1-11 with food, but took medication on days 12 through 14 in a fasted state. Tyramine dosing took place in a fasted state.

The results of this study are considered so anomalous by the review team that some have raised the possibility that the tyramine formulation was improperly weighed out for the challenge on days 12 through 14. A second interpretation of this study is that the results are accurate, with neither marketed selegiline nor Zelapar (at any dose) being as selective for MAO-B as anyone would like. A third interpretation is that, under conditions of this study, the result for marketed selegiline 5 mg bid is spurious, while the result for Zelapar is valid, truly worse than marketed selegiline based on historical results for selegiline. This third interpretation would seem unlikely, but for the unblinded conditions of the study.

Since one of the 3 possible interpretations of the study 101 results suggests that marketed selegiline may perform differently, less safely than previously predicted, Dr. Kapcala has devoted considerable attention to reviewing the historical data on tyramine sensitivity and marketed selegiline. Unfortunately, the information currently available to us about these studies does not allow us to fully account for the 3 sources of variability described at the beginning of this section. None of the studies were performed beyond 2 weeks and the fed/fasting state of the subjects during intake of selegiline in these studies has not been explored. Therefore, while study 101 is clearly an outlier with respect to marketed selegiline, the results cannot be totally dismissed. If true, must stricter Warnings would be warranted for marketed selegiline.

As a first step, the sponsor should carefully re-review all available resources for study 101 to investigate for methodological flaws to include poorly controlled tyramine dosing.

If some obvious methodological flaw is not uncovered, the sponsor of marketed selegiline should be notified that DNDP currently possesses information suggesting a loss of MAO-B selectivity even when marketed selegiline is used as directed. That sponsor should be asked to make an argument why further tyramine sensitivity testing is not needed for marketed selegiline. Such an argument would have to address the sources of variability identified here, to include the food effect and duration of treatment.

Finally, as a condition of approval, the sponsor of Zelapar must first address the conflicting information on food effect. Then, incorporating that information, the sponsor must perform an additional tyramine challenge study with Zelapar, investigating tyramine sensitivity at multiple timepoints, perhaps monthly, until a plateau in pharmacodynamic effect is observed.

Biopharmaceutics

The biopharmaceutics information provided has been deemed acceptable by the review team. The biopharm review team requests that more data on metabolism

of selegiline be collected either by literature search or in vitro study. Depending on the results, additional drug-drug interaction studies may be needed.

Biopharm also requests that the sponsor perform a meta-analysis to better characterize the effect of gender on the PK of Zelapar.

Pertinent to the tyramine sensitivity issue, the biopharm review highlights the fact that there is accumulation of selegiline over time with some evidence supporting a 10-fold increase in AUC by day 28 and a 3-fold increase in Cmax by day 28. Such a finding suggests that the most informative time for a tyramine challenge would be day 28 at a minimum.

The biopharm review team requests that the sponsor conduct PK studies in patients with hepatic and renal impairment as phase 4 commitments.

Chemistry

The chemistry information has been deemed acceptable. The sponsor has made a commitment to develop a _____ HPLC assay method for the drug product and establish a specification for _____ unless _____ is demonstrated to be insignificant during manufacture and on storage.

b(4)

Comments on carton and container labeling were sent to the sponsor on July 15, 2002. The sponsor has not responded to these. They should be incorporated into the action letter. (See Nomenclature below.)

Preclinical Issues

Dr. Lois Freed has commented on preclinical issues and made recommendations for labeling. She has requested reproduction studies.

Inspections

Two clinical study sites were inspected. One enrolled 27 patients and one enrolled 24 patients. Overall, the data generated at these sites were deemed acceptable for review.

Nomenclature

The Division of Medication Errors and Technical Support (DMETS) reviewed the name Zelapar and the potential for name confusion in the marketplace. Overall, DMETS believes the risk for name confusion is low. A re-review prior to approval

is appropriate. DMETS has some comments about carton and container labeling that were forwarded to the sponsor on July 15, 2002. DMETS believes these changes could improve the safe use of the product. Because the sponsor has yet to address these points, they should be reiterated in the action letter.

Recommendations

The sponsor should be sent an Approvable letter. As a condition of Approval, the sponsor should be asked to perform another tyramine challenge study as described above. The sponsor should also be asked to explain the wide range of p-values which resulted from seemingly small changes in the LOCF analysis techniques in study 25. The review team has drafted labeling with numerous questions to the sponsor embedded throughout. The sponsor must respond to these issues prior to Approval. One of the questions asks the sponsor to explain discrepant results for different food effect studies.

Given the public health implications of the tyramine testing results submitted in this application, I believe a strict timeline should be imposed on Elan to go back and thoroughly investigate the conduct of study 101. Particular attention should be paid to the calibration of the machinery which generated the tyramine dosage forms. One of my suspicions is that, while the calibration may have been correct for the baseline tyramine testing, the calibration for the *lower* tyramine dosage forms (used while on Zelapar or marketed selegiline) may have been incorrect.

I would allow Elan 60 days to conduct the above investigation and thought should be given to having FDA personnel participate in that investigation. If, at the end of 60 days, an obvious explanation for these outlier results is not forthcoming, then I believe the maker of marketed selegiline should be informed of these results and asked to address them in an expeditious manner. At that point, particular attention might be paid to clarifying the food effect on selegiline exposure and investigating the role of food in previously conducted tyramine studies with marketed selegiline.

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/s/

John Feeney
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MEDICAL OFFICER

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MEMORANDUM

DATE: February 7, 2003

FROM: Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-479

SUBJECT: Action Memo for NDA 21-479 for the use of Zydis Selegiline in patients with advanced Parkinson's Disease

NDA 21-479, for the use of Zydis Selegiline in patients with advanced Parkinson's Disease (PD), was submitted by Elan Pharmaceuticals, Inc., on 3/29/02. Selegiline is currently approved in a conventional tablet formulation as Eldepryl (the sponsor is Somerset Pharmaceuticals) for the treatment of patients with advanced PD. The approved dose is 5 mg BID. Selegiline is an MAO-B inhibitor, and is thought to work primarily in the central nervous system (CNS) by inhibiting the enzyme that degrades dopamine. Zydis selegiline is an orally disintegrating tablet, which is primarily absorbed across the buccal mucosa; this dosage form results in a greater plasma C_{max} of selegiline than that derived from the same dose given as oral selegiline (at least 2 ½-3 times that derived from the conventional tablet) because of the avoidance of first-pass metabolism. For this reason, lower doses of the Zydis formulation can be given to achieve effectiveness.

The application contains the results of two randomized controlled trials in patients with advanced PD being treated with L-dopa, as well as with other specific PD therapy, whose clinical status was characterized by significant Off periods. In addition, the sponsor has presented safety data, and, in particular, has submitted the results of several tyramine challenge tests, designed to examine the potential of selegiline to inhibit MAO-A. Presumably, at the proposed doses (see below), selegiline selectively inhibits central MAO-B; inhibition of peripheral MAO-A can result in serious hypertensive reactions resulting from the ingestion of tyramine-containing foods (so-called "cheese reaction"). While rare cases of the "cheese reaction" have been reported at the approved dose of Eldepryl (5 mg BID), it has generally been considered that, at this dose, the conventional oral selegiline tablet causes no appreciable MAO-A inhibition.

The application has been reviewed by Dr. Leonard Kapcala, medical officer, Drs. Mona Zarifa and Haripada Sarker, chemists, Dr. Lois Freed, pharmacologist, Dr. Fanhui Kong, statistician, Drs. Vaneeta Tandon and Andre Jackson, Office of Clinical Pharmacology and Biopharmaceutics, Dr. Bryan Riley, Microbiology, and Dr. John Feeney, Neurology Team Leader. The review team recommends that the sponsor be sent an Approvable letter, with requests for additional data.

In this memo, I will briefly describe the data, and provide the rationale for the division's action.

Effectiveness

As described by the clinical review team, the sponsor has presented the results of two identically designed randomized, parallel group, placebo-controlled trials in patients with PD with significant Off periods. The treatment periods were 12 weeks long; for the first 6 weeks patients were treated with 1.25 mg once a day of Zydys selegiline, and for the second 6 weeks, with 2.5 mg once a day. The primary outcome was the percent change from baseline in Off time during the waking hours.

As described by the review team, one study (Study 26) yielded strongly significant results in favor of selegiline, while the other study (Study 25) did not. As all three clinical reviewers note, the primary analysis was not entirely clearly stated in the protocol. However, regardless of which analysis was performed (we relied primarily on the intent-to-treat, last observation carried forward [ITT-LOCF] analysis, as described by Dr. Feeney), the results for Study 26 were unambiguously and robustly positive. Importantly, the decrease in Off time does not come at the expense of an increase in On time with dyskinesias or increased sleep (see Dr. Kapcala's review, page 102). Further, regardless of the analysis performed, Study 25 did not detect statistically significant between-treatment differences (although the ITT-LOCF analysis yielded the smallest p-values in favor of selegiline). It is not clear why the different analyses performed for Study 25 yielded such widely disparate p-values; we will ask the sponsor to address this. However, it does appear that the absence of statistical significance is likely explained by the rather large placebo effect in this study; the percent changes from baseline in Off time in the Zydys-treated groups are about the same in both Studies 25 and 26.

In any event, we had agreed with the sponsor prior to the submission of the NDA that a single robustly positive study in this population, combined with the experience with the conventional oral tablet, would be sufficient to support the conclusion that Zydys selegiline is effective. Study 26 provides that evidence, and the absence of significance in Study 25 poses no bar to concluding that Zydys selegiline, given as 2.5 mg once a day, is an effective treatment in patients with advanced PD.

A brief comment about the effective dose is worth making.

The protocol-specified primary outcome was to be the average Off time for Weeks 10 and 12. As noted above, this analysis yielded highly significant results in Study 26, and supports the conclusion that 2.5 mg once a day is an effective dose. An analogous analysis, evaluating the average Off time for weeks 4 and 6,

also yielded highly significant results ($p=0.003$, see Dr. Kapcala's review, page 98, Sponsor's Table 35), and supports the view that 1.25 mg once a day is also an effective dose. It is true that this was not prospectively specified as a primary comparison of interest, and we have no information about the persistence of this effect (given that patients were increased to the higher dose after Week 6), but nonetheless, I believe that the data strongly suggest that this is an effective dose, and that this should be noted in labeling.

Safety

As noted by the review team, a total of 578 patients contributed safety data, in addition to 219 normal volunteers. Dr. Feeney has highlighted the important safety concerns that persist, as described in detail in Dr. Kapcala's review.

Of primary importance is the finding from the tyramine challenge study, Study 101. The details of this study are provided by Dr. Kapcala.

In this study, the tyramine pressor ratios (the dose of tyramine giving rise to an increase in systolic BP of at least 30 mm Hg, prior to selegiline/the dose giving rise to such an increase during treatment with selegiline) for the studied doses were as follows (patients were treated with selegiline for 12 days):

| | |
|-------------------|-----|
| Zydis 1.25 mg | 6.7 |
| Zydis 2.5 mg | 2.8 |
| Zydis 5 mg | 4.8 |
| Eldepryl 5 mg BID | 6.8 |

In addition, the percent of patients who reached the pre-specified BP criterion at a tyramine dose of 50 mg or less in the treatment groups was as follows:

| | |
|-------------------|-----|
| Zydis 1.25 mg | 43% |
| Zydis 2.5 mg | 20% |
| Zydis 5 mg | 33% |
| Eldepryl 5 mg BID | 59% |

As Dr. Feeney notes, this study (and ancillary data) raises a number of important, and as yet unanswered, questions.

First, and most important, the results seen in this study for the marketed Eldepryl tablets are anomalous and of considerable concern. Previous studies of Eldepryl have suggested that the tyramine pressor ratios are much smaller than the 6.8 determined here (closer to 2), and the percent of patients who reached the threshold BP values at low tyramine doses has been markedly lower. These previous results have led to the conclusion, expressed earlier, that Eldepryl at the recommended dosing regimen (5 mg BID) causes no appreciable MAO-A

inhibition. The results in this study, if reliable, strongly suggest that Eldepryl has considerable MAO-A inhibitory activity at the recommended dose.

Obviously, the results seen with the Zydis formulation are difficult, if not impossible, to interpret, given the odd dose-response relationship seen, and the unexpected results for Eldepryl. Further, there are other complicating issues, as discussed by Dr. Feeney.

While previous data suggest that there is a 2-3 fold increase in the exposure to parent drug when the conventional tablet is given with food, a study in this application suggests that there is a 2-3 fold decrease in selegiline concentration when the Zydis formulation is taken with food, as well as a similar decrease in selegiline C_{max} when Eldepryl is administered. As Dr. Feeney notes, the degree of MAO-A inhibition is presumably related to the dose (exposure) of selegiline; given this, it is important to sort out as precisely as possible what the effects of food are on plasma levels of selegiline for both the Zydis formulation and the conventional tablet (it is not obvious to me, for example, why food should have any appreciable effect on plasma levels derived from the Zydis formulation, since it is not expected that much is swallowed).

Further, data in this application give conflicting results regarding when steady-state (which would be expected to occur after only several days of treatment) is reached; Study 101 suggests that the AUC at Day 10 is about 3-4 times that on Day 1 (drug levels were not assessed beyond Day 10, or between Days 1 and 10), while in another study, the AUC at Day 28 was about 9-10 times that on Day 1. While cross study comparisons are often treacherous, these data suggest that there is continued accumulation up to at least 4 weeks. If this is true, the tyramine challenge study may not have been performed at the maximum possible selegiline levels at steady-state.

The sponsor performed two other tyramine challenge studies, in which Eldepryl was given as a single 10 mg dose. The results in the first study (which compared Zydis 1.25 mg to Eldepryl 10 mg) yielded Pressor Ratios of 3.4 and 2.8 for Zydis and Eldepryl, respectively. The second study, which compared Zydis 10 mg to Eldepryl 10 mg, yielded Pressor Ratios of 4.5 and 3.7 for Zydis and Eldepryl, respectively.

While Zydis never performed worse than Eldepryl, the results of Study 101, the best performed of the challenge studies, raise significant concerns which cannot be dismissed.

As noted, it is not clear that the conditions of the study (duration, food status) ensured that the maximum possible effect of selegiline on MAO-A inhibition was assessed. Further, and of course critically, the results themselves are difficult to interpret, given the highly unexpected finding for Eldepryl, and the shape of the dose response for Zydis.

One could, I suppose, argue that, in all studies, Zydys was (at worst) comparable to Eldepryl. Because we have considerable past information about Eldepryl which supports the view that 5 mg BID does not cause appreciable MAO-A inhibition, this supports the conclusion that the results seen for Eldepryl are anomalous, and can be dismissed. In that case, the argument would go, we can conclude, given that Zydys has been uniformly shown to be equivalent to Eldepryl, that Zydys, too, causes no appreciable MAO-A inhibition.

I do not find this argument persuasive, because, even if we could conclude that the results seen in Study 101 for Eldepryl were anomalous, the basis for dismissing them would be dependent upon our previous knowledge about Eldepryl. However, we have no previous experience with Zydys selegiline, and the greater Cmax with Zydys, compared to Eldepryl, could be responsible for a greater degree of MAO-A inhibition with it.

Of course, it is also possible that the results seen with Eldepryl should not be dismissed, but should instead be considered to raise serious questions about Eldepryl's capacity to inhibit MAO-A (and, therefore, of course raise the same concerns for Zydys), despite what we have previously believed to be true about Eldepryl in this regard. This is a particular concern for Dr. Feeney.

I am inclined to believe that the results for Eldepryl are, in fact, not representative of Eldepryl's true effect on MAO-A, but I take Dr. Feeney's point that previous data on this question may not have adequately addressed the problem, and, in any event, I cannot conclude with any reasonable degree of certainty that the results are "wrong". I agree with the review team that a definitive tyramine challenge study should be performed before we can safely conclude that Zydys selegiline, given as 2.5 mg once a day, causes no appreciable MAO-A inhibition, and, therefore, does not require dietary restrictions for its safe use. Such a study should incorporate appropriate features as described by Drs. Feeney and Kapcala, including placebo and positive control, blinding, treatment for an appropriate duration, and appropriate food intake status.

Additionally, as Dr. Feeney notes, based on Dr. Kapcala's review, there is an increased incidence of orthostatic hypotension in patients treated with Zydys compared to placebo treated patients; this was seen on measurements not taken at Cmax. While there was not a significant incidence of clinical hypotension (although this conclusion is hampered somewhat by the presentation of the clinical data), I agree that this should be adequately evaluated at Cmax. As Dr. Feeney explains, this information can be obtained in a repeat tyramine challenge study, but this would likely be performed in normal volunteers, not patients. This will provide useful information, but we might expect a different response in PD patients. We should ask the sponsor to address this issue in our action letter.

Dr. Kapcala has also raised a question about whether or not Zydys causes QT

prolongation. I do not believe that the data suggest this strongly (one controlled trial demonstrated a negative effect of the drug, one demonstrated a 7 msec prolongation compared to placebo, although this was largely due to a negative change in the placebo patients). Further, there is some suggestion of a prolongation in the open, uncontrolled experience. In any event, I agree that if the tyramine challenge study is repeated, EKGs at Cmax should be obtained.

There are other issues that need further clarification; for example, as the team notes, the sponsor's presentation of the results of examinations of the oral cavity hamper somewhat our interpretation of this data, and they should be asked to submit a re-analysis of this information. The team also requests that the sponsor submit additional data on several issues (metabolism, studies in special populations, additional animal studies, etc.). I agree that these requests should be made.

Recommendations

I agree with the review team that this application is Approvable.

Before the application may be approved, however, the sponsor will need to perform a more definitive tyramine challenge test, incorporating the features described above. While the sponsor needs to provide data from such a study, do not agree with Dr. Feeney's recommendation to require the sponsor of Eldepryl to address the results of Elan's Study 101 at this time. As I noted above, I believe that the experience gained with Eldepryl (and generic selegiline) for more than a decade suggests that the risk of hypertensive crises with these marketed formulations at the recommended doses is small, and does not warrant immediate action on the part of Somerset. I do, however, agree that Elan should move quickly to resolve this matter.

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I further agree with Dr. Feeney's other requests for additional data.

For the reasons stated above, then, I will issue the attached Approvable letter, with appended labeling.

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/s/

Russell Katz
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