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APPLICATION NUMBER:

21-641/S-008

MEDICAL REVIEW

CLINICAL REVIEW

Application Type	NDA
Submission Number	21641
Submission Code	SE8
Letter Date	2/6/09
Stamp Date	2/9/09
PDUFA Goal Date	12/9/09
Reviewer Name	Leonard P. Kapcala, M.D.
Review Completion Date	December 2, 2009
Established Name	rasagiline
(Proposed) Trade Name	Azilect
Therapeutic Class	Monoamine Oxidase Inhibitor
Applicant	TEVA Pharmaceuticals
Priority Designation	S
Formulation	Oral tablets
Dosing Regimen	Once daily
Indication	Treatment of Parkinson's Disease
Intended Population	Adults

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1 EXECUTIVE SUMMARY

Background / Introduction

Rasagiline is a monoamine oxidase (MAO) inhibitor (MAOI), that the sponsor has purported as being selective for MAO B. The sponsor had submitted an NDA for approval for treatment of early and advanced Parkinson's Disease. After several review cycles, rasagiline (AZILECT; NDA 21641) was approved in 5/06. However, because the sponsor had not provide adequate documentation of the selectivity for rasagiline for inhibiting solely MAO-B and not also MAO-A, rasagiline was approved as a non-selective MAO-B inhibitor requiring dietary tyramine restrictions. One of several Phase 4 commitments was for the sponsor to conduct an adequate tyramine challenge study characterizing the tyramine sensitivity after rasagiline treatment. The DNP gave the sponsor specific, detailed recommendations for conducting an adequate tyramine challenge study at the time of rasagiline approval and also subsequently provided the sponsor with detailed feedback for conducting this study and also for analyzing the study and presenting results. The present submission provides results for the final study report for study TVP-1012-120-TYR.

Brief Summary of Study Design

The sponsor has conducted a randomized, double-blind, placebo-controlled study in which healthy subjects were studied at baseline/pre-treatment (Period 1) for the ability of increasing tyramine doses to produce a threshold systolic blood pressure increase of at least 30 mm Hg on 3 consecutive occasions at least 5 minutes apart ($TYR30_3$). Subjects were then randomized to one of several treatments (placebo, rasagiline 1, 2, 4, or 6 mg daily, or selegiline 10 mg daily, as 5 mg BID, or phenelzine). All treatments, except phenelzine were conducted under double-blind conditions and phenelizine was conducted under open-label conditions. After treatment were 14 days (Period 2), subjects were studied for the ability of increasing doses of tyramine to produce tyramine threshold, pressor response ($TYR30_3$) after various treatments. The effect of treatment on tyramine sensitivity was assessed by determining the tyramine sensitivity factor (TSF). The TSF is calculated by assessing the ratio of the $TYR30_3$ before treatment in Period 1/ $TYR30_3$ after treatment in Period 3. The effect of the various treatments on TSF is shown in the summary table below here.

Summary of Tyramine Sensitivity Factor-TSF ($TYR30_3$ in Period 3 After Treatment/$TYR30_3$ Before Treatment)

	Arithmetic Mean	Geometric Mean	Median
Phenelzine (1)	20.14	17.32	17
Selegiline (2)	3.87	2.47	2
1 mg Rasagiline (3)	2.98	2.03	2
2 mg Rasagiline (4a)	4.67	3.33	4
2 mg Rasagiline (4b)	2.79	2.45	3
4 mg Rasagiline (5)	8.22	4.50	4
6 mg Rasagiline (6)	7.31	5.10	5
Pooled Placebo (4a,2,3,5,6)	4.98	1.50	1

The following table shows the frequency of $TYR30_3$ threshold pressor responses after treatment to various, relatively low dose of tyramine ($\leq$ 200 mg).

Table A (Reviewer Table) Frequency of Post-Treatment $TYR30_3$ Threshold Dose at $\leq$ 200 mg According to Treatment

Tyramine Potentiation of SBP to Threshold Increment	Treatment (Period 3)							
	Phenelzine N=15 (%)	Selegiline N=15 (%)	Pooled Placebo N=38 (%)	Rasagiline 1 mg/day N=15 (%)	Rasagiline 2 mg/day (14 days) N=13 (%)	Rasagiline 2 mg/day (30 days) N=14 (%)	Rasagiline 4 mg/day N=17(%)	Rasagiline 6 mg/day N=13(%)
5 mg	1 (7)							
12.5 mg		1 (7)	2 (5.)		1 (7)		2 (12)	1 (8)
15 mg	1 (7)			1 (7)				
25 mg	7 (47)	1 (7)	1 (3)				1 (6)	1 (8)
35 mg	3 (20)							
45 mg	2 (13)							
50 mg	3 (20)		1 (3)		1 (8)			2 (15)
75 mg	1 (7)							
100 mg		5 (33)	1 (3)	0 (0)	3 (23)	3 (21)	5 (29)	4 (31)
200 mg		3 (20)	1 (3)	7 (47)	5 (38)	7 (50)	8 (47)	5 (38)
$\leq$ 50 mg	14 (93)	2 (13)	4 (11)	1 (7)	2 (15)	0 (0)	3 (18)	4 (31)
$\leq$ 100 mg	15 (100)	7 (47)	5 (13)	1 (7)	5 (38)	3 (21)	8 (47)	8 (62)
$\leq$ 200 mg	15 (100)	10 (67)	6 (16)	8 (53)	10 (77)	10 (71)	16 (94)	13 (100)

Reviewer Summary of Study Results

- **Rasagiline (1 mg daily) treatment produced increased TSF (geometric mean, median, arithmetic mean) compared to placebo treatment.**

- **Increased tyramine sensitivity of 1 mg rasagiline treatment is exhibited by :**

1) the increased incidence of $TYR30_3$ responses to lower tyramine doses after treatment (n Period 3) compared to baseline-pre-treatment responses (in Period 3); and
2) the increased incidence of $TYR30_3$ responses to lower tyramine doses compared to placebo treatment.

- **Rasagiline-induced increased tyramine sensitivity is dose-dependent (across daily doses of 1-6 mg) but the effect at 6 mg (highest dose studied) is numerically less than the increased tyramine sensitivity produced by phenelzine, a completely non-selective MAO inhibitor.**

- **Increased tyramine sensitivity produced by 1 mg rasagiline treatment appears to be similar to the increased tyramine sensitivity produced by 10 mg selegiline treatment.**

Reviewer Conclusions

1. **Rasagiline (1 mg daily) treatment (presently FDA approved) is a relatively selective MAO-B inhibitor**

2. **Tyramine dietary restriction is not ordinarily required with 1 mg rasagiline treatment. However caution should be exercised about ingesting large amounts of tyramine (e.g., > 150 mg tyramine, possibly in certain products such as aged cheese) because of the possibility of a hypertensive, "cheese" reaction because of the mildly increased tyramine sensitivity associated with 1 mg rasagiline treatment.**

3. **The relative selectivity of 1 mg daily rasagiline for MAO-B appears to be similar to the relative selectivity of 10 mg daily selegiline for MAO-B.**

4. **The rasagiline label (and oral swallowed selegiline label) should be revised to reflect this new information.**

2 INTRODUCTION AND BACKGROUND

Tyramine is formed by the degradation of protein in foods. Protein, with ageing, breaks down into free amino acids one of which is tyrosine, which is then converted to tyramine. Therefore, tyramine is found in relatively large amounts in many foods that have undergone aging such as many aged cheeses, sausages, salami, sauerkraut and tap beer. Once systemically absorbed, tyramine is taken up by adrenergic neurons and displaces norepinephrine from synaptic vesicles. This causes large amounts of norepinephrine to be released into the synaptic cleft. Clinically this produces what is known as the .cheese effect.. One of the classic signs is a large increase in systolic blood pressure (SBP). An increase in pulse and palpitations are also characteristic of the .cheese effect.. In rare cases there may be hypertensive emergencies with acute target organ injury.

Monoamine oxidase (MAO) A acts as a natural protective barrier to guard against excessive tyramine by catalyzing the oxidative deamination of tyramine. Most of this occurs presystemically by MAO-A in the intestinal wall and by some MAO-A in the liver. Thus very small amounts of tyramine are normally absorbed systemically.
Traditional inhibitors of MAO such as phenelzine and tranylcypromine, indicated for the treatment of depression, are non selective i.e., in addition to inhibiting the MAO-B enzyme they also inhibit MAO-A at clinical doses and thereby allow large amounts of tyramine to enter the systemic circulation. Therefore, when these agents are used foods and beverages with high tyramine content are prohibited.

The large majority of the clinical development program for rasagiline was performed without dietary restrictions. There was no indication that rasagiline, at clinical doses of 0.5 to 1 mg, is non-selective. The purpose of this tyramine challenge study was to confirm the selectivity of rasagiline for MAO-B.

Relevant Regulatory History

Rasagiline is a monoamine oxidase (MAO) inhibitor (MAOI), that the sponsor has purported as being selective for MAO B. The sponsor had submitted an NDA for approval for treatment of early and advanced Parkinson's Disease. After several review cycles, rasagiline (AZILECT; NDA 21641) was approved in 5/06. However, because the sponsor had not provide adequate documentation of the selectivity for rasagiline for inhibiting solely MAO-B and not also MAO-A, rasagiline was approved as a non-selective MAO-B inhibitor requiring dietary tyramine restrictions. One of several Phase 4 commitments was for the sponsor to conduct an adequate tyramine challenge study characterizing the tyramine sensitivity after rasagiline treatment. The DNP gave the sponsor specific, detailed recommendations for conducting an adequate tyramine challenge study at the time of rasagiline approval and also subsequently provided the sponsor with detailed feedback for conducting this study and also for analyzing the study and presenting results. The present submission provides results for the final study report for study TVP-1012-120-TYR.

3. STUDY TVP-1012-120-TYR RESULTS

3.1 Study Description (Study Design and Details)

STUDY OBJECTIVES

Primary

To assess tyramine sensitivity when administered with rasagiline, and the selectivity of rasagiline for MAO-B.

Secondary

To investigate orthostatic BP and pulse timed to rasagiline dosing.

INVESTIGATIONAL PLAN

Overall Study Design and Plan

Type of study

This was a double-blind, placebo-controlled, randomized, positive control, comparator, multiple dose study in 7 groups. The positive control group (Group 1) included 16 subjects, all receiving active drug as open label. The other groups were to include 24 subjects, 16 subjects on active drug treatment and 8 subjects on placebo in each group.

Each group had 3 treatment periods. All subjects were enrolled in Period 1 (Days 1-10) to determine baseline tyramine sensitivity (tyramine threshold). Subjects were selected based on their response to tyramine challenge without concomitant receipt of the test drug. Subjects experiencing significant elevation of BP, defined as an increase in SBP of $\geq$ 30 mmHg for 3 consecutive measurements in a 10 minute or more period [thereafter referred to as .the predefined target elevation in SBP.], were randomized to receive treatment in Period 2 (active drug or placebo) and in Period 3 (tyramine challenge in the presence of active drug or placebo).

The study was executed in 2 steps.
Step 1: Subjects in Period 2 received 2 mg rasagiline or placebo for 14 days (Group 4a), or for 30 days (Group 4b).
Step 2: Subjects in Period 2 received phenelzine 15 mg t.i.d., selegiline 5 mg b.i.d. or placebo, or rasagiline 1 mg, 4 mg, 6 mg q.d. or placebo for 14 days.

Screening and pre-study

Subjects reported to the medical screening facility in Zuidlaren for the eligibility screening within 4 weeks prior to the first drug administration of the study. Eligibility screening consisted of full physical examination, body temperature, AEs, previous and concomitant medication, vital signs and orthostatic BP, 12-lead ECG, medical history, bicycle exercise test, serology, alcohol and drug screen, cotinine test and pregnancy test (females only). A blood and a urine sample were taken for routine hematology and clinical chemistry tests.

Treatment period

Subjects arrived at the clinic at approximately 15:00 h on the afternoon preceding the day

of the first drug administration (Day 1) and they ultimately left the clinic no later than Day 36, or Day 52 (Group 4b only), i.e., no sooner than 24 hours following the last drug administration of tyramine that caused the predefined target elevation in SBP in Period 3. Subjects who did not reach the predefined target elevation in SBP during Period 1 were confined until at least 4 hours after their last tyramine dose on Day 10.

In Period 1 the subjects left the clinic approximately 24 h after last tyramine administration that caused the predefined target elevation in SBP and returned for the start of Period 2 on the day before first drug administration in Period 2 (Day 11, Groups 1 [phenelzine], 2 [selegiline], 5 [4 mg rasagiline] and 6 [6 mg rasagiline]). Subjects in Groups 3 and 4 (1 mg rasagiline and 2 mg rasagiline, respectively, once daily (o.d.) during Days 11-35 in Groups 3 and 4a, Days 11-51 in Group 4b) were ambulatory, i.e., not confined in the clinical research unit, from the start of Period 2 (Day 11) until the evening of Day 22 (Groups 3 and 4a), or Day 38 (Group 4b). During this period, dosing was at home or at a site close to home, in a staggered fashion, and always in the presence of a single authorized (by Sponsor or [redacted] independent witness who also documented the dosing. In the morning of Day 11, subjects visited the clinical research centre to receive a randomization number, take the first dose of rasagiline and receive the medication for dosing at home or at a site close to home. b(4)

On Day 25 of Period 2, a telephone interview was conducted with subjects in Group 4b. Subjects were asked about their health status, AEs, use of any medication, any visit to healthcare facilities and/or physician since Day 11. A summary of this telephone interview was documented in the source documents.

Upon first admission (Day -1), clinical laboratory and the pregnancy test were repeated from screening. Upon first admission (Day -1) and on Day 11 (Groups 1, 2, 5 and 6), Day 22 (Groups 3 and 4a) and Day 38 (Group 4b), drug and alcohol screen and a cotinine test were repeated from screening.

For Groups 3, 4a and 4b the pregnancy test (females only) was also repeated upon admission in Period 2 (Day 22 for Groups 3 and 4a, Day 38 for Group 4b). The occurrence of baseline complaints/AEs and the use of concomitant medication were checked and recorded.

Orthostatic BP measurements and pulse rate were measured on Day -1 for Groups 3, 4a and 4b, 5 and 6; the test was repeated 3 times within approximately 10-20 minute intervals between each measurement. The average of the readings served as the integrated baseline/pre-treatment value for comparison to post-treatment values.

During the study, orthostatic BP, vital signs and 12-lead ECGs were recorded at regular intervals. Continuous ECG monitoring was performed on each day of tyramine administration. Blood samples for pharmacodynamics (PD; DHPG) and PK (rasagiline and tyramine) were taken at regular intervals. AEs and concomitant medication were recorded throughout the study. Clinical laboratory and pregnancy test (females only) were

performed at discharge in Period 1. Physical examination was performed at final discharge.

Follow-up
The follow-up medical examination was performed following the last drug administration, before subject discharge (Day 36 or before in Groups 1-3, 4a, 5 and 6; Day 52 or before in Group 4b). In case of early withdrawal of a subject in Period 1, Period 2, or Period 3, a complete follow-up medical examination was performed upon discharge, if possible. If not possible (e.g. the subject was at home at the time of withdrawal), an appointment for follow-up was to be made as soon as possible. In case of early withdrawal of a subject in Period 1, the daily telephone interviews 7 days following the last drug administration were not conducted. Follow-up medical examination consisted of: full physical examination, body temperature, vital signs, orthostatic BP, 12-lead ECG, clinical laboratory tests, recording of concomitant medications and AE monitoring.

Daily telephone interviews were conducted with all subjects for 7 days following the last drug administration. Subjects were asked about their health status, use of any medication, any visit to healthcare facilities and/or physician since the last drug administration. Summaries of the telephone interviews were documented.

See also the summary of clinical procedures and assessments in Table 6.

Table 6 Schedule of Assessments

Visit	Assessment Period						
	Screening	Admission	Period 1	Period 2	Period 3	Discharge (Follow-up)	Follow-up
Study Day	-28 to -1	-1	1-10	11-24 or 11-40 (Group 4b)	25-35 or 41-51 (Group 4b)	24 h after last tyramine dose	36-42 or 52-58 (Group 4b)
Confinement[1]		X	X	X	X	X	
Outpatient[1]	X			X (Groups 3 and 4)		X	
Informed consent and medical history	X						
Demographics	X						
Physical examination	X					X	X
Body temperature	X					X	
Vital signs[2]	X		X	X	X	X	
Orthostatic BP[3]	X	X		X		X	
Inclusion/exclusion criteria	X						
ECG (12-lead)[4]	X		X		X	X	
ECG (3-lead)[5]			X		X		
Bicycle test	X						
Clinical laboratory	X	X	X (Discharge)			X	
Urine drug, cotinine and alcohol screen[6]	X	X		X (Day 11, Day 22 or Day 38[11])			
HBsAg, HCV and HIV tests	X						
Pregnancy test (females only)	X	X	X (Discharge)	X[12]			X
Study drug administration tyramine[7]			X		X		
Study drug administration[8]				X	X		
Previous and concomitant medication	X	X	X	X	X	X	X
PK sampling blood tyramine[9]			X (Days 3-10)		X		
PK sampling blood rasagiline[10]				X (Day 23 or 39)			
PD sampling blood DHPG[11]			X (Day 1)	X (Day 24 or 40)			
AEs	X	X	X	X	X	X	
Telephone follow-up for AEs				X (G4b only, Day 25)			X

Footnotes are on the next page.

1 Groups 3 and 4 confined from evening of Day 22, or Day 38 (Group 4b only), onwards; discharge ultimately Day 36, or Day 52 (Group 4b only); ambulatory visit on Day 11 for Groups 3 and 4

2 Vital signs: During Periods 1 and 3: Supine BP and HR approximately every 5 minutes during the 35 minutes preceding administration of tyramine. From 5 minutes after tyramine administration, SBP and HR approximately every 5 minutes for at least 2 hours and approximately every 15 minutes for an additional 2 hours. In case of significant BP elevations, HR reduction, or AEs suggestive of a clinically significant tyramine reaction SBP and HR approximately every 5 minutes until the SBP was decreased to less than 30 mmHg above baseline for 3 consecutive readings, or until the HR returned to baseline, or AE was resolved, respectively. Then the usual vital signs monitoring protocol was followed again. Subjects that did not achieve tyramine potentiation on Day 10 of Period 1 had an additional 2 hours of supine BP and HR measurements performed every 15 minutes (applicable only for part of Group 1 and Groups 3, 5 and 6).
During Period 2: SBP and HR every day before rasagiline, phenelzine, selegiline or placebo administration and approximately 1 and 2 hours post-dose on Days 11-24 (11-40 for Group 4b), except Groups 3, 4a and 4b when ambulatory

3 Orthostatic BP measurements and pulse rate after at least 5 minutes in supine position and after 2 minutes in standing position. Part of Group 1 and Groups 3, 4a and 4b, 5 and 6 on Day -1; the test was repeated 3 times within approximately 10-20 minute intervals between each measurement. For Group 4a on Day 23 and for Group 4b on Day 39 the test was repeated 3 times within approximately 10-20 minute intervals between each measurement before dosing and one test at approximately 0.25, 0.5, 0.75, 1, 1.5, 3 and 4 hours post-dose rasagiline administration. For part of Group 1 and Groups 3, 5 and 6 on Day 23 the test was repeated 3 times within approximately 10-20 minute intervals between each measurement before dosing and one test at approximately 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 5, 8, 12, 16 and 24 hours after drug administration

4 12-lead ECG: at screening, before tyramine administration and 0.5, 1, 2, and 4 h thereafter on each day of tyramine administration and at final discharge

5 Continuous ECG: from 0.5 h before tyramine administration until 4 h thereafter on each day of tyramine administration, by alarm, according to manufacturer's specifications and PRA SOPs

6 Drug and alcohol screen and cotinine test at screening, upon first admission and on Day 11 (Groups 1, 2, 5 and 6), Day 22 (Groups 3 and 4a) and Day 38 (Group 4b)

7 Period 1: increasing doses of tyramine (levels 25, 50, 100, 200, 300, 400, 500, 600, 700 and 800 mg); Period 3: Group 1 increasing doses of tyramine (levels 5, 15, 25, 35, 45, 55, 65, 75, 85, 95 and 105 mg); Period 3 Groups 2-6: tyramine (levels 12.5, 25, 50, 100, 200, 300, 400, 500, 600, 700 and 800 mg)

8 Phenelzine (Group 1), selegiline (Group 2), rasagiline (Groups 3-6) or placebo (Groups 2-6)

9 Pre-dose (within 60 minutes before tyramine administration), 5, 15, 30 and 60 (Part of Group 1 and Groups 3, 5 and 6 only) min after tyramine administration starting on Day 3 until last administration of tyramine (Period 1); pre-dose (within 60 minutes before tyramine administration), 35, 45, 60 and 90 (Part of Group 1 and Groups 3, 5 and 6 only) min after first tyramine dosing in Period 3 until last administration of tyramine

10 Pre-dose and 15, 30, 45 min and 1, 1.5, 3, 4 h after rasagiline administration (Group 4a: Day 23, Group 4b: Day 39); pre-dose and 15, 30, 45 min and 1, 1.5, 2, 3, 5, 8, 12, 16 and 24 h after rasagiline administration (Groups 3, 5 and 6: Day 23)

11 Before and 2 hours after tyramine administration on Day 1, and 0.5 and 2.5 hours after drug administration on Day 24 or Day 40; samples to be taken at the same time of day on Days 1 and 24 / 40

12 Pregnancy test upon admission on Day 22 (Groups 3 and 4a) or Day 38 (Group 4b)

Discussion of Study Design

This study was intended to provide additional data on the potential interaction between rasagiline and tyramine. A comparison was made between the effect on SBP of escalating doses of tyramine at baseline and after achieving a steady state of plasma rasagiline. In Period 1, all subjects received ascending dose levels of tyramine up to 800 mg (tyramine challenge). Subjects who did not present an increase in SBP of $\geq$ 30 mmHg for 3 consecutive measurements in a 10 minute or more period were excluded from participation in the remainder of the study.

Step 1 of the protocol (Groups 4a and 4b, 2 mg rasagiline once daily during 14 and 30 days, respectively) was executed first, in order to assess whether an interaction between rasagiline and tyramine, if any, is dependent on prolonged (over 14 days) rasagiline dosing. Based on previous studies, a steady state PD effect of rasagiline was expected to have been reached by 14 days of dosing, and a difference was not expected between 14 and 30 days of dosing. Therefore, in the current study, the interaction between tyramine and rasagiline, if any, was assessed after 14 days of dosing at 2 mg rasagiline once daily in Group 4a, and compared to the interaction between tyramine and rasagiline, if any, after 30 days of dosing at 2 mg rasagiline once daily in Group 4b.

Following the start of Step 1, Step 2 proceeded in slight parallel to Step 1, with 14 days dosing of rasagiline, phenelzine and selegiline. In the blinded evaluation of Step 1, all relevant safety, tolerability, PK and PD observations were taken into account in a comprehensive approach, with the tyramine interaction data as the primary factor. Based on this, it was decided that unblinding was not necessary and no interim analysis would be performed.

Phenelzine was administered to Group 1 as a positive control for tyramine interaction. Selegiline was administered for comparison with rasagiline. Placebo controls were added to assist the medical assessment whether or not any abnormalities observed were related to the study medication or to study procedures, and not for a formal comparison between active drug and placebo. The study was performed in different groups of subjects since the number of doses to be tested, and all assessments associated with these sessions, were too extensive to be performed in a single group of repeatedly participating subjects.

Selection of Study Population

In total, 160 subjects were to be enrolled in Period 2. The subjects were healthy males or females, at least 85% non-smokers, at most 15% smokers (smoking was allowed up to 10 cigarettes/day until screening; no smoking during the study); up to 3 subjects who were smokers were allowed per treatment group. A non-smoker was defined as someone who stopped smoking at least 6 months prior to Day 1 of the study. All groups were to include at least 40% subjects of each gender.

Key Inclusion Criteria

Subjects were eligible for the study if they met all the following inclusion criteria:

- Gender : male or female;

- Age : between 40 and 70 years of age, inclusive;
- Body Mass Index (BMI) : 19.0 . 30.0 kg/m2;

Exclusion Criteria

Subjects were excluded from participation if any of the following exclusion criteria applied:

- Clinically significant illnesses, as judged by the Medical Investigator, within 8 weeks prior to the first administration of tyramine.
- Abnormal laboratory tests judged clinically significant.
- The mean of 3 consecutive supine SBP and diastolic BP (DBP) readings taken within 10 minutes exceeded 140 mm Hg and 90 mmHg, respectively, and/or was not stable (supine SBP exceeded a maximum range of 10 mmHg between the lowest and highest value
- History of significant alcohol abuse or drug abuse within 1 year prior to the screening visit.
- Regular use of alcohol within 6 months prior to the screening visit (more than 24 units of alcohol per week [1 unit=150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol]).
- Use of any drugs known to induce or inhibit hepatic drug metabolism (examples of inducers: barbiturates, carbamazepine, phenytoin, glucocorticoids, omeprazole, crisrofulvin; examples of inhibitors: cimetidine, ciprofloxacin, fluvoxamine, furafylline, methozsalen, diltiazem, macrolides, imidazoles, neuroleptics, verapamil, fluoroquinolones, antihistamines) within 30 days prior to the first administration of tyramine.
- Use of an investigational drug with unknown mechanism of action/unknown half-life or participation in an investigational first-in-man study within 90 days prior to the first administration of tyramine, or participation in any other investigational study within 60 days or 5 half-lives of the investigational study drug, whichever is longer, prior to the first administration of tyramine.
- Use of prescription medication within 14 days prior to the first administration of tyramine or over-the-counter products within 7 days prior to the first administration of tyramine, especially sympathomimetics (including cold remedies - nasal or oral, natural food supplements, vitamins, garlic as a supplement, dextromethorphan, pethidine, St. John's Wort and gentamicin) and except for topical products without systemic absorption or hormonal contraceptives.
- Use of grapefruit products (e.g., fresh, canned, or frozen) within 7 days prior to Period 1.
- Known adverse reactions associated with ingestion of tyramine-containing food.
- History of orthostatic hypotension (and/or SBP decrease of ≥20 mmHg 2 minutes after standing, compared to supine SBP).
- Use of tricyclic antidepressants, selective serotonin re-uptake inhibitors (SSRIs), and selective norepinephrine re-uptake inhibitors (SNRIs; applicable for Groups 1A, 3, 5, 6 only that were included after approval of Protocol Amendment No. 3) within 14 days preceding the first administration of tyramine, MAO inhibitors (MAOIs) within 90 days preceding the first administration of tyramine, and fluoxetine within 5 weeks

preceding the first administration of tyramine.
- Requirement for any medication contraindicated for use with a MAOI.

Treatments
Treatments Administered
The following treatments were administered:
Period 1, all groups
All subjects received escalating doses of tyramine in Period 1, i.e., on Days 1-10.
Tyramine was administered under fasting conditions to each subject with 240 mL of water. Tablets were ingested within 5 minutes.
Tyramine was administered as presented in Table 1.

Table 1 Administration of Tyramine in Period 1

Day	1	2	3	4	5	6	7	8	9	10
Total dose (mg)	25	50	100	200	300	400	500	600	700	800
No. of units x strength (mg)	1x25	2x25	1x100	2x100	3x100	4x100	5x100	6x100	7x100	8x100

When the predefined target elevation in SBP was reached, tyramine dosing was terminated. Subjects who did not meet the predefined elevation in SBP within 4 hours after their last, highest tyramine dose on Day 10 were released from the study.

Subjects who met the predefined target elevation in SBP were administered the following treatments, according to the randomization schedule (randomization to active drug or placebo within groups only).

Period 2, Groups 1, 2, 3, 5 and 6
Subjects in Group 1 received 15 mg phenelzine three times a day (t.i.d.; after gradual titration of dose), for 14 consecutive days in Period 2 (Days 11-24). Phenelzine was administered to each subject of Group 1 with 240 mL of water, t.i.d. and at the same time every day, except for Days 11, 12 and 13, when only one or two doses was administered (o.d. dosing of 15 mg phenelzine on Day 11, twice a day (b.i.d.) dosing of 15 mg phenelzine on Days 12 and 13).

Subjects in Group 2 received 5 mg selegiline b.i.d., for 14 consecutive days in Period 2 (Days 11-24). Selegiline or placebo was administered with 240 mL water, in the morning (AM dosing) and 12 hours later (PM dosing), at the same time every day.
Dosing in Period 2 was as follows for Groups 3, 5 and 6:
Group 3: 1 mg rasagiline or placebo, o.d. for 14 days (Days 11-24)
Group 5: 4 mg rasagiline or placebo, o.d. for 14 days (Days 11-24)
Group 6: 6 mg rasagiline or placebo, o.d. for 14 days (Days 11-24)
Rasagiline or placebo tablets were administered to each subject with 240 mL of water, o.d., and at the same time every morning.

Period 2, Group 4
Subjects in Group 4a were randomized to receive 2 mg rasagiline or placebo o.d. for 14 days in Period 2 (Days 11-24); subjects in Group 4b were randomized to receive 2 mg rasagiline or placebo o.d. for 30 days in Period 2 (Days 11-40). Rasagiline or placebo tablets were administered with 240 mL of water, o.d., and at the same time of day every morning.

Period 3, Groups 1, 2, 3, 4a, 4b, 5 and 6
In Period 3, Days 25-35 (Groups 1 to 3, 4a, 5 and 6) or Days 41-51 (Group 4b), subjects received the same treatment as they received in Period 2, co-administered with escalating doses of tyramine, starting from 12.5 mg (see schedule below, except Group 1 starting from 5 mg), until the predefined target elevation in SBP was obtained.
For Group 1, tyramine was administered in Period 3 as presented in Table 2. For Groups 2 to 6, tyramine was administered in Period 3 as presented in Table 3.

Table 2 Administration of Tyramine in Period 3, Group 1

Day	25	26	27	28	29	30	31	32	33	34	35
Total dose (mg)	5	15	25	35	45	55	65	75	85	95	105
No. of Units x strength (mg)	1x5	3x5	1x25	1x25 + 2x5	1x25 + 4x5	2x25 + 1x5	2x25 + 3x5	3x25	3x25 + 2x5	3x25 + 4x5	1x100 +1x5

Table 3 Administration of Tyramine in Period 3, Groups 2 to 6

Day	25	26	27	28	29	30	31	32	33	34	35
Day *	41	42	43	44	45	46	47	48	49	50	51
Total dose (mg)	12.5	25	50	100	200	300	400	500	600	700	800
No. of Units x strength (mg)	1x 12.5	1x 25	2x 25	1x 100	2x 100	3x 100	4x 100	5x 100	6x 100	7x 100	8x 100

* for Group 4b only

In Period 3, phenelzine was administered to each subject of Group 1 with 240 mL of water, t.i.d. and at the same time every day.

To each subject of Group 2, selegiline or placebo was administered with 240 mL water, in the morning (AM dosing) and 12 hours later (PM dosing), at the same time every day.
To each subject of Groups 3 to 6, rasagiline or placebo tablets were administered with 240 mL of water, at the same time every morning.

Tyramine was administered to each subject with 240 mL of water, 30 minutes following the daily morning dose of phenelzine, selegiline, rasagiline or placebo, in escalating doses over Days 25-35 (Days 41-51 in Group 4b) until the predefined target elevation in SBP was observed. Tablets were ingested within 5 minutes.

Administration of the medication was supervised by the Investigator or his/her deputy. After drug administration, a mouth and hand inspection took place.

Physical activity
In Periods 1 and 3, for safety reasons and due to procedural requirements, subjects were required to remain supine and completely at rest (unless activity was medically necessary, procedurally required, or subject needed to go to the bathroom) from 30 minutes prior to tyramine administration until 4 hours post-dose. All ambulant activity, except for scheduled procedures, was documented in source documents. Subjects were accompanied by a staff member during ambulant activity.

On Day 23 (Day 39 in Group 4b), i.e., PK sampling days, subjects of Groups 2 to 6 were engaged in normal activity and avoided lying down or sleeping, unless medically necessary or procedurally required, for 4 hours after rasagiline/placebo administration. Vigorous activity was prohibited at all times during the confinement.

Daily outings were allowed during confinement. Subjects were under supervision while outside the clinic.

Selection and Timing of Dose for Each Subject
Timing of Doses for Each Subject in Relation to Meals and Snacks
In Period 1, Days 1-10, and in Period 3, Days 25-35 or Days 41-51 (Group 4b), no food was allowed from at least 10 hours before tyramine administration and until at least 4 hours post-tyramine dose. The last evening snack or light supper on the days before was consumed before 22:00 hours. Medication was administered between 08:00 and 11:00 h, and lunch was consumed at least 4 hours after dosing.

During Period 2, breakfast could be consumed starting 30 minutes after drug intake. Except for water given with medications, no fluids were allowed from 1 hour before every dosing occasion until 1 hour post-dose. In cases where the administration of rasagiline, phenelzine, selegiline or placebo was followed by the administration of tyramine 30 minutes later (i.e., every morning of Period 3), no fluids were allowed from 1 hour before rasagiline, phenelzine, selegiline or placebo dosing until 1 hour after tyramine dosing. Water was provided ad libitum at all other times.

Meals During the Study
Meals were served by the clinical facility while subjects were confined, and subjects were given dietary instructions, and instructed to avoid intake of tyramine-rich foods and drinks, when entering ambulatory days. For the duration of the entire study, all meals had low tyramine content according to the recommended low tyramine diet (i.e., avoid tyramine-rich foods and beverages).

Standardized meals, with calculated caloric content, were provided during hospitalization on Day 23 (Day 39 in Group 4b), i.e., on PK sampling days. In the event such standard meals were provided, food that was not eaten was documented in the source documents.

On all other study days, when subjects were confined, meals were provided according to standard practice of the institute, without documentation in the source documents or CRF. A light supper was provided on the evening before those days where fasting was required until lunch time.

Snacks (such as decaffeinated coffee, herbal tea, fruit, biscuits) were provided during every morning (except in Periods 1 and 3), afternoon and evening.
An example of the daily menu during the study was provided for review by the Sponsor, and was documented in the site file.

Blinding
Period 1 was open-label. All subjects were administered tyramine according to the study design. Only subjects experiencing the predefined target elevation in SBP were assigned a 3-digit study number and were randomized according to the randomization scheme. Group 1 included 16 subjects, all receiving active drug. Groups 2-6 included 24 subjects each with 2:1 ratio of active dose vs. placebo.

Periods 2 and 3 were blinded for active drug and placebo within each group (Groups 2-6). Subjects in Group 1 were administered the positive control phenelzine. Subjects in Group 2 were administered either selegiline or matching placebo according to the randomization scheme, and both subjects and clinical personnel were blinded regarding whether subjects received selegiline or its placebo. Subjects in Groups 3 to 6 were administered either rasagiline or matching placebo according to the randomization scheme and both subjects and clinical personnel were blinded regarding whether they receive rasagiline or its placebo. All subjects were administered tyramine according to the study design, in an open-label fashion. The block randomization scheme was produced by the Sponsor.

Prior and Concomitant Therapy and Other Restrictions During Study
No concomitant drug therapy was allowed during the study except one(s) used due to an AE. Any concomitant medication use, other than hormonal contraceptives, was evaluated on a case-by case basis by the Sponsor. In the event medication was used, the name of the drug, the dose and dosage regimen were to be recorded in the CRF.

The use of food or beverages containing xanthine derivatives or xanthine-related compounds (e.g., coffee, caffeine-containing sodas, tea, cola, chocolate, or caffeinated products), energy drinks or alcohol was not allowed from 48 hours (2 days) prior to Period 1 until after the end of Period 3.

The use of cold medication (ephedrine, pseudoephedrine) was not allowed from 7 days prior to Period 1 until after the end of Period 3.

The use of vitamins and any food supplements (including garlic as a supplement, St. John.s wort) was not allowed from 7 days prior to Period 1 until after the end of Period 3.

The use of grapefruit products (e.g., fresh, canned, or frozen) was not allowed from 7 days prior to Period 1 until after the end of Period 3.

The use of charbroiled-grilled meat and vegetables such as broccoli and Brussels sprouts was not allowed during the entire study as these could be inducers of CYP1A2.

Strenuous activity was not allowed from 48 hours (2 days) prior to Period 1 until after the end of Period 3.

Subjects were advised that they were not allowed to take MAOI for 90 days before Period 1 and until 14 days after the last drug administration.

Smoking was not allowed during the study from the first screening visit until the last follow-up visit.

Consumption of foods or beverages with a high concentration of tyramine or dopamine was not allowed for 48 hours prior to Period 1 and until 14 days after the last drug (phenelzine, rasagiline, selegiline or placebo) administration. Foods and beverages to be avoided are listed in an Appendix.

Female subjects of childbearing potential who had sexual intercourse with a non-sterile male partner, were required to use an acceptable method of contraception prior to Period 1 until 7 days following the end of Period 3. The accepted methods of contraception are listed under section .exclusion criteria..

Subjects who completed the study according to protocol were advised that they should not participate in other studies at least 60 days after termination.

Endpoint Variables

Description of Study Days
An assessments flow chart is presented in Table 6.

Blood Samples for Tyramine
From Day 3 until the last day of tyramine administration of Period 1 and from Day 25 or Day 41 (Group 4b) until the last day of tyramine administration of Period 3, blood samples were collected before tyramine administration and at the time points indicated in Table 6. Blood sampling was done using butterfly needles (or via iv cannula when present). Each blood sample was 5 mL. Blood was collected in chilled NaEDTA tubes kept on ice. To separate the plasma, the samples were centrifuged for 10 minutes at 2000 g, at 4°C, as soon as possible after collection, but starting within 30 minutes from collection. Plasma was stored in 2 polypropylene tubes, each containing at least 1 mL. Plasma samples were stored at -70°C or below until analysis. At [redacted] samples were stored in a freezer at -75°C ± 10°C. These samples were analyzed to determine tyramine plasma concentrations. b(4)

Blood Samples for Rasagiline
Blood samples were collected on Day 23 (Group 4a) or Day 39 (Group 4b), before rasagiline or placebo administration and 15, 30, 45 minutes and 1, 1.5, 3 and 4 hours post-dose. These time points were chosen given the rapid absorption of rasagiline, and the terminal elimination half-life for rasagiline at clinical doses being in the order of 0.6-2h. Following recommendations of the FDA that were incorporated through Protocol Amendment No. 3, for Groups 3, 5 and 6 blood samples were collected on Day 23, before rasagiline or placebo administration and 15, 30, 45 minutes and 1, 1.5, 2, 3, 5, 8, 12, 16 and 24 h post-dose. (A longer collection period for the higher doses was considered necessary since preliminary data suggested that the terminal elimination halflife increased to approximately 6-7 h at 6 mg.) Blood samples were collected via an iv cannula. If applicable, appropriate procedures were followed to assure that the blood sample collected was not contaminated with the saline (or heparin) that was used to prevent blockage of the catheter.

Each blood sample was 6 mL. Blood was collected in chilled lithium heparin tubes and centrifuged for 10 minutes at 2000 g, at 4°C, as soon as possible after collection, but starting within 30 minutes from collection. Plasma was stored in 2 polypropylene tubes, each containing at least 1.2 mL. Plasma samples were stored at -70°C. During the process, care was taken to ensure that blood and plasma were not unnecessarily exposed to direct light. At [redacted] samples were stored in a freezer at -24°C ± 6°C. These samples were analyzed to determine rasagiline and 1-AI plasma concentrations. b(4)

Blood Samples for DHPG
On Day 1, 2 blood samples for determination of DHPG as a measure of MAO-A activity were collected, one before and one 2 hours after tyramine administration. On Day 24 or Day 40 (Group 4b), blood samples were collected 0.5 and 2.5 h after the rasagiline, phenelzine, selegiline or placebo administration. On both sampling days, the blood draws were made at the same time of the day.

Each blood sample was 5 mL. Blood was collected in chilled EDTA tubes. Immediately after manual agitation, the blood was spiked with 100 µL of a sodium metabisulfite solution (15% in water). Tubes were put on ice immediately. Blood was centrifuged for 10 minutes at 2000 g, at 4°C, as soon as possible after collection, but starting within 30 minutes from collection. Plasma was stored in 2 polypropylene tubes, each containing at least 1.1 mL. Plasma samples were stored at -70°C. At [redacted] samples were stored in a freezer at -75°C ± 10°C. These samples were analyzed to determine DHPG plasma concentrations. b(4)

Blood Sampling - General
The exact date and time of each blood sample collected was recorded. When blood draws and vital signs coincided, blood draws were performed as soon as possible after the scheduled vital signs.

Safety and Tolerability Measurements

Safety and tolerability assessments consisted of AEs, vital signs, ECG, clinical laboratory and physical examination. Assessments were performed in accordance with the assessments flow chart presented in Table 6.

Adverse Events
Just before drug administration and throughout the entire study, subjects were asked non-leading questions to determine the occurrence of AEs. Subjects were asked in general terms about any AEs at regular intervals during each study period. In addition, all AEs reported spontaneously during the course of the study were recorded. For Group 4b on Day 25, the subjects were called at home for AE monitoring and concomitant medications.

All answers were interpreted by the Investigator, using the Medical dictionary for Regulatory Activities Terminology (MedDRA; Version 10.1) for AEs and were recorded in the AEs Record.

ECG
3-lead continuous ECG was monitored (by alarm, according to manufacturer's specifications and — SOPs) from 30 minutes before until 4 hours after administration of tyramine on Days 1-10 and 25-35 or 41-51 (Group 4b only). b(4)

A standard supine 12-lead ECG was performed before and at regular intervals during the first 4 hours after each administration of tyramine on Days 1-10 and 25-35 or 41-51 (Group 4b). The following ECG parameters were recorded: heart rate (HR), PR-interval, QRS-duration, QT-interval, QTc-interval and Medical Investigator's conclusion on ECG profile.

If ECG and vital signs measurement times coincided, ECG was performed prior to the scheduled vital signs, for practical reasons relating to the measurement of supine and standing BP. If deemed necessary by the Investigator, additional ECGs could be performed.

Vital Signs
In Periods 1 and 3:
Supine BP and HR were measured approximately every 5 minutes during the 35 minutes preceding administration of tyramine. Once SBP was stable (3 consecutive readings with a maximum range of 10 mmHg between the lowest and highest values), the mean of these 3 readings was taken as the pre-tyramine baseline value and further readings before administration of tyramine were not performed. If this criterion was not reached within the 35 minutes, the mean of all 7 readings were taken as the baseline value.

If the average baseline BP was too high (SBP $\geq$ 140 mmHg), the baseline could be repeated after 1 hour. If it was still too high, no tyramine was to be dosed on that day and the measurement was to be repeated the next day. If more than 2 dosing occasions were skipped this way, the subject had to be withdrawn from the study.

Beginning 5 minutes after tyramine administration, supine BP and HR were measured approximately every 5 minutes for at least 2 hours and then approximately every 15 minutes for an additional 2 hours. Subjects that did not achieve tyramine potentiation on Day 10 of Period 1 had an additional 2 hours of supine BP and HR measurements performed every 15 minutes.

Subjects who experienced at any time during the active monitoring period significant elevation of BP, defined as an increase from baseline in SBP of $\geq$ 30 mmHg maintained for at least 3 consecutive measurements in a period of 10 minutes or more, had reached the tyramine threshold dose. The dose escalation of tyramine and administration of rasagiline, phenelzine, selegiline or matching placebo was terminated.

Subjects that reached the tyramine threshold dose on Day 1 of Period 1 (25 mg tyramine) were withdrawn from the study out of a safety point of view.

Subjects who experienced significant BP elevations (increase in SBP of $\geq$ 30 mmHg for 3 consecutive measurements in a 10 minute or more period), HR reduction (bradycardia with HR $\leq$ 40 bpm lasting for 10 minutes or more), or AEs that were suggestive of a clinically significant tyramine reaction in the opinion of the Investigator at any time during the active monitoring period had SBP and HR measured approximately every 5 minutes until the SBP had decreased to less than 30 mmHg above baseline for 3 consecutive readings, or until HR returned to baseline or AE was resolved, respectively. Then the usual vital signs monitoring protocol was followed again.

Only if a significant BP elevation took place during the 15-minute interval monitoring period (i.e., 2-4 h post-tyramine administration), the vital signs measurements were measured every 30 minutes for 2 additional hours (i.e., 4-6 h post-tyramine administration). This was not done if the significant BP elevation took place during the 5-minute interval monitoring period (i.e., the first 2 h post-tyramine administration).

The above mentioned is elaborated for specific cases in the following table:

Orthostatic hypotension was measured for Groups 3, 4a, 5 and 6 on Day 23 and for Group 4b on Day 39 at the time points indicated in the flow chart (Table 6, time points paralleling the PK measurements).

Unless otherwise specified or for subject safety, when vital signs measurements and other procedures coincided, vital signs measurements had precedence and other scheduled activities followed within 5 minutes. The maximum SBP, HR and threshold systolic blood pressure (TSBP) were recorded when observed.

A vital signs measurement had to be repeated at least once under the following conditions: 1) scheduled SBP measurement lower than 90 mmHg, or equal or higher than 160 mmHg; 2) scheduled DBP measurement lower than 40 mmHg, or equal or higher than 90 mmHg; 3) scheduled HR measurement lower than 35 bpm, or equal or higher than 120 bpm; or 4) upon physician's request. The physician had to be notified of all repeated vital sign measurements that were still outside the normal range values mentioned above to evaluate the significance of the results and decide further action if needed.

Physical examination was performed according to SOPs at — b(4)

Clinical Laboratory testing consisting of Hematology, biochemistry, urinalysis and urine pregnancy test (for all female subjects of childbearing potential) were performed during screening, on Day -1 (i.e., before first tyramine administration), at discharge in Period 1 (i.e., before rasagiline, phenelzine, selegiline or placebo administration) and at final discharge. For Groups 3, 4a and 4b, the pregnancy test was also repeated upon admission after the ambulatory part of Period 2.

Urine samples for drug and alcohol screen and the assessment of cotinine were collected at screening, upon first admission and on Day 11 (Groups 1, 2, 5 and 6), Day 22 (Groups 3 and 4a) and Day 38 (Group 4b).

Bicycle exercise test
The bicycle exercise test at screening was performed according to — SOP. During the bicycle exercise test vital signs were measured at different time points at different work loads. Only the last BP measurement at the maximum work load (Wmax) was recorded in the CRF. All vital signs during the bicycle exercise test were measured by hand and not with an automated device, as was used for all other vital sign measurements during the study. Therefore these values were only valid for this test and not used for any other assessments or exclusion criteria. b(4)

Exercise testing was performed using a Marquette . Hellige EC-1200 (Tunturi) exercise bicycle.

During the screening period, the subjects performed a bicycle exercise test to determine the Wmax, using a modified Bruce protocol. The work load was increased until the subject indicated that he/she was exhausted and had reached at least 85% of the theoretical

Table 5 Measurement of Vital Signs in Case of Significant BP Elevation

IF a significant BP elevation* took place	THEN
AND was resolved** within the 5-minute interval monitoring period (1-2 hours after tyramine administration)	vital signs were measured every 15 minutes, 2-4 hours after tyramine administration. No additional 2 hours were measured
at the end of the 5-minute interval monitoring period (first 2 hours after tyramine administration)	vital signs were continued to be measured every 5 minutes until the significant BP elevation had resolved. Vital signs were then measured every 15 minutes, 2-4 hours after tyramine administration. No additional 2 hours were measured.
AND was resolved within the 15-minute interval monitoring period (2-4 hours after tyramine administration)	vital signs were measured every 15 minutes, 2-4 hours after tyramine administration. Vital signs were then measured every 30 minutes for an additional 2 hours (4-6 hours after tyramine administration).
at the end of the 15-minute interval monitoring period (2-4 hours after tyramine administration)	vital signs were measured every 5 minutes until the significant BP elevation had resolved. Vital signs were then measured every 30 minutes for an additional 2 hours (4-6 hours after tyramine administration)
and was NOT resolved within the 15-minute interval monitoring period (2-4 hours after tyramine administration)	vital signs were measured every 5 minutes until the significant BP elevation had resolved. Vital signs were then measured every 30 minutes, 4-6 hours after tyramine administration.

* 'Significant BP elevation' means an increase from baseline in SBP of ≥ 30 mmHg maintained for at least 3 consecutive measurements in a period of 10 minutes or more

** 'Resolved' means that SBP has decreased to less than 30 mmHg above baseline for 3 consecutive readings with 5 minutes interval between measurements

If during the 15-minute interval monitoring period one SBP was measured of 30 mmHg or more above baseline, 2 more measurements were done with a 5-minute interval. If these 2 measurements were also 30 mmHg or more above baseline, vitals signs were continued to be monitored every 5 minutes, as described above. If 1 or 2 of these measurements were less than 30 mmHg above baseline, the normal 15-minute interval monitoring period was continued.

In the event that orthostatic tests and vital signs had to be measured at exactly the same scheduled time point, ONLY orthostatic tests were performed.

Period 2
For all study groups, except Groups 3, 4a and 4b when ambulatory, supine BP and HR were measured every day before rasagiline, phenelzine, selegiline or placebo administration and approximately 1 and 2 hours post-dose on Days 11-24 or 11-40 (Group 4b) (i.e. Days 22-24 for Groups 3 and 4a and 38-40 for Group 4b).
Orthostatic hypotension

maximum HR (220 - age). The maximal test was performed with emergency equipment nearby. Wmax is the highest work load that could be maintained during at least 2 minutes.

The starting work load was 50 Watt for males, 30 Watt for females, and this was increased by 25 Watt every 3 minutes. There was continuous monitoring of the ECG (change from baseline), and BP was recorded at the start and during the last minute of each work load. Stopping criteria were:
• ST depression on the ECG of more than 0.1 mV in a lead without Q, with complaints of chest pain
• Decrease in BP of more than 10 mmHg or BP remaining below baseline values
• Moderate to severe complaints of angina pectoris
• Central nervous system symptoms (dizziness, ataxia, fainting)
• Decreased circulation (cyanotic, pale)
• Persisting ventricular tachycardia (VT)
• Technical problems which impair proper safety monitoring of the volunteer (e.g., no ECG monitoring, no BP measurement)
• Exhaustion of volunteer
Following the exercise, there was a 3-minute cool down at 50 watts on the bicycle, followed by rest on the bed. Subjects were monitored until:
• ECG returned to baseline rhythm
• BP returned to within 10% of baseline
Evaluation of cardiovascular symptomatology included:
• (the absence of) cardiac ischemia
• normal BP response, i.e., especially no decrease during exercise

Treatment of clinically significant hypertension
In case of a noteworthy increase in BP, or based on subjects. complaints, the Medical Investigator could decide to insert an iv cannula for the management of a hypertensive crisis, if any.

If SBP was ≥ 60 mmHg higher than baseline or ≥ 190 mmHg, if DBP was ≥ 30 mmHg higher than baseline or ≥ 115 mmHg, or if the Investigator believed that the subject was experiencing a clinically significant tyramine reaction that required therapy, anti-hypertensive therapy was initiated according to the following protocol:
1. Administration of labetalol, an alpha-beta adrenergic blocking agent could be given in a dose of 5 mg in 2 minutes, followed by continuous infusion of 1 mg per minute. After 5 to 7 minutes, the effect was to be checked. Further labetalol treatment was discontinued only after a decrease of 10 to 20 mmHg in SBP appeared. If no decrease in the SBP appeared, the infusion rate of the labetalol was increased to 2 mg per minute and the effect judged after 5 minutes. The subject had to remain in the supine position to avoid orthostatic hypotension for at least 30 minutes (or until the reaction was over).
2. Alternatively, if there was an absolute contraindication to the use of labetalol (i.e., history of bronchial asthma, sick sinus syndrome, first degree atrioventricular block with PR > 0.24 seconds), the subject was to be treated orally with nitroglycerin spray

SI and was to be immediately taken to the Intensive Care Unit for treatment with nitroprusside iv according to standard guidelines in a unit capable of continuous cardiac and BP monitoring.
3. If neither therapy yielded acceptable clinical results, the subjects had to be transferred to the nearest emergency department for further evaluation and treatment.
4. Ganglionic blocking agents, including guanethedine, guanadrel and reserpine were not to be given.

Timing of Assessments
For PK, pre-dose samples were obtained between waking up and dosing; and post-dose samples were obtained with time margins of +/- 5% of the time that passed since (last) dosing.
For safety assessments, pre-dose assessments were also performed between waking up and dosing; serial post-dose assessments (e.g., multiple assessments within any given day) were performed with time margins of +/- 20% of the time that passed since (last) dosing, incidental post-dose assessments (e.g., 1 or 2 assessments within a given day) were performed within +/- 1 hour of the planned scheme time.
The actual assessments times were recorded in the CRF and any deviations were explained according to [redacted] SOPs. b(4)
In the event assessments were planned for the same scheme time, the order of the assessments had to be arranged in such a way that ECG was performed prior to vital signs (for practical reasons related to the measurement of supine and standing BP), and these were followed by blood sampling.

Outcome Measures
Primary Outcome Measure
TYR30 is defined as the tyramine dose associated with an increase from baseline in SBP of $\geq$ 30 mmHg maintained for at least 3 consecutive measurements in a period of 10 minutes or more. Once a subject reached the TYR30, dose escalation of tyramine and administration of rasagiline, phenelzine, selegiline or matching placebo were terminated. TYR30 ratio is calculated as the tyramine dose associated with 3 consecutive increases from baseline in SBP $\geq$ 30 mmHg in tyramine threshold test at Period 1, divided by the dose associated with the same change in SBP in Period 3.

Secondary Outcome Measures
Orthostatic BP timed to rasagiline dosing. Orthostatic hypotension was defined as a fall in BP from supine to standing position of $\geq$ 10 or $\geq$ 20 mmHg for DBP and SBP, respectively. Subjects for whom the orthostatic BP was measured in Period 2 (Groups 3-6 only) were included in the analysis of the secondary endpoint.

Pharmacokinetic and Pharmacodynamic Measures
PD: plasma DHPG concentrations
PK: plasma tyramine, rasagiline and 1-AI concentrations, PK parameters.
Using non-compartmental analysis, the following PK endpoints were calculated from rasagiline, 1-AI and tyramine concentration.time profiles:

Cmax	Maximum observed plasma concentration
tmax	Nominal time to reach max *C*
kel (if possible)	Terminal elimination rate constant, determined by linear regression on the Ln-transformed concentration versus time data of the data-points that belong to the terminal elimination phase. This phase was determined by visual inspection of the semi-logarithmic concentration time profiles and contained at least three timepoints
t1/2 (if possible)	Terminal elimination half-life; calculated as ln 2 / kel
AUC0-last	Area under the plasma concentration-time curve up to time *last t* , where *last t* is the last point with a concentration above the lower limit of quantification (LLQ) (calculated using the log-linear trapezoidal rule)

AUC0-24 (if possible) Area under the plasma concentration-time curve from time zero extrapolated to 24 hour; calculated by:

$$AUC_{0-24} = AUC_{0-last} + \frac{\hat{C}_{last}}{k_{el}} - \frac{\hat{C}_{24h}}{k_{el}}$$

Rounded concentration data (as defined by the Bioanalytical Study Protocol) and actual blood sampling and dosing times were used in the PK calculations. In the PK calculations, for time points t<tmax values below the LLQ were set to zero; for time points t>tmax incidental values below the LLQ were regarded as missing. In case of 2 or more consecutive values below the LLQ, the subsequent data (if any) were not taken into account.
AUC values were calculated using the log-linear trapezoidal rule.
For tyramine, only Cmax and tmax were calculated.

For tyramine, only Cmax and tmax were calculated.

Safety and Tolerability Measures
Additional safety end-points include AEs, vital signs, ECG (12-lead and continuous 3-lead) recordings, clinical laboratory test results, and physical examination.
The evaluation of these parameters was done on the subjects who were treated with at least one dose of MAOI or placebo. Safety measures for the subject who only participated in Period 1 were listed only.

Drug Concentration Measurement
The drug concentration measurements were performed by validated methods (tyramine: LLQ = 0.500 ng/mL, ALQ = 50.0 ng/mL; rasagiline: LLQ = 0.250 ng/mL, ALQ = 10.0 ng/mL; 1-AI: LLQ = 0.500 ng/mL, ALQ = 10.0 ng/mL; DHPG: LLQ = 50.0 pg/mL, ALQ = 2000 pg/mL). The bioanalytical methodologies and procedures for the determination of tyramine, DHPG, rasagiline and 1-AI in plasma samples were documented in a combined Bioanalytical Study Report (included in an Appendix).

Statistical Methods Planned in the Protocol and Determination of Sample Size
Determination of Sample Size
In total, 160 subjects were to be enrolled in Period 2. No formal statistical analysis was planned. Therefore, no power calculations were performed.

All provided p-values (as requested by FDA) are given without Type I error correction for multiplicity.

Interim Analysis
Although interim reporting was originally planned after completion of step 1, it was decided not to unblind Groups 4a and 4b and to continue to step 2 with 14 days of treatment with rasagiline (as described in Protocol Amendment No. 4).

Randomization
Only subjects who reach tyramine potentiation during Period 1 were randomized to the study. Within each treatment group (Groups 2 to 6 only) subjects were randomized to active drug or matching placebo in a ratio of 2:1 respectively.

Stratification for smokers and non-smokers were to be performed in a ratio of up to 2 smokers for active drug and up to 1 smoker for matching placebo such that there are at least 14 non-smokers on active drug and at least 7 non-smokers on matching placebo. Randomization of non-smokers was always preferable/superior to that of smokers. A randomization number was assigned to the subjects after admission in Period 2. In addition to the subject number, randomized subjects received the lowest available randomization number for the stratum that they belonged to. Since Group 1 (phenelzine) did not include a placebo arm, subjects entering group 1 were not randomized. Each subject that entered Period 1 of the study and was dosed with at least one dose of tyramine received a subject number. Subject numbers were assigned depending on the group as indicated in Table 4.

Primary Study Population
Subjects who completed all 3 periods of the study were included in the analysis of the primary endpoint.

Demographics and Baseline Characteristics
All demographic and baseline characteristics are listed. Individual demographic data are listed and the parameters age, gender, race, height, weight and BMI are summarized by descriptive statistics.

Baseline Definition
In general, baseline is defined as the last non-missing value before the first dose.

Baseline Vital Signs for the Purpose of Assessing Tyramine Potentiation
Baseline supine SBP, diastolic blood pressure (DBP) and HR before tyramine uptake were calculated as the rounded mean of the first 3 stable pre-dose measurements on each of the tyramine dosing days. Pre-tyramine uptake measurements were considered stable when the range of 3 consecutive SBP measurements did not exceed 10 mmHg. If the measurements were stable, further measurements until tyramine administration were not needed and thus (even if these extra measurements were done) they were excluded from analysis. If this criterion was not reached during the 35 minute period from the first

baseline measurement up to the tyramine dosing, then the baseline value was calculated as the rounded mean of all valid pre-tyramine readings available. All valid measurements for baseline calculation were flagged as such in the database by the Investigator. These indications were used for baseline calculation. See Note to File No. 27 for detail of discrepancies in baseline determination.

Baseline Vital Signs for the Purpose of the Secondary Endpoint Assessment (Orthostatic Hypotension)
Baseline SBP and DBP as well as HR is defined as the rounded mean of 3 pre-dose measurements performed on Day 23 (all groups except Group 4b, end of Period 2) or Day 39 (end of Period 2 for Group 4b).

Baseline ECG for the Purpose of the QTc evaluation
Baseline ECG for evaluating QTc changes is defined as the last QTc measurement before tyramine uptake on each day tyramine was administered.

Imputation of Missing Values
In general, missing values are not imputed. In case that a subject did not reach the TYR30 endpoint (i.e. the increase in SBP of $\geq$ 30 mmHg for 3 consecutive measurements in a 10 minute or more period) during Period 3, a dose of 800 mg tyramine is used for TSF calculation. There was one subject in the study for whom imputation was required (Subject 405).

Repeated Measurement
Repeated measurements are listed in the individual data listing together with the Physician's comment. Repeated measurements for all but vital signs measurements are excluded from the descriptive statistical analysis, except for repeated measurements that were performed immediately after the scheduled measurement in case of a previous measurement error (e.g. equipment failure). In these cases, the repeated measurement is used, and the original erroneous measurement is excluded from the analysis. For vital signs (BP) measurements, all unscheduled (additional/repeated) measurements were done because of reasons stated in the protocol or to monitor safety. Therefore, none of the additional measurements invalidate any previous measurement. Also the additional measurements themselves are regarded as valid measurements and were also used by the Medical Investigator in the evaluation. Therefore all unscheduled BP measurements are included in the primary endpoint analysis.

Primary End Point - TYR30 Ratio
TYR30 is defined as the tyramine dose associated with an increase from baseline in SBP of $\geq$ 30 mmHg maintained for at least 3 consecutive measurements in a period of 10 minutes or more. Once a subject reached the TYR30, dose escalation of tyramine and administration of rasagiline, phenelzine, selegiline or matching placebo were terminated. TYR30 ratio is calculated as the tyramine dose associated with 3 consecutive increases from baseline in SBP $\geq$ 30 mmHg in tyramine threshold test at Period 1, divided by the dose associated with the same change in SBP in Period 3.

Primary End Point - Analysis
Individual values of TYR30 and TYR30 ratios (i.e., TSF) are presented, together with descriptive statistics describing the number of subjects, geometric mean, minimum, median and maximum by treatment group.

Additions to the Primary End Point - Analysis as Defined in SAP
Descriptive statistics of TYR30 are presented by period (pre treatment and post treatment) for each treatment group (i.e. Groups 4a, 4b, 2, 3, 5, and 6) versus matching placebo. Because the TYR30 ratio is log-normal distributed, the geometric mean is also calculated. Geometric mean and median are the statistics of choice when reporting the TYR30 ratios results in-text. Wilcoxon rank test is used to compare TSFs between each group and its matching placebo. Kaplan Meier (KM) survival curves are presented by group (SAS LIFETEST Procedure with STRATA=period). The graphs X-axis on these graphs presents the TYR30. Early terminated subjects who did not reach TYR30 were right censored with their last tyramine dose. A table with the 50% quartile value of TYR30 along with its confidence interval as derived from the KM analysis is presented by group. Graphical presentations showing individual subject changes from baseline in SBP, DBP and HR on all tyramine challenge days is also provided.
Plots showing change from baseline in SBP, DBP and HR on all tyramine challenge days are presented for each subject by period (for Periods 1 and 3).

Secondary Endpoint – Orthostatic Hypotension (Groups 3 - 6)
Orthostatic hypotension is defined as a change in BP from supine to standing position of ≥ 20 or ≥ 40 mmHg for systolic BP and ≥ 10 or ≥ 20 for diastolic BP, measured after 5 minutes at supine position and after 2 minutes at standing position.

On Day -1: for Groups 3, 4a and 4b, 5 and 6 the test was repeated 3 times within approximately 10-20 minute intervals between each measurement. The average of the readings serves as the integrated baseline/pre-treatment value.

On Day 23 for Groups 3 and 4a and on Day 39 for Group 4b, the test was repeated 3 times within approximately 10-20 minute intervals between each measurement before dosing and one test at approximately 0.25, 0.5, 0.75, 1, 1.5, 3 and 4 hours post-dose rasagiline administration. On Day 23 for Groups 5 and 6 the test was repeated 3 times within approximately 10-20 minute intervals between each measurement before dosing and one test at approximately 0.25, 0.5, 0.75, 1, 1.5, 2, 5 and 7 hours after drug administration (paralleling the PK measurements). The average of each 3 pre-dose readings serves as the integrated on-treatment values for comparison to post-treatment values. Individual results of orthostatic BP and HR measurements are listed, and occurrences of orthostatic hypotension are indicated. Outlier analysis for each vital sign parameter change from pre-dose on treatment, for each position (supine, standing or standing-supine) are conducted according to threshold values presented in Table 7.

Table 7 Threshold Values for Outlier Analysis for Vital Sign Parameters

Test name	Decrement from Pre-Dose	Increment from Pre-dose
Supine-Standing/ Standing-Supine SBP (mmHg)	≤ -20 mmHg	≥ 20 mmHg
	≤ -40 mmHg	≥ 40 mmHg
Supine-Standing/ Standing-Supine DBP (mmHg)	≤ -10 mmHg	≥ 10 mmHg
	≤ -20 mmHg	≥ 20 mmHg
Supine-Standing/ Standing-Supine Pulse (bpm)	≤ -15 bpm	≥ 15 bpm
	≤ -30 bpm	≥ 30 bpm

Incidence of vital sign outliers at each post-dose time point and at any time post-dose are summarized for placebo and for rasagiline treatments separately (as well as for all rasagiline treatments combined.

Descriptive statistics of vital sign parameters are presented for placebo, rasagiline treatments separately, and for all rasagiline treatments combined. Descriptive statistics of vital sign parameters, changes from pre-dose, are presented for placebo, rasagiline treatments separately, and for all rasagiline treatments combined.

Prevalence of orthostatic hypotension over time is summarized and expressed as a percentage of all subjects tested, as well as a percentage of all subjects with orthostatic hypotension at baseline.

Pharmacokinetic/Pharmacodynamic Evaluation

Pharmacodynamic evaluation

The pharmacodynamic evaluation was performed for the primary study population (i.e, subjects who completed all 3 periods of the study). The DHPG plasma concentrations are listed and descriptive statistics are presented by treatment group and time point. Results for rasagiline treated subjects of Groups 4a and 4b are presented both separately and pooled.

Pharmacokinetic evaluation

All subjects who received rasagiline treatment and for whom the PK data were considered to be sufficient and interpretable and who did not have any protocol violations interfering with pharmacokinetics, were included in the statistical analyses.

Using non-compartmental analysis, the pharmacokinetic endpoints presented in Table 8 are calculated from rasagiline, 1-AI, and tyramine concentration-time profiles.

Table 8 Pharmacokinetic Endpoints

Parameter	Description/calculation
C_{max}	maximum observed plasma concentration
t_{max}	nominal time to reach C_{max}
k_{el}	terminal elimination constant, determined by linear regression on the Ln-transformed concentration versus time data of the data-points that belong to the terminal elimination phase. This phase will be determined by visual inspection of the semi-logarithmic concentration time profiles and contained at least three time points.
$t_{1/2}$	terminal elimination half-life; calculated as ln 2 / k_{el}
$AUC_{0\text{-}last}$	area under the plasma concentration-time curve up to time t_{last}, where t_{last} is the last point with a concentration above the lower limit of quantification (calculated using the log-linear trapezoidal rule)
$AUC_{0\text{-}24}$	area under the plasma concentration-time curve from time zero extrapolated to 24 hour; calculated by: $AUC_{0-24} = AUC_{0-last} + \frac{\hat{C}_{last}}{k_{el}} - \frac{\hat{C}_{24h}}{k_{el}}$

Rounded concentration data (as defined by the bio-analytical study protocol) and actual blood sampling and dosing times are used in the pharmacokinetic calculations. In the pharmacokinetic calculations, for time points t<tmax values below the LLQ are set to zero; for time points t>tmax incidental values below the LLQ are regarded as missing. In case of two or more consecutive values below the LLQ, the subsequent data (if any) are taken into account. AUC values are calculated using the linear trapezoidal rule.

For tyramine, PK parameters are calculated if applicable.

Statistical Analysis of Concentration Data
Descriptive statistics including the number of observations (n), arithmetic and geometric mean (except for tmax), standard deviation (SD), coefficient of variation (%CV), median, minimum value (min), and maximum value (max) are presented.

The rasagiline and 1-AI plasma concentrations are listed and summarized by descriptive statistics in tables by treatment and time-point. Results for rasagiline-treated subjects of Groups 4a and 4b are presented both separately and pooled.
The tyramine plasma concentrations are listed and summarized by descriptive statistics in tables by treatment and time-point.

Protocol scheme times were used to calculate and present descriptive statistics on the concentration data. For the calculation of geometric mean and median concentrations, values below the LLQ were set to half the LLQ value. If more than half the values are below the LLQ no statistics were presented. Geometric mean plasma concentration-time profiles are presented by treatment group. Combined individual concentration-time profiles

are presented for each treatment. Individual PK parameters for rasagiline, 1-AI and tyramine are tabulated together with descriptive statistics.

Evaluation of Safety and Tolerability Parameters
AEs, clinical laboratory data, ECG parameters, physical examination, and early terminations due to AEs were assessed.

Changes in Conduct of the Study or Planned Analyses
Changes in Conduct
The original protocol was issued on 10 October 2006. Changes to this protocol were instituted by way of 4 formal protocol amendments and by the SAP. The first amendment was issued on 21 November 2006, before the start of the study. The second amendment was issued on 20 March 2007, at which point 44 subjects had entered at least Period 1. The third and fourth amendments were issued on 07 August 2007 and 23 August 2007, at which point 99 and 105 subjects had entered at least Period 1, respectively (at that time Groups 4a and 4b were completed and Groups 1, 2 and 3 were still ongoing). The more substantive changes introduced to this study via amendment are summarized in Table 11. The SAP was completed and signed off on 02 October 2008. It was subsequently submitted to the FDA on 06 October 2008 (SN 276). The study blind was broken on 06 October 2008.

Table 11 Substantive Changes Made to Original Protocol via Protocol Amendments

Change Made To	Change Made Via	Description of Change	Reason for Change
1. Planning of clinical phase	Amendment No.1	Step 2 of the study proceeded in slight parallel to Step 1 of the study.	In order to reduce the overall time for this study.
2. CRF	Amendment No.1	An electronic CRF was to be used instead of a paper CRF.	
3. Vital signs	Amendment No. 2	Additional vital signs measurements for specific detailed cases were included.	
4. Orthostatic BP measurements and tyramine and rasagiline PK blood sampling time points	Amendment No. 3	Additional orthostatic BP measurements and tyramine and rasagiline PK blood sampling time points were added for part of Group 1 (subjects who entered the study after the amendment was approved) and Groups 3, 5 and 6	To adopt a number of recommendations received from the FDA on 30 July 2007.
5. Exclusion criterion No. 29	Amendment No. 3	The use of SNRIs was added to exclusion criterion No. 29.	To adopt a number of recommendations received from the FDA on 30 July 2007.
6. Dose level	Amendment No. 4	The dose levels have been increased for Groups 5 (from 3 to 4 mg rasagiline) and 6 (from 4 to 6 mg rasagiline).	To adopt a number of recommendations received from the FDA on 30 July 2007.
7. Interim Analysis	Amendment No. 4	After Step 1, the study was to be continued without performing the interim analysis and without unblinding Step 1 of the study.	It could be assumed from the blinded data of Step 1 (Groups 4a and 4b) that there was no increase in TYR30 ratio when comparing 30 days exposure to 14 days exposure to rasagiline.

Changes in Planned Analysis

• In the SAP it was mentioned that the terminal elimination phase would be determined by visual inspection of the semi-logarithmic concentration time profiles. In consultation with TEVA, the standard WinNonlin algorithm for determination of terminal elimination phase was used.

• In the SAP it was specified that descriptive statistics in tables would use the same precision for decimal places as the raw data. In practice, the arithmetic and geometric means for TSF ratios are presented with 2 decimal places, while the median results are rounded to an integer.

Changes in BP Automatic Scheduling

In line with protocol guidelines, BP measurements were taken every 5 minutes during the first 2 hours after tyramine administration, and every 15 minutes from 2 to 4 hours after dosing. Due to automatic scheduling of the BP measurements during the tyramine challenge days, and the way the equipment performs the automatically scheduled measurements, these were not always exactly 5 minutes apart during the first 2 hours after tyramine dosing or 15 minutes during the period between 2 and 4 hours after dosing. Therefore, for the time interval calculation the last measurement in the sequence of ≥ 30 mmHg change from baseline minus the time of first measurement in the sequence of ≥ 30 mmHg change from baseline +1 was used to determine valid measurements to use for potentiation calculation. In two cases (see Note to File No. 27) the potentiation was measured over an interval of 9 minutes (Subject 422, Period 1, Day 9 and Subject 508, Period 3, Day 31). For these cases potentiation was also confirmed by the Medical Investigator.

3.2 Study Results

3.2.1 Subject Disposition

Disposition of Subjects

A total of 509 subjects were screened for study eligibility. Three hundred and fourteen subjects failed screening mainly due to not meeting the exclusion criterion no. 7 relating to blood pressure (Figure 1).

Of the 195 subjects found eligible, 179 subjects commenced with Period 1. During Period 1, 14 subjects were withdrawn or dropped out (one of whom reached potentiation at 25 mg) and 9 subjects did not reach the tyramine threshold dose (i.e., did not show a tyramine reaction in Period 1 even at 800 mg tyramine). These subjects were not randomized in Period 2. Thus, a total of 156 subjects were randomized in Period 2. During Periods 2 and 3, 7 subjects dropped out (2 during Period 2 and 5 during Period 3; 3x withdrew consent, 3x baseline BP too high and 1x AE). Therefore, altogether 149 subjects completed all 3 period of the study and comprise the population for the primary analysis. The disposition of the subjects from screening to randomization in Period 2 is given below in Figure 1. The disposition of the subjects per treatment group is given below in Figure 2.

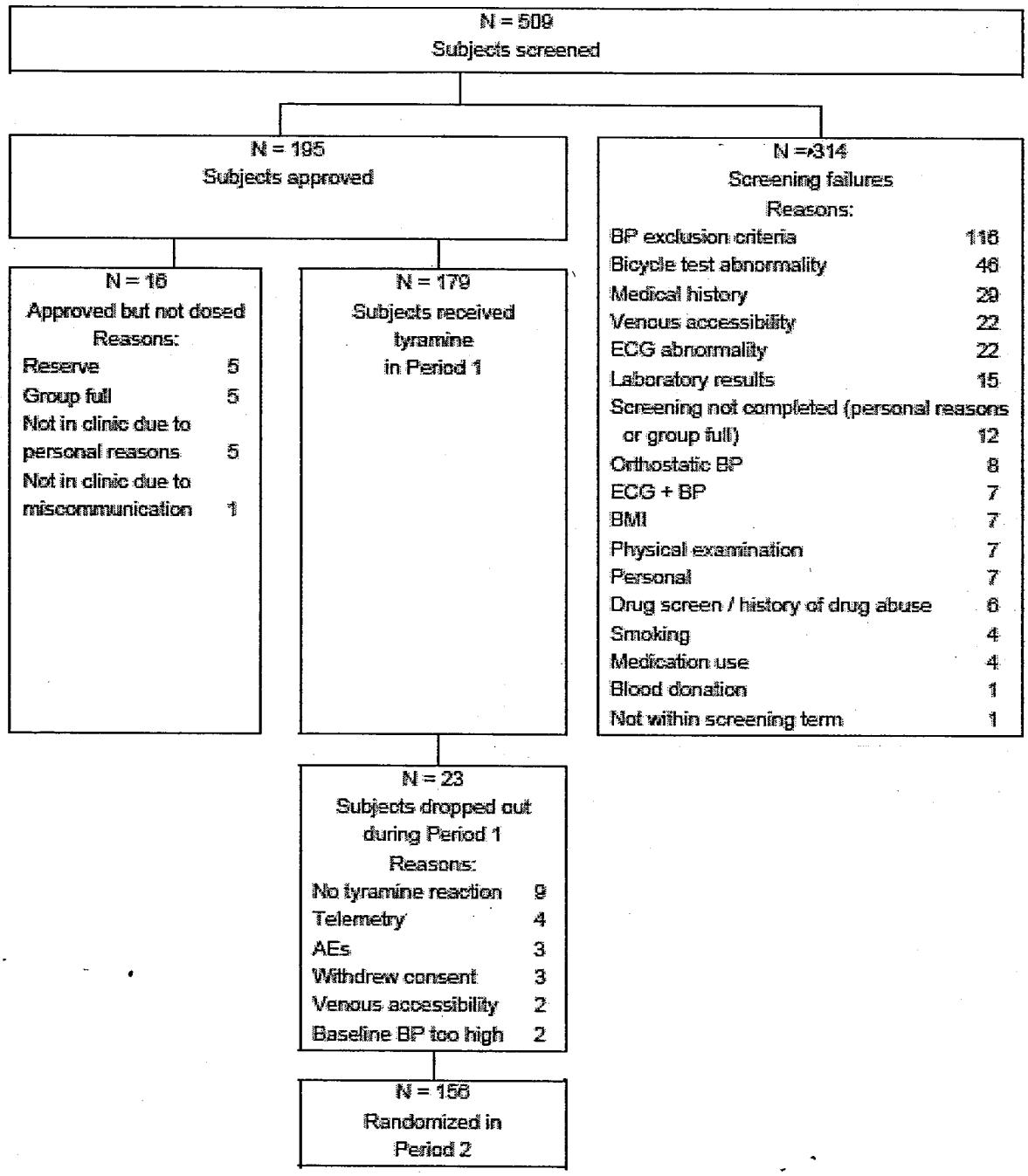


Figure 1 Disposition of Subjects from Screening to Randomization in Period 2

Source: Subject enrolment log (data on file) and Listing 17.2.5-2

Group	Period 1	Period 2	Period 3	Completed
1 (Phenelzine 15 mg)	n = 17 dosed n = 1 withdrawn - SAE (Subject 108)	n = 16 dosed phenelzine	n = 16 dosed phenelzine n = 1 withdrawn - Baseline BP (Subject 101)	n = 15 phenelzine
2 (Selegiline 5 mg)	n = 24 dosed n = 2 withdrawn - No tyramine reaction (Subject 223) - Telemetry (Subject 205)	n = 15 dosed selegiline n = 7 dosed placebo	n = 15 dosed selegiline n = 7 dosed placebo	n = 15 selegiline n = 7 placebo
3 (Rasagiline 1 mg)	n = 25 dosed n = 2 withdrawn - Venous accessibility (Subject 308) - Baseline BP (Subject 324)	n = 16 dosed rasagiline n = 7 dosed placebo	n = 16 dosed rasagiline n = 1 withdrawn - Baseline BP (Subject 318) n = 7 dosed placebo	n = 15 rasagiline n = 7 placebo
4a (Rasagiline 2 mg)	n = 28 dosed n= 4 withdrawn - No tyramine reaction (Subject 415) - Telemetry (Subject 408) - Baseline BP (Subject 411) - Withdrew consent (Subject 416)	n = 15 dosed rasagiline n = 1 withdrawn - Withdrew consent (Subject 408) n = 9 dosed placebo	n = 14 dosed rasagiline n = 1 withdrawn - Baseline BP (Subject 426) n = 9 dosed placebo	n = 13 rasagiline n = 9 placebo
4b (Rasagiline 2 mg, 30 days dosing)	n = 29 dosed n = 6 withdrawn - No tyramine reaction (Subjects 452, 472, 473, 477) - Telemetry (Subject 454) - Withdrew consent (Subject 453)	n = 14 dosed rasagiline n = 9 dosed placebo	n = 14 dosed rasagiline n = 9 dosed placebo	n = 14 rasagiline n = 9 placebo
5 (Rasagiline 4 mg)	n = 27 dosed n = 3 withdrawn - No tyramine reaction (Subjects 511, 523) - AE (Subject 513)	n = 17 dosed rasagiline n = 7 dosed placebo	n = 17 dosed rasagiline n = 7 dosed placebo	n = 17 rasagiline n = 7 placebo
6 (Rasagiline 6 mg)	n = 29 dosed n = 5 withdrawn - No tyramine reaction (Subject 606) - Withdrew consent (Subject 610) - Venous accessibility (Subject 611) - AE (Subject 614) - Telemetry (Subject 628)	n = 15 dosed rasagiline n = 1 withdrawn - Withdrew consent (Subject 617) n = 9 dosed placebo	n = 14 dosed rasagiline n = 2 withdrawn - Withdrew consent (Subject 605) - AE (Subject 627) n = 9 dosed placebo	n = 12 rasagiline n = 9 placebo
Overall	n = 179 dosed n = 23 withdrawn	n = 156 dosed n = 2 withdrawn	n = 154 dosed n = 5 withdrawn	n = 149

Figure 2 Disposition of Subjects per Treatment Group from Period 1 to Completion of Study
Source: Subject enrolment log (data on file), Listing 17.2.1-1 and Listing 17.2.5-2

3.2.2 Subject Demographics and Other Baseline Characteristics

Demographics

A summary of demographic data for all randomized subjects is given in Table 12.

Table 12 Summary of Demographic Characteristics (Randomized Subjects)

		Placebo Groups 2, 3, 4a, 4b, 5, 6	Placebo Groups 2, 3, 4a, 5, 6	15 mg PHE-TID	5 mg SEL-BID	All randomized
		N = 48	N = 39	N = 16	N = 15	N = 156
Age (yr)	Mean (SD)	59 (8)	59 (8)	57 (8)	54 (9)	58 (8)
	Range	41 – 70	41 – 70	40 – 68	40 – 68	40 – 70
Weight (kg)	Mean (SD)	73.7 (10.5)	72.4 (10.3)	76.4 (9.3)	73.4 (10.7)	74.1 (10.6)
	Range	48.2 – 102.1	48.2 – 102.1	60.8 – 89.3	52.5 – 89.4	48.2 – 114.8
Height (m)	Mean (SD)	171 (9)	170 (9)	173 (8)	171 (10)	171 (9)
	Range	150 – 192	150 – 192	158 – 191	155 – 186	150 – 194
BMI (kg/m^2)	Mean (SD)	25.2 (2.6)	24.9 (2.7)	25.6 (2.4)	25.2 (2.5)	25.2 (2.5)
	Range	19.3 – 30.1	19.3 – 30.1	20.1 – 29.0	21.3 – 29.0	19.3 – 30.7
Gender - n (%)	Female	22 (45.8%)	18 (46.2%)	7 (43.8%)	8 (53.3%)	74 (47.4%)
	Male	26 (54.2%)	21 (53.8%)	9 (56.3%)	7 (46.7%)	82 (52.6%)

		1 mg RAS-OD	2 mg RAS-OD	2 mg RAS-OD/30D	4 mg RAS-OD	6 mg RAS-OD
		N = 16	N = 15	N = 14	N = 17	N = 15
Age (yr)	Mean (SD)	59 (8)	58 (7)	61 (6)	54 (7)	56 (9)
	Range	45 – 69	44 – 70	49 – 69	41 – 70	40 – 67
Weight (kg)	Mean (SD)	70.8 (8.8)	78.8 (12.0)	71.2 (9.4)	72.8 (10.3)	76.9 (13.2)
	Range	59.9 – 90.7	57.9 – 100.9	52.4 – 88.0	56.9 – 92.3	63.0 – 114.8
Height (m)	Mean (SD)	170 (7)	174 (10)	169 (10)	172 (8)	173 (11)
	Range	157 – 185	164 – 192	152 – 184	155 – 188	158 – 194
BMI (kg/m^2)	Mean (SD)	24.6 (1.9)	25.9 (2.7)	24.8 (2.2)	24.6 (2.8)	25.6 (3.0)
	Range	20.5 – 27.2	20.3 – 30.1	21.0 – 28.3	21.2 – 30.7	20.1 – 30.5
Gender - n (%)	Female	11 (68.8%)	5 (33.3%)	8 (57.1%)	6 (35.3%)	7 (46.7%)
	Male	5 (31.3%)	10 (66.7%)	6 (42.9%)	11 (64.7%)	8 (53.3%)

Source: Table 15.1-1, Table 15.1-2 and Table 15.1-3

A total of 156 subjects were randomized and dosed in Period 2 of the study. Of these subjects, 144 were Caucasian, 6 were Asian / oriental, 1 was black of African heritage, 1 was a native Hawaiian or other Pacific Islander and 4 were of another race. On average, all treatment groups were similar with regard to age, height, weight and BMI.
The male to female ratio was between 40/60 and 60/40 in each treatment group, with the exception of Group 3 in which the male to female ratio was 39.1/60.9.

3.2.3 Evaluation of Primary Endpoint (Characterization of Tyramine Sensitivity Factor-TSF)

Data Sets Analyzed
The following study populations were defined:
Primary Study Population
Subjects who completed all 3 periods of the study.
All Subjects Treated (AST) Population
All subjects who were treated with at least 1 dose of tyramine. This population included the subjects that did not receive treatment with a MAOI or placebo. These subjects received a subject number and the measurements that were done prior and during the tyramine treatment were listed. (NB: AST = MIT + TO)

MAO Inhibitor Treated (MIT) Population
All subjects who were treated at least once with a MAOI (phenelzine, selegiline or rasagiline) or placebo. For these subjects, safety measurements were included in the summaries. This population is sometimes referred to as the .all subjects randomized. population, although Group 1 was not actually randomized to treatment.

Tyramine Only (TO) Population
All subjects belonging to the AST populations but not to the MIT population. In other words: all subjects not having shown tyramine potentiation in Period 1 up to the highest tyramine dose (800 mg) and subjects that dropped-out prior to administration of phenelzine, selegiline, rasagiline or placebo. These subjects received a subject number and the measurements that were done prior and during the tyramine treatment were listed only and not included in the safety summaries.

PK Population
All subjects who received rasagiline treatment and for whom the primary PK data are considered to be sufficient and interpretable and who did not have any protocol violations interfering with PK, were included in the PK calculations.

A summary of the number of subjects per study population is presented in Table 14.

Table 14 Summary of Study Populations

	Population				
Group	Primary	AST	MIT	TO	PK
Phenelzine (1)	15	17	16	1	0
Selegiline or placebo (2)	22	24	22	3	0
1 mg Rasagiline or placebo (3)	22	25	23	2	16
2 mg Rasagiline or placebo (4a)	22	28	24	4	14
2 mg Rasagiline or placebo (4b)	23	29	23	6	14
4 mg Rasagiline or placebo (5)	24	27	24	3	17
6 mg Rasagiline or placebo (6)	21	29	24	5	14
total	149	179	156	23	75

Source: Listing 17.2.3-1

Primary Endpoint - Tyramine Challenge Results
TYR30 Ratios and Tyramine Pressor Doses

Table 15 summarizes the effects of various treatments on various central tendency presentations of tyramine sensitivity factor (TSF or $TYR30_3$). The central tendency (e.g., arithmetic mean, geometric mean, median) TSF ($TYR30_3$) is determined by assessing the tyramine threshold dose that increases systolic blood pressure by $\geq$ 30 mm Hg (vs the mean of several pre-treatment measurements) for at least 3 consecutive measurements obtained 5 minutes apart (e.g., minimum duration of at least 10 minutes) for each treatment in the pre-treatment period and dividing this number by the tyramine threshold, pressor dose after treatment.

Table 15 Summary Table of $TYR30_3$ Ratios

	Arithmetic Mean	Geometric Mean	Median
Phenelzine (1)	20.14	17.32	17
Selegiline (2)	3.87	2.47	2
1 mg Rasagiline (3)	2.98	2.03	2
2 mg Rasagiline (4a)	4.67	3.33	4
2 mg Rasagiline (4b)	2.79	2.45	3
4 mg Rasagiline (5)	8.22	4.50	4
6 mg Rasagiline (6)	7.31	5.10	5
Pooled Placebo (4a,2,3,5,6)	4.98	1.50	1

Table 15.2-1. Summary Table and Statistical Analysis of TYR30 and TYR30 Ratio (TSF) by Treatment Group vs. Matching Placebo

TVP-1012-120-TYR		Study Period						
		Period 1		Period 3		TSF (Period1/Period3)		P-Value*
		Matching Placebo	Active	Matching Placebo	Active	Matching Placebo	Active	
Phenelzine (1)	N		16		15		15	
	Mean		481.25		31.00		20.14	
	Geometric Mean		463.36		27.02		17.32	
	SD	NA	132.76	NA	15.95	NA	12.76	NA
	Min							
	Median		450		25		17	
	Max							
Selegiline (2)	N	7	15	7	15	7	15	
	Mean	471.43	396.67	375.00	182.50	2.74	3.87	
	Geometric Mean	430.08	331.27	257.47	134.04	1.67	2.47	
	SD	197.60	195.00	222.20	116.86	3.00	5.71	0.322748
	Min							
	Median	600	400	500	200	1	2	
	Max							
1mg Rasagiline (3)	N	7	16	7	15	7	15	
	Mean	485.71	456.25	387.50	248.33	9.96	2.98	
	Geometric Mean	445.01	441.58	266.71	218.60	1.67	2.03	
	SD	203.54	120.93	182.15	94.71	23.83	4.72	0.021931
	Min							
	Median	500	400	400	200	1	2	
	Max							
2mg Rasagiline (4a)	N	9	15	9	13	9	13	
	Mean	488.89	486.67	351.39	174.04	9.14	4.67	
	Geometric Mean	462.47	445.58	218.28	135.91	2.12	3.33	
	SD	176.38	176.74	250.35	95.26	20.79	5.93	0.069151
	Min							
	Median	400	500	300	200	1	4	
	Max							
4mg Rasagiline (5)	N	7	17	7	17	7	17	
	Mean	528.57	511.76	428.57	144.12	1.39	8.22	
	Geometric Mean	495.88	480.44	397.03	106.68	1.25	4.50	
	SD	205.87	179.87	197.60	82.10	0.72	11.73	0.001141
	Min							
	Median	400	500	300	200	1	4	
	Max							
6mg Rasagiline (6)	N	9	15	8	13	8	13	
	Mean	544.44	450.00	537.50	118.27	1.05	7.31	
	Geometric Mean	527.27	397.78	528.08	89.89	1.01	5.10	
	SD	142.40	172.17	106.07	73.00	0.28	8.02	0.000187
	Min							
	Median	500	400	550	100	1	5	
	Max							

*Wilcoxon Rank Test

b(4)

Reviewer Comments

- Table 15 and Table 15.2-1 above shows TSF results for each active drug group vs each, respective matching placebo group (with exception of phenelzine). Because each matching placebo consists of relatively small numbers of subjects, some comparisons

results are extremely important because they provide perspective about the possible significance of this mild increased tyramine sensitivity. Selegiline has been marketed for many years and we are not aware that the approved 10 mg daily dose of selegiline is associated with notably increased sensitivity to tyramine and a significant risk for serious hypertensive "cheese" reactions/hypertensive crises. These observations seem to be reasonably reassuring that treatment with 1 mg rasagiline ought to have a similar safety profile for serious hypertensive reactions from eating and drinking without any dietary tyramine restrictions

Although selegiline, was considered to be a potential "negative" control for increased tyramine sensitivity, inclusion of this treatment showed that it can also increase tyramine sensitivity mildly. I do not believe that this observation is recognized because selegiline was approved many years ago without a good tyramine sensitivity challenge study submitted at the time of the NDA review prior to approval. Neither am I aware of any randomized, double-blind, placebo-controlled studies in which 10 mg daily selegiline was evaluated for its effect on tyramine sensitivity. If the rasagiline label ultimately describes a mild increase of tyramine sensitivity from the approved dose of 1 mg daily, I believe that the selegiline label should similarly describe this observation if it is possible from a regulatory perspective because these results have been derived from a different sponsor than the sponsor for selegiline.

- Table 15.2-2 further provides perspective about the markedly increased sensitivity to tyramine produced by a recognized non-selective MAO inhibitor that was included in this study as a "positive" control. The dose (45 mg daily; 15 mg TID) used in this study is the initially recommended dose for treatment of depression. The recommended dose for maximal benefit is considered to be at least 60 mg daily, and can be increased as high as 90 mg daily. Phenelzine treatment with this submaximal dose markedly increased tyramine sensitivity by all central tendency comparisons. Whereas TSF for pooled placebo was 1.50 for geometric mean, 1 for median, and 4.98 for arithmetic mean, TSF for phenelzine was 17.32 for geometric mean, 17 for median, and 20.14 for arithmetic mean. All these presentations showed that phenelzine treatment markedly increased tyramine sensitivity.

- Although increasing doses of rasagiline dose-dependently increased tyramine sensitivity, the magnitude of increased tyramine sensitivity (approximately 5 fold) for the highest rasagiline dose (6 mg daily) evaluated was considerably much less than the increased tyramine sensitivity (approximately 17 fold) for phenelzine. These results further support the **relatively selective effect** of rasagiline on MAO-B inhibition. However, these results also demonstrate the phenomenon that has been recognized previously, that the selectivity for MAO-B inhibition decreases (and may ultimately be lost if dose is sufficiently increased) as one uses increasing doses of "selective" MAO-B inhibitors.

with active drug are not statistically significant. Also, the mean placebo TSF for some groups (1 and 2 mg rasagiline) is greater than that of the active groups while the geometric mean and median for these placebo groups are less than those for the respective active drug groups. These results suggest that more useful and reliable active drug group comparisons with placebo can be seen when active drug groups are compared to a pooled placebo population derived from pooling the small, "matching" placebo groups. Nevertheless, the statistical comparisons with the highest rasagiline dose groups (4 and 6 mg) are highly statistically different and show that TSF for these groups are considerably greater than the matching placebo.

- In contrast, Table 15.2-2 below shows comparative central tendency TSF results for each active drug group with pooled placebo (derived from pooling each of the 4 rasagiline matching placebo groups and the selegiline matching placebo group). **Each active drug group (notably including 1 mg rasagiline and 10 mg selegiline, both of which are FDA approved doses) are highly statistically greater than pooled placebo for TSF indicating that each treatment increases the sensitivity to tyramine.**

- Table 15 also shows that central tendency presentations by geometric mean or median are better than the presentation by arithmetic mean TSF, which is commonly quite higher than the geometric TSF or median not only for each active drug group but also for the pooled placebo.

- Whereas the geometric mean TSF for pooled placebo was minimally increased at 1.50, the geometric mean TSF was numerically and statistically greater for 1 mg rasagiline (2.03), 2 mg rasagiline (3.33), 4 mg rasagiline (4.50), and 6 mg rasagiline (5.10), indicating all treatments with rasagiline dose-dependently increases sensitivity to tyramine, and the risk for increasing blood pressure.

- Whereas the median TSF for pooled placebo was "normal" at 1, the median TSF was increased for 1 mg rasagiline (2), 2 mg rasagiline (4), 4 mg rasagiline (4), and 6 mg rasagiline (5), similarly indicating (as geometric mean) that all these rasagiline treatments dose-dependently increase sensitivity to tyramine, and thereby the risk for increasing blood pressure.

- A major goal of this study was to determine if the approved dose of rasagiline (1 mg) increases sensitivity to tyramine and these results suggest that this dose does mildly enhance tyramine sensitivity.

- In view of this increased tyramine sensitivity to the approved rasagiline dose, it is particularly important to note that the approved dose of selegiline (10 mg) also increases tyramine sensitivity (numerically and statistically). The geometric mean TSF was 1.50 for placebo and 2.47 for selegiline. The median TSF was 1 for pooled placebo and 2 for selegiline. **Thus, the increased tyramine sensitivity from approved selegiline treatment is similar to that for approved rasagiline treatment. These comparator**

Table 15.2-2. Summary Table and Statistical Analysis of TYR30 and TYR30 Ratio (TSF) by Treatment Group vs. Pooled Placebo

TVP-1012-120-TYR		Study Period						
		Period 1		Period 3		TSF (Period1/Period3)		
		Pooled Placebo (4a,2,3,5,6)	Active	Pooled Placebo (4a,2,3,5,6)	Active	Pooled Placebo (4a,2,3,5,6)	Active	P-Value*
Phenelzine (1)	N	39	16	38	15	38	15	
	Mean	505.13	481.25	415.79	31.00	4.98	20.14	
	Geometric Mean	473.15	463.36	313.97	27.02	1.50	17.32	
	SD	176.14	132.76	200.27	15.95	14.24	12.76	<0.0001
	Min							
	Median	500	450	400	25	1	17	
	Max							
Selegiline (2)	N	39	15	38	15	38	15	
	Mean	505.13	396.67	415.79	182.50	4.98	3.87	
	Geometric Mean	473.15	331.27	313.97	134.04	1.50	2.47	
	SD	176.14	195.00	200.27	116.86	14.24	5.71	0.008553
	Min							
	Median	500	400	400	200	1	2	
	Max							
1mg Rasagiline (3)	N	39	16	38	15	38	15	
	Mean	505.13	456.25	415.79	248.33	4.98	2.98	
	Geometric Mean	473.15	441.58	313.97	218.60	1.50	2.03	
	SD	176.14	120.93	200.27	94.71	14.24	4.72	0.002641
	Min							
	Median	500	400	400	200	1	2	
	Max							
2mg Rasagiline (4a)	N	39	15	38	13	38	13	
	Mean	505.13	486.67	415.79	174.04	4.98	4.67	
	Geometric Mean	473.15	445.58	313.97	135.91	1.50	3.33	
	SD	176.14	176.74	200.27	95.26	14.24	5.93	0.000267
	Min							
	Median	500	500	400	200	1	4	
	Max							
4mg Rasagiline (5)	N	39	17	38	17	38	17	
	Mean	505.13	511.76	415.79	144.12	4.98	8.22	
	Geometric Mean	473.15	480.44	313.97	106.68	1.50	4.50	
	SD	176.14	179.87	200.27	82.10	14.24	11.73	0.000026
	Min							
	Median	500	500	400	200	1	4	
	Max							
6mg Rasagiline (6)	N	39	15	38	13	38	13	
	Mean	505.13	450.00	415.79	118.27	4.98	7.31	
	Geometric Mean	473.15	397.78	313.97	89.89	1.50	5.10	
	SD	176.14	172.17	200.27	73.00	14.24	8.02	0.000083
	Min							
	Median	500	400	400	100	1	5	
	Max							

*Wilcoxon Rank Test

b(4)

Table 15.2-3. TYR30 Ratios Matrix of Statistical Comparisons Across all Drug Treatments

	Selegiline (2)	1mg Rasagiline (3)	4mg Rasagiline (5)	6mg Rasagiline (6)	2mg Rasagiline (4a)	2mg Rasagiline (4b)
	*P-value	*P-value	*P-value	*P-value	*P-value	*P-value
Phenelzine (1)	<.0001	<.0001	0.0009	0.0005	<.0001	<.0001
Selegiline (2)		0.2665	0.0601	0.0210	0.2842	0.8779
1mg Rasagiline (3)			0.0003	0.0012	0.0072	0.1369
4mg Rasagiline (5)				0.4362	0.4210	0.0627
6mg Rasagiline (6)					0.1146	0.0170
2mg Rasagiline (4a)						0.2270

*Wilcoxon Rank Test

Reviewer Comments

- Table 15.2-3 above shows nominal statistical differences between different active treatments without correction/adjustment for multiple comparisons. Rasagiline (1 mg) is not statistically different from selegiline, suggesting similar effect on tyramine sensitivity. However, 1 mg rasagiline is statistically different from progressively higher doses of rasagiline (2,4,6 mg) and associated with a lower increase in tyramine sensitivity than these higher doses. This statistical difference for 1 mg is only observed for the 2 mg dose (group 4 a) that was studied at a similar time (after 14 days treatment) than the 2 mg group studied at a much later time (30 days for group 4 b) but the p value (0.1369) is trending toward statistical significance.

  Phenelzine is highly statistically different from each of these treatments.

  The two different 2 mg dose groups (4 a and 4b) studied at different times are not statistically different suggesting similar effects.

Table 15.2-4. Summary Table and Statistical Analysis of TYR30 and TYR30 Ratio (TSF) for 2mg Rasagiline from Group 4a vs. 2mg Rasagiline from Group 4b

TVP-1012-120-TYR	Study Period						
	Period 1		Period 3		TSF (Period1/Period3)		
	2mg Rasagiline (4a)	2mg Rasagiline (4b)	2mg Rasagiline (4a)	2mg Rasagiline (4b)	2mg Rasagiline (4a)	2mg Rasagiline (4b)	P-Value*
N	15	14	13	14	13	14	
Mean	486.67	492.86	174.04	207.14	4.67	3.79	
Geometric Mean	445.58	474.42	135.91	193.57	3.33	3.45	
SD	176.74	138.48	95.26	73.00	5.93	1.55	0.216961
Min							
Median	500	450	200	200	4	3	
Max							

*Wilcoxon Rank Test

b(4)

Reviewer Comments

- Table 15.2-4 above further shows various data for tyramine threshold responses in period 1 (before treatment) and period 2 (after treatment) for the two 2 mg groups studied after different treatment times and the effect of longer time on tyramine threshold dose and TSF. In both periods the mean, geometric mean, and median tyramine threshold doses are relatively similar. The most notable possible difference is that the geometric mean tyramine threshold dose for group 4a is somewhat lower (136 mg) than that (194 mg) for group 4b.

  The reason this evaluation was conducted because of the possibility that TSF increases after treatment based upon previously results suggested by the study of a different MAO B inhibitor. These results clearly show that TSF does not increase for rasagiline with continued treatment after achieving pharmacokinetic (PK) steady state and presumably even pharmacodynamic steady state. If there is any effect of longer treatment period, there does not seem to be a concern for increasing TSF but the possibility exists that TSF may become somewhat lower or perhaps that tyramine sensitivity may potentially decrease over time.

  It is not possible to determine if these modest, possible differences are related to duration of treatment and if they may or may not be real and reproducible or if they could be shown statistically by studying larger numbers. More specifically, it is not possible to know if the results for group 4b after 30 days of treatment are merely random variance and that if a similar study were conducted that opposite results might be observed further supporting the random variance of these results. **However, because results for the other treatment groups were not similarly studied at 30 days, I would argue that all comparisons for the 2 mg dose should focus on results for group 4a that was studied after a similar treatment duration (14 days) as most of the other treatment groups (1, 4, and 6 mg rasagiline, phenelzine, selegiline, and most of the placebo subjects) because it is possible that all other groups could have somewhat different results suggesting a consistent effect of longer treatment duration.**

  Even if all TSF results for 2 mg rasagiline treatment groups 4a and 4b were averaged, these mean results for geometric mean (2.89), median (3.5), and arithmetic mean (3.73) are consistently numerically greater than the geometric mean (2.03), median (2), and arithmetic mean (2.98) for 1 mg rasagiline and suggests that there is an additional increase in tyramine sensitivity produced by 2 mg treatment vs 1 mg treatment. This observation further supports the view that there is a dose relationship for increasing tyramine sensitivity for the 2 mg dose above the increased sensitivity observed at the 1 mg dose.

Reviewer Comments

- Table 15.2-5 below shows the distribution of tyramine threshold, pressor dose before (open-label Period 1) and after (double-blinded Period 3) treatment for subjects who were

randomized to placebo and were included in the pooled placebo group (matching placebo subjects for selegiline, 1, 2, 4, and 6 mg rasagiline treatments after 14 days of treatment). In period 1, the lowest tyramine threshold dose was 200 mg for only 5 % of subjects and the highest threshold dose was 800 mg for 13 % of subjects. Approximately 74 % of subjects showed threshold responses between 300-600 mg tyramine. Of additional interest, comprehensive results of all subject studied in Period 1 showed that 95 % of 174 subjects exhibited a threshold, pressor response at some tyramine dose up to 800 mg.

Interestingly, there is some shift of these same subjects to demonstrating threshold, pressor dose to a lower distribution of tyramine doses ranging between 12.5 and 100 mg tyramine for five subjects. This seems to be a "placebo effect" associated with the double-blinded study conditions in Period 3 but cannot easily be explained. **This observation further underscores the critical importance of utilizing a placebo-group in characterizing tyramine sensitivity for a drug because if these same subjects were treated with a drug that is clearly known not to increase tyramine sensitivity, there would be a concern that the drug increased tyramine sensitivity when in fact all that had occurred was the subjects had demonstrated a "placebo effect."** Still, the vast majority of responses in Period 3 were at similar doses (300-600 mg) for 76 % of subjects. Overall, there was a slight shifting of the distribution of threshold, pressor doses to lower tyramine doses for the whole group of pooled placebo subjects associated with conducting the same testing under double-blinded conditions after initially conducting the same study under open-label conditions.

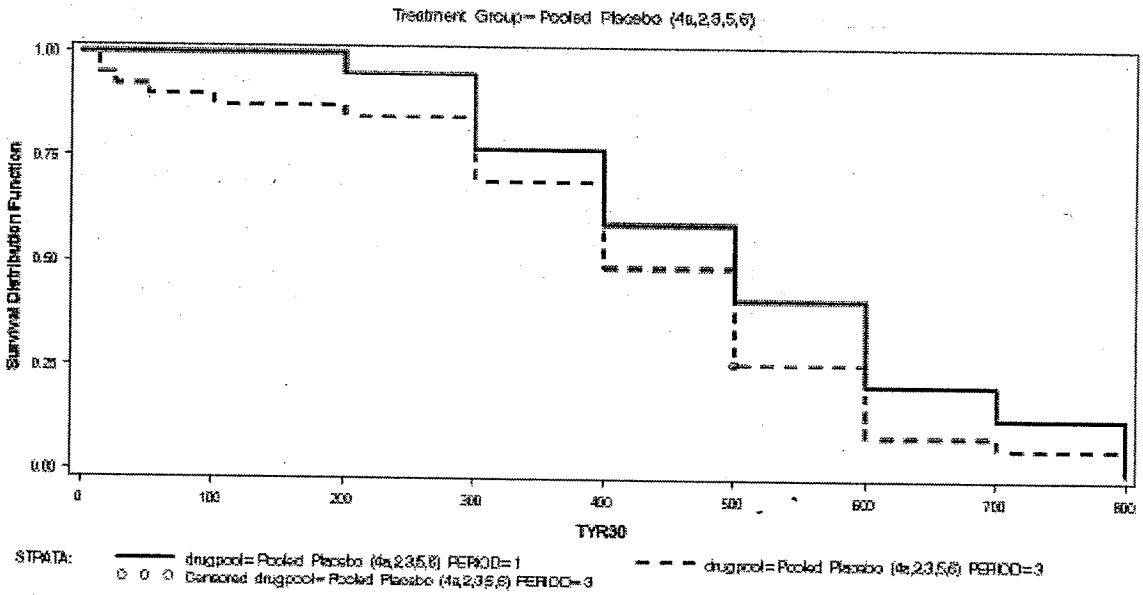
Figure 15.2-6 visually illustrates this slight shifting of tyramine doses with treatment but overall shows that there is relatively little change in the tyramine threshold, pressor doses for placebo-treated subjects.

I strongly believe that more robust and reliable comparisons with placebo can be obtained by reviewing various pooled placebo results. I have not focused much attention on results of the matching placebo groups because these matching "treatment" groups for various treatment are very small (N = 7-9) and much smaller than the active drug treatments (N = 13-17). Thus, my comments and analyses throughout this review will typically focus on active drug comparisons with pooled placebo (N = 38) instead of matching placebo. I recommend that the reader also focus attention on comparisons of active drug treatment with pooled placebo rather than those of matched placebo. I am unable to accept a convincing argument why it would not be best to make comparisons with pooled placebo rather than matching placebo. Furthermore, results for the various, individual, matching placebo groups are generally quite similar to those for the much larger pooled placebo group.

Table 15.2-5. Distribution of Subjects by Pressor Dose at each Period – Pooled Placebo (2,3 4a, 5, 6)

TVP-1012-120-TYR	Study Period			
	Period 1		Period 3	
	Pooled Placebo (4a,2,3,5,6)		Pooled Placebo (4a,2,3,5,6)	
	N	%	N	%
TYR30 (Tyramine Potentiation)				
12.5	.	.	2	5.3
25.0	.	.	1	2.6
50.0	.	.	1	2.6
100.0	.	.	1	2.6
200.0	2	5.1	1	2.6
300.0	7	17.9	6	15.8
400.0	7	17.9	8	21.1
500.0	7	17.9	9	23.7
600.0	8	20.5	6	15.8
700.0	3	7.7	1	2.6
800.0	5	12.8	2	5.3
All	39	100.0	38	100.0

Figure 15.2-6. Dose to Pressor Endpoint – Pooled Placebo



Reviewer Comments

- Figure 15.2-7 shows tyramine threshold doses for individual subjects in the pooled placebo group. In the vast majority of cases, tyramine threshold doses are identical or similar in each study period (1 and 3). The difference may be a lower or higher response in each period. In the vast majority of cases where there is a difference, the difference is relatively small (almost always $\leq$ 200 mg and frequently $\leq$ 100 mg). **When there is a more marked difference, the difference usually shows the pattern that the threshold dose is much lower in Period 3 after double-blinded treatment, further emphasizing the importance of characterizing tyramine sensitivity of a drug with a placebo group and double-blinded treatment conditions.**

Figure 15.2-7. Pressor Doses for Each Placebo Subject at Each Period

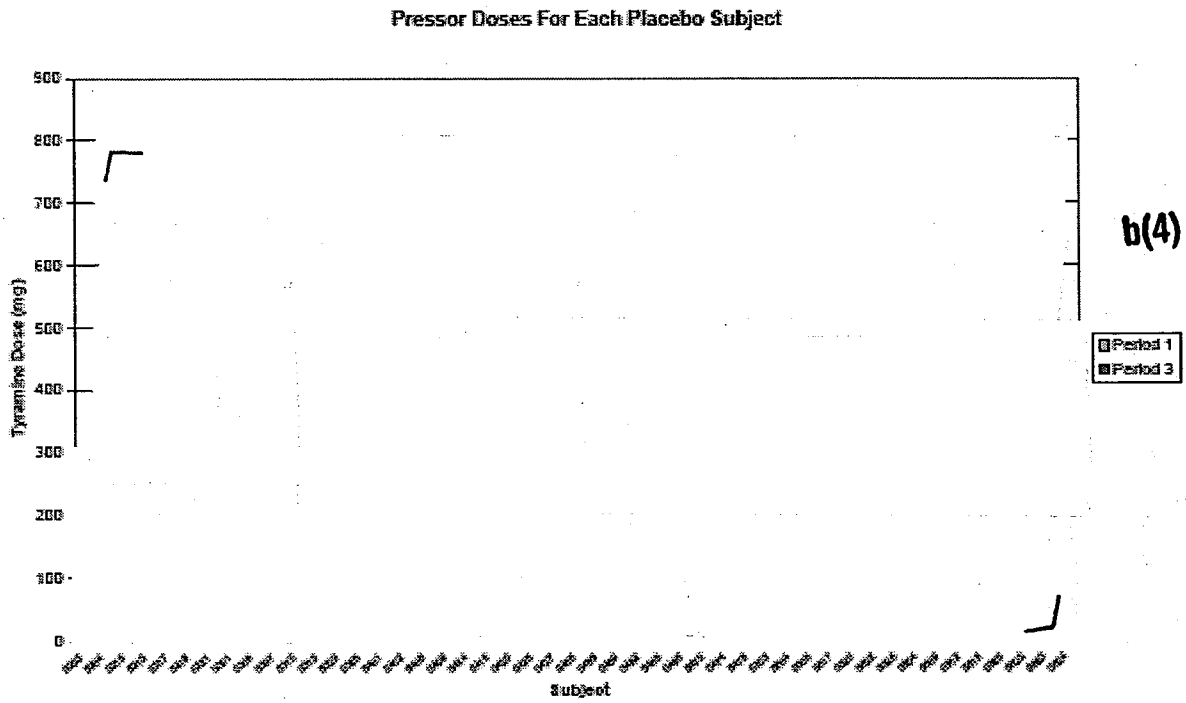


Table 15.2-8. Distribution of Subjects by Pressor Dose at each Period – Phenelzine (Group 1)

TVP-1012-120-TYR	Study Period			
	Period 1		Period 3	
	Active		Active	
	N	%	N	%
TYR30 (Tyramine Potentiation)				
5.0	.	.	1	6.7
15.0	.	.	1	6.7
25.0	.	.	7	46.7
35.0	.	.	3	20.0
45.0	.	.	2	13.3
75.0	.	.	1	6.7
300.0	3	18.8	.	.
400.0	5	31.3	.	.
500.0	1	6.3	.	.
600.0	6	37.5	.	.
700.0	1	6.3	.	.
All	16	100.0	15	100.0

Reviewer Comments

- Pre- and post-treatment results for the non-selective MAO inhibitor, phenelzine (45 mg), that was studied as a positive control, show a marked shift in the distribution of tyramine threshold, pressor doses (Table 15.2-8). Pre-treatment (Period 1) distribution was similar to that for the pooled placebo but there is overall markedly lower distribution of doses in Period 3 after treatment. There is no overlap in distribution and post-treatment doses range from 5-75 mg, with the vast majority occurring at 25-45 mg tyramine, a range of tyramine content that could occur with ingestion of tyramine-rich food or beverages. Figure 15.2-9 further shows this marked change in distribution of doses visually.

Figure 15.2-9. Dose to Pressor Endpoint – Phenelzine (Group 1)

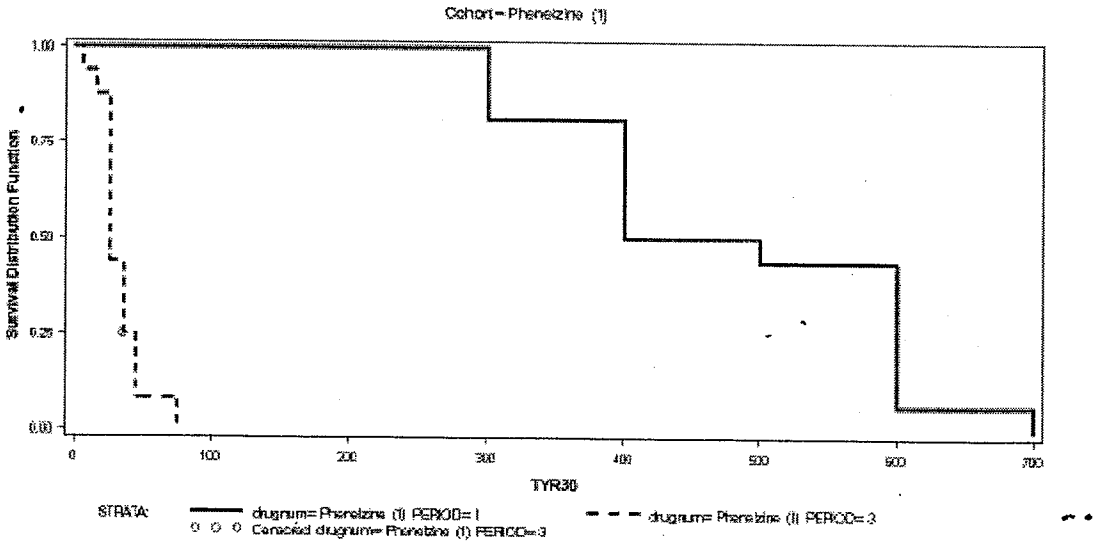


Table 15.2-10. Distribution of Subjects by Pressor Dose at each Period - Selegiline (Group 2) vs. Matching Placebo

TVP-1012-120-TYR	Study Period							
	Period 1				Period 3			
	Matching Placebo		Active		Matching Placebo		Active	
	N	%	N	%	N	%	N	%
TYR30 (Tyramine Potentiation)								
12.5	.	.	.	.	.	.	1	6.7
25.0	.	.	.	.	1	14.3	1	6.7
50.0	.	.	1	6.7	.	.	.	.
100.0	.	.	1	6.7	1	14.3	5	33.3
200.0	1	14.3	1	6.7	.	.	3	20.0
300.0	2	28.6	3	20.0	.	.	4	26.7
400.0	.	.	3	20.0	1	14.3	1	6.7
500.0	.	.	3	20.0	3	42.9	.	.
600.0	3	42.9	1	6.7	1	14.3	.	.
700.0	1	14.3	2	13.3	.	.	.	.
All	7	100.0	15	100.0	7	100.0	15	100.0

Reviewer Comments

- Pre- and post-treatment results for 10 mg selegiline, that was studied as a comparator for a U.S. marketed "selective" MAO B inhibitor, show a modest shift in the distribution of tyramine threshold, pressor doses (Table 15.2-10). In the pre-treatment (Period 1), the bulk of doses were distributed between 200-600 mg but after selegiline treatment the bulk of doses were distributed between 100-300 mg indicating an increase in tyramine sensitivity. Two subjects also showed very low dose responses (12.5 or 25 mg). Figure 15.2-11 further shows this change in dose distribution visually for selegiline treatment. Attention to this table and figure and similar ones for other active drug treatments should focus on active drug treatment results and not those of matching placebo.

Figure 15.2-11. Dose to Pressor Endpoint – Selegiline, Matching Placebo (Group 2)

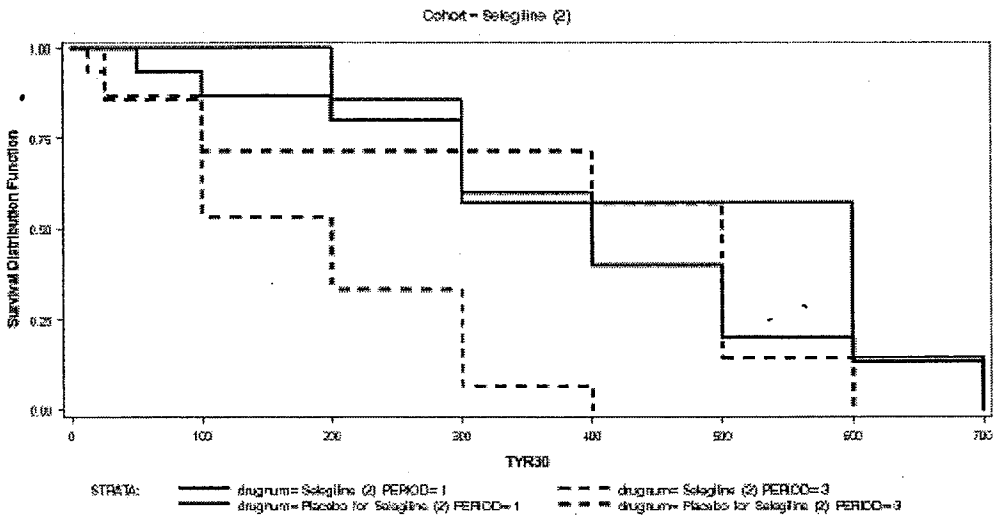


Table 15.2-12. Distribution of Subjects by Pressor Dose at each Period - 1 mg Rasagiline (Group 3) vs. Matching Placebo

TVP-1012-120-TYR	Study Period							
	Period 1				Period 3			
	Matching Placebo		Active		Matching Placebo		Active	
	N	%	N	%	N	%	N	%
TYR30 (Tyramine Potentiation)								
12.5	.	.	.	.	1	14.3	.	.
25.0	.	.	.	.	.	.	1	6.7
200.0	1	14.3	.	.	.	.	7	46.7
300.0	1	14.3	3	18.8	.	.	5	33.3
400.0	1	14.3	6	37.5	4	57.1	2	13.3
500.0	1	14.3	3	18.8	1	14.3	.	.
600.0	2	28.6	3	18.8	1	14.3	.	.
700.0	.	.	1	6.3	.	.	.	.
800.0	1	14.3	.	.	.	.	.	.
All	7	100.0	16	100.0	7	100.0	15	100.0

Reviewer Comments

- Pre- and post-treatment results for1 mg rasagiline show a modest shift in the distribution of tyramine threshold, pressor doses (Table 15.2-12). In the pre-treatment (Period 1), the bulk of doses were distributed between 300-600 mg but after rasagiline treatment the bulk of doses were lower (200-400 mg). One subject also showed a very low dose response (25 mg). Nearly half (47 %) of the subjects showed a tyramine, threshold, pressure response at 200 mg, a dose that is rarely a threshold pressor dose for subjects in the pre-treatment Period 1 or even in the post-treatment Period 3 for pooled placebo (previous Table 15.2-5). **Eight subjects (53 %) treated with 1 mg rasagiline showed threshold, pressor response at 200 mg or lower compared to a much smaller percentage (16 %) of pooled placebo patients, clearly indicating that this dose of rasagiline increases tyramine sensitivity.** Figure 15.2-13 further shows this change in distribution of doses visually for rasagiline treatment.

Figure 15.2-13. Dose to Pressor Endpoint – 1 mg Rasagiline, Matching Placebo (Group 3)

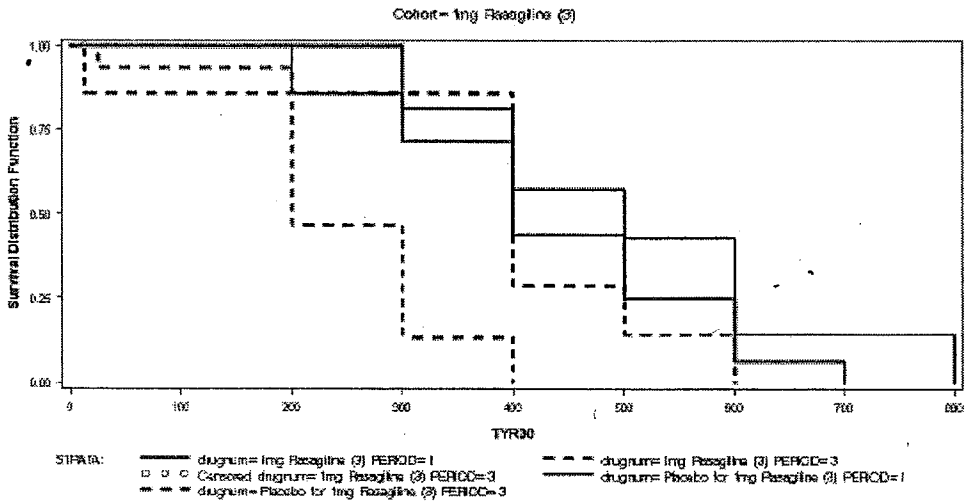


Table 15.2-14. Distribution of Subjects by Pressor Dose at each Period - 2 mg Rasagiline (Group 4a) vs. Matching Placebo

TVP-1012-120-TYR	Study Period							
	Period 1				Period 3			
	Matching Placebo		Active		Matching Placebo		Active	
	N	%	N	%	N	%	N	%
TYR30 (Tyramine Potentiation)								
12.5	.	.	.	.	1	11.1	1	7.7
50.0	.	.	.	.	1	11.1	1	7.7
100.0	.	.	1	6.7	.	.	3	23.1
200.0	.	.	.	.	1	11.1	5	38.5
300.0	2	22.2	1	6.7	2	22.2	3	23.1
400.0	3	33.3	5	33.3	.	.	.	.
500.0	1	11.1	3	20.0	3	33.3	.	.
600.0	1	11.1	2	13.3	.	.	.	.
700.0	1	11.1	2	13.3	.	.	.	.
800.0	1	11.1	1	6.7	1	11.1	.	.
All	9	100.0	15	100.0	9	100.0	13	100.0

Reviewer Comments

- Pre- and post-treatment (**14 days**) results for 2 mg rasagiline show a shift in the distribution of tyramine threshold, pressor doses (Table 15.2-14). In pre-treatment Period 1, the bulk of doses were distributed between 400-700 mg but after rasagiline treatment the bulk of doses were considerably lower (100-300 mg). Two subjects also showed very low dose responses (12.5 and 50 mg). Most subjects (77 %) showed a tyramine, threshold response at doses of ≤ 200 mg, doses that rarely exert a threshold pressor response for subjects in pre-treatment Period 1 or even in the post-treatment Period 3 for pooled placebo (previous Table 15.2-5). These responses indicated that 2 mg rasagiline increases tyramine sensitivity and a dose-dependent effect because increased tyramine sensitivity was greater for 2 mg vs 1 mg. Figure 15.2-15 further shows this change in distribution of doses visually for rasagiline treatment and that the shift is greater for 2 mg vs 1 mg.

Figure 15.2-15. Dose to Pressor Endpoint – 2 mg Rasagiline, Matching Placebo (Group 4a)

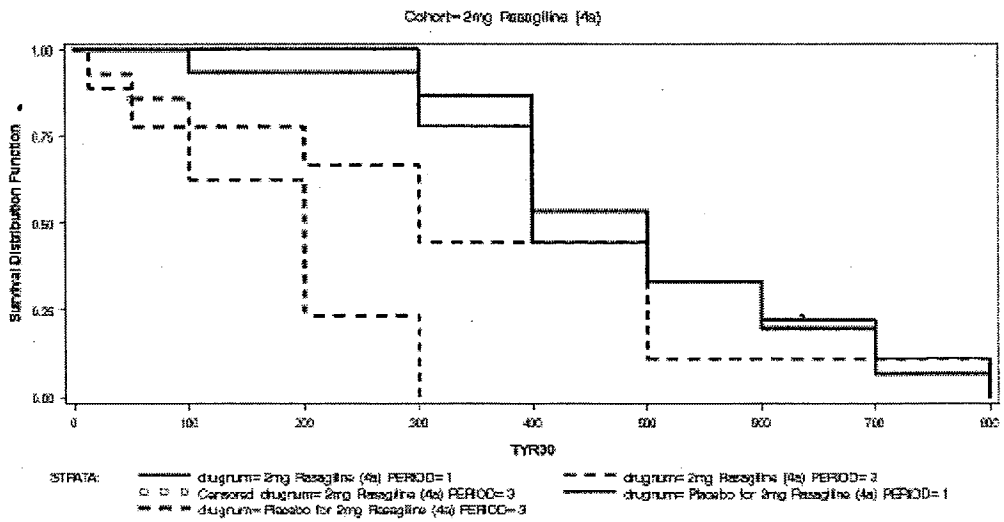


Table 15.2-16. Distribution of Subjects by Pressor Dose at each Period - 2 mg Rasagiline (Group 4b) vs. Matching Placebo

TVP-1012-120-TYR	Study Period							
	Period 1				Period 3			
	Matching Placebo		Active		Matching Placebo		Active	
	N	%	N	%	N	%	N	%
TYR30 (Tyramine Potentiation)								
12.5	.	.	.	.	1	11.1	.	.
100.0	.	.	.	.	.	.	3	21.4
200.0	.	.	.	.	2	22.2	7	50.0
300.0	3	33.3	2	14.3	1	11.1	4	28.6
400.0	2	22.2	5	35.7	3	33.3	.	.
500.0	1	11.1	1	7.1	.	.	.	.
600.0	2	22.2	4	28.6	2	22.2	.	.
700.0	.	.	2	14.3	.	.	.	.
800.0	1	11.1	.	.	.	.	.	.
All	9	100.0	14	100.0	9	100.0	14	100.0

Reviewer Comments

- Pre- and post-treatment (**30 days**) results for 2 mg rasagiline show a shift in the distribution of tyramine threshold, pressor doses (Table 15.2-16). In pre-treatment Period 1, the bulk of doses were distributed between 300-600 mg but after rasagiline treatment all doses were considerably lower (100-300 mg). Most subjects (71 %) showed a tyramine, threshold response at doses of ≤ 200 mg, doses that rarely exert a threshold pressor response in the untreated state. **These responses were similar to those after 14 days treatment and indicated that rasagiline-induced increased tyramine sensitivity does not increase with duration of treatment after achieving PK steady state.** 15.2-17 visually shows that the shift in sensitivity in distribution of threshold doses visually is similar for 2 mg rasagiline treatment after 30 days vs 14 days (Figure 15.2-15).

Figure 15.2-17. Dose to Pressor Endpoint – 2 mg Rasagiline, Matching Placebo (Group 4b)

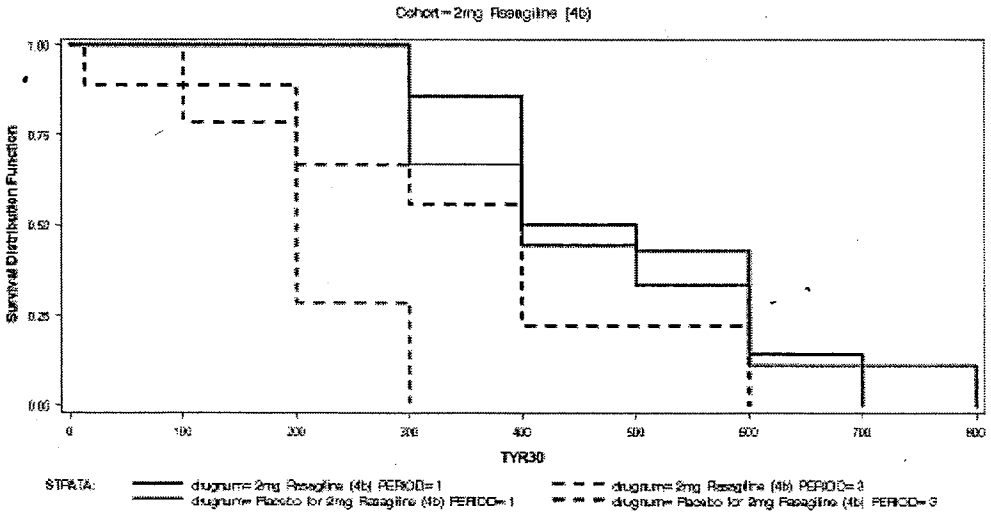


Table 15.2-18. Distribution of Subjects by Pressor Dose at each Period - 4 mg Rasagiline (Group 5) vs. Matching Placebo

TVP-1012-120-TYR	Study Period							
	Period 1				Period 3			
	Matching Placebo		Active		Matching Placebo		Active	
	N	%	N	%	N	%	N	%
TYR30 (Tyramine Potentiation)								
12.5	.	.	.	.	.	.	2	11.8
25.0	.	.	.	.	.	.	1	5.9
100.0	.	.	.	.	.	.	5	29.4
200.0	.	.	1	5.9	.	.	8	47.1
300.0	1	14.3	2	11.8	4	57.1	1	5.9
400.0	3	42.9	3	17.6	1	14.3	.	.
500.0	.	.	6	35.3	.	.	.	.
600.0	1	14.3	1	5.9	1	14.3	.	.
700.0	.	.	1	5.9	.	.	.	.
800.0	2	28.6	3	17.6	1	14.3	.	.
All	7	100.0	17	100.0	7	100.0	17	100.0

Reviewer Comments

- Pre- and post-treatment results for 4 mg rasagiline show a marked shift in the distribution of tyramine threshold, pressor doses (Table 15.2-18). In pre-treatment Period 1, the bulk of doses were distributed between 300-800 mg but after rasagiline treatment the bulk of doses were much lower (100-200 mg) with minimal overlap with threshold dose in the pre-treatment period. Three subjects also showed very low dose responses (12.5 - 25 mg). Almost all subjects (94 %) showed a tyramine, threshold response at doses of $\leq$ 200 mg, doses that rarely exert a threshold pressor response in the untreated state. These responses indicated that 4 mg rasagiline dose-dependently further increases tyramine sensitivity beyond that of 2 mg. Figure 15.2-19 further shows this change in distribution of doses visually for rasagiline treatment and that the shift is greater for 4 mg vs 2 mg.

Figure 15.2-19. Dose to Pressor Endpoint – 4 mg Rasagiline, Matching Placebo (Group 5)

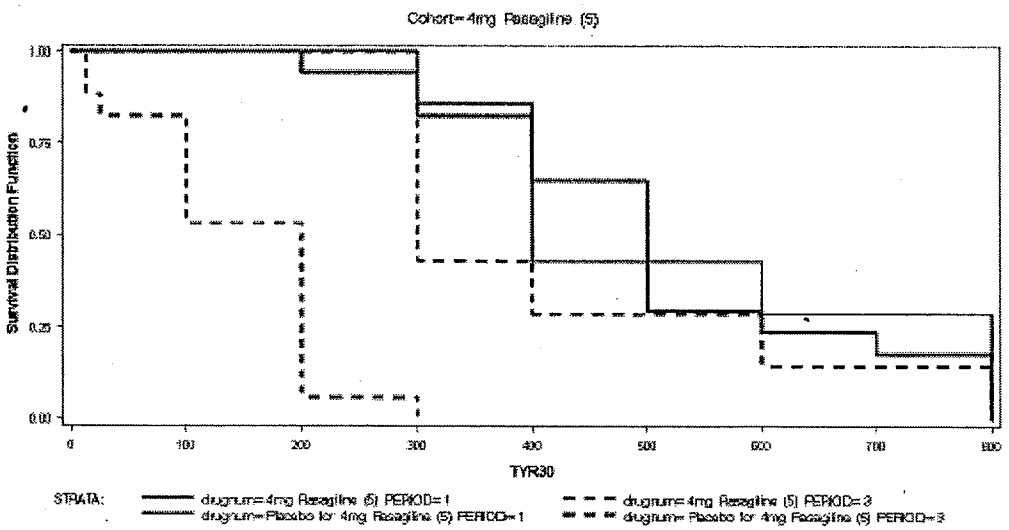


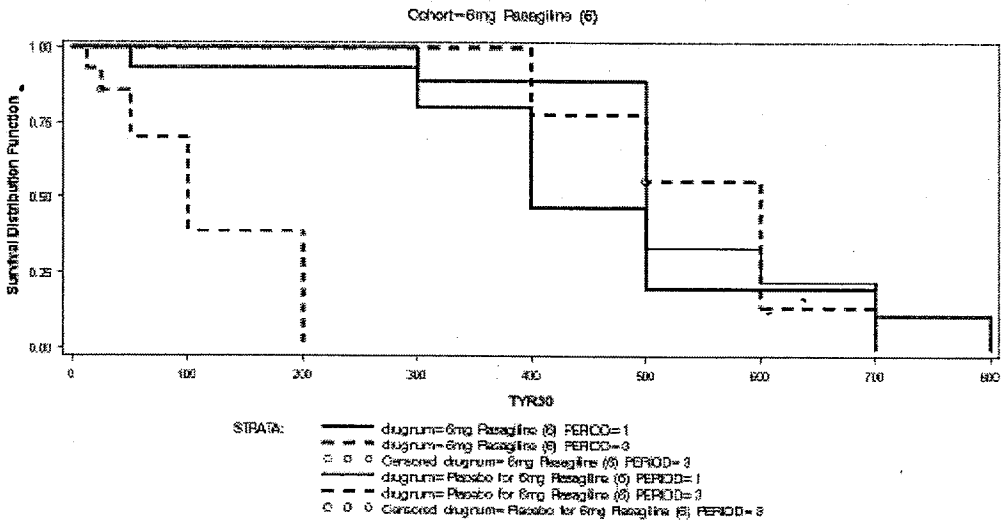
Table 15.2-20. Distribution of Subjects by Pressor Dose at each Period - 6 mg Rasagiline (Group 6) vs. Matching Placebo

TVP-1012-120-TYR	Study Period							
	Period 1				Period 3			
	Matching Placebo		Active		Matching Placebo		Active	
	N	%	N	%	N	%	N	%
TYR30 (Tyramine Potentiation)								
12.5	.	.	.	.	.	.	1	7.7
25.0	.	.	.	.	.	.	1	7.7
50.0	.	.	1	6.7	.	.	2	15.4
100.0	.	.	.	.	.	.	4	30.8
200.0	.	.	.	.	.	.	5	38.5
300.0	1	11.1	2	13.3	.	.	.	.
400.0	.	.	5	33.3	2	25.0	.	.
500.0	5	55.6	4	26.7	2	25.0	.	.
600.0	1	11.1	.	.	3	37.5	.	.
700.0	1	11.1	3	20.0	1	12.5	.	.
800.0	1	11.1	.	.	.	.	.	.
All	9	100.0	15	100.0	8	100.0	13	100.0

Reviewer Comments

- Pre- and post-treatment results for 6 mg rasagiline show a very marked shift in the distribution of tyramine threshold, pressor doses (Table 15.2-20). In pre-treatment Period 1, the bulk of doses were distributed between 300-700 mg but after rasagiline treatment the bulk of doses were much lower (100-300 mg) **with no overlap with threshold dose in the pre-treatment period**. Four subjects (31 %) also showed very low dose responses (12.5 - 50 mg). All subjects showed a tyramine, threshold response at doses of $\leq$ 200 mg, doses that rarely exert a threshold pressor response in the untreated state. These responses indicated that 6 mg rasagiline dose-dependently further increases tyramine sensitivity beyond that of 4 mg. Figure 15.2-19 further shows this change in distribution of doses visually for rasagiline treatment and that the shift is marked and greater for 6 mg vs 4 mg.

Figure 15.2-21. Dose to Pressor Endpoint – 6 mg Rasagiline, Matching Placebo (Group 6)



Reviewer Comments

- **I have created Table A to summarize the frequency of tyramine threshold pressor responses and corresponding TSF for relatively low tyramine doses (< 200 mg) for all the different treatments**. Table A shows that phenelizine was an excellent positive control for tyramine threshold responses and that 93 % of subjects showed a threshold response at ≤ 50 mg and that 100 % showed a threshold response at ≤ 100 mg. Table A also clearly shows that rasagiline treatment at all doses 1-6 mg) increased tyramine sensitivity. At 1 mg, this increased tyramine sensitivity occurs at a dose of 200 mg tyramine hydrochloride (i.e., 158 mg free tyramine; as tyramine occurs in food) based upon an increased percentage (53 %) of subjects treated with 1 mg rasagiline showing a tyramine threshold, pressor response compared to a much lower percentage (16 %) for placebo-treated patients. At tyramine doses up to 200 mg, all higher rasagiline treatments showed progressively higher percentages of subjects showing tyramine threshold pressor responses, ranging from 77 % at 2 mg (14 days) to 100 % at 6 mg. There is also an increased tyramine sensitivity (vs placebo and 1 mg rasagiline) at doses up to 50 mg or up to 100 mg for these higher than recommending doses (2-6 mg) in the label and this increase tyramine sensitivity is dose-dependent.

  It is also quite noteworthy that the approved/recommended dose of selegiline (i.e., Eldepryl) also increased tyramine sensitivity (vs placebo). This increased tyramine sensitivity for selegiline was demonstrated by the increased percentages of subjects (vs placebo) who had tyramine threshold pressor responses at all tyramine doses up to either 100 mg (47 % vs 13 %) or 200 mg (67 % vs 16 %). This demonstration of selegiline-induced increased tyramine sensitivity appeared to be similar to that caused by 1 mg rasagiline.

- Table B, which I also created, shows the percentage of subjects who had various high TSF thresholds (e.g., > 5, > 10, > 20) for the various treatments. Both 4 and 6 mg rasagiline treatment groups had increased percentages of subjects with TSFs > 5, > 10, and > 20 vs pooled placebo. The 6 mg dose had higher numerical percentages of subjects for TSF > 5 and > 10 compared to percentages for 4 mg. The percentage of subjects with TSF > 20 was slightly lower for the 6 mg group than the 4 mg group.

- The subsequent listing shows results for individual TSFs and tyramine threshold, pressor dose for Periods 1 and 3 for each treatment. This listing shows the variability of results for individual subjects in all treatment groups including those for placebo subjects.

Table A (Reviewer Table) Frequency of Post-Treatment $TYR30_3$ Threshold Dose at ≤ 200 mg According to Treatment

Tyramine Potentiation of SBP to Threshold Increment	Treatment (Period 3)							
	Phenelzine N=15 (%)	Selegiline N=15 (%)	Pooled Placebo N=38 (%)	Rasagiline 1 mg/day N=15 (%)	Rasagiline 2 mg/day (14 days) N=13 (%)	Rasagiline 2 mg/day (30 days) N=14 (%)	Rasagiline 4 mg/day N=17(%)	Rasagiline 6 mg/day N=13(%)
5 mg	1 (7)							
12.5 mg		1 (7)	2 (5.)		1 (7)		2 (12)	1 (8)
15 mg	1 (7)			1 (7)				
25 mg	7 (47)	1 (7)	1 (3)				1 (6)	1 (8)
35 mg	3 (20)							
45 mg	2 (13)							
50 mg	3 (20)		1 (3)		1 (8)			2 (15)
75 mg	1 (7)							
100 mg		5 (33)	1 (3)	0 (0)	3 (23)	3 (21)	5 (29)	4 (31)
200 mg		3 (20)	1 (3)	7 (47)	5 (38)	7 (50)	8 (47)	5 (38)
≤ 50 mg	14 (93)	2 (13)	4 (11)	1 (7)	2 (15)	0 (0)	3 (18)	4 (31)
≤ 100 mg	15 (100)	7 (47)	5 (13)	1 (7)	5 (38)	3 (21)	8 (47)	8 (62)
≤ 200 mg	15 (100)	10 (67)	6 (16)	8 (53)	10 (77)	10 (71)	16 (94)	13 (100)

Table B (Reviewer Table) $TYR30_3$/TSF in Periods 1 and 3, and Frequency of Various Increased Tyramine Sensitivity Factor (TSF) Thresholds According to Treatment

$TYR30_3$ Potentiation Dose of SBP in Periods 1 and 3 and Various Tyramine Sensitivity Factor (TSF) Thresholds	Treatment (14 Days for Phenelzine, Selegiline, and 1, 4, and 6 mg Daily Rasagiline for Treatments Not Specified)							
	Phenelzine	Selegiline	Placebo * 14 Days 30 Days 14+30 Days	Rasagiline 1 mg/day	Rasagiline 2 mg/day 14 days 14+30 days	Rasagiline 2 mg/day 30 days	Rasagiline 4 mg/day	Rasagiline 6 mg/day
$TYR30_3$ Period 1 (Pre-treatment) < 200 mg	0/16 (0 %)	3/15 (20 %)	2/39 (5 %) 0/9 (0 %) 2/48 (4 %)	0/16 (0 %)	1/15 (7 %) 1/29 (3 %)	0/14 (0 %)	1/17 (6 %)	1/15 (7 %)
$TYR30_3$ Period 3 (Post-treatment) < 50 mg	14/15 (93 %)	2/15 (13 %)	4/38 (11 %) 1/9 (11 %) 5/47 (11 %)	1/15 (7 %)	2/13 (15 %) 2/27 (7 %)	0/14 (0 %)	3/17 (18 %)	4/13 (31 %)
TSF = $TYR30_3$ Period 1 $TYR30_3$ Period 3 > 5.0	15/15 (100 %)	2/15 (13 %)	5/38 (13 %) 1/9 (11 %) 6/47 (13 %)	1/15 (7 %)	3/13 (15 %) 4/27 (15 %)	1/14 (7 %)	3/17 (18 %)	7/13 (54 %)
TSF = $TYR30_3$ Period 1 $TYR30_3$ Period 3 > 10.0	13/15 (87 %)	1/15 (7 %)	3/38 (8 %) 1/9 (11 %) 4/47 (9 %)	1/15 (7 %)	1/13 (8 %) 2/27 (7 %)	1/14 (7 %)	2/17 (12 %)	2/13 (15 %)
TSF = $TYR30_3$ Period 1 $TYR30_3$ Period 3 > 20.0	7/15 (58 %)	1/15 (7 %)	2/38/ (5 %) 1/9 (11 %) 3/47 (6 %)	1/15 (7 %)	1/13 (8 %) 2/27 (7 %)	1/14 (7 %)	2/17 (12 %)	1/13 (8 %)

* Placebo (Pooled) for 14 Days and 14+30 Days; 30 Day Placebo (Not Pooled)

Listing of Tyramine Threshold Pressor Doses in Periods 1 and 3 and TSF for Individual Subjects According to Treatment

Subject Number	Treatment Group	TYR30 Potentiation at Period 1 (P1)	TYR30 Potentiation at Period 3 (P3)	Tyramine Sensitivity Factor (TSF) P1/P3
101	Phenelzine (1)			
102	Phenelzine (1)			
103	Phenelzine (1)			
104	Phenelzine (1)			
105	Phenelzine (1)			
107	Phenelzine (1)			
108	Phenelzine (1)			
109	Phenelzine (1)			
110	Phenelzine (1)			
111	Phenelzine (1)			
112	Phenelzine (1)			
113	Phenelzine (1)			
114	Phenelzine (1)			
115	Phenelzine (1)			
116	Phenelzine (1)			
117	Phenelzine (1)			
201	Selegiline (2)			
202	Selegiline (2)			
203	Placebo for Selegiline (2)			
204	Placebo for Selegiline (2)			
206	Selegiline (2)			
207	Selegiline (2)			
208	Selegiline (2)			
209	Selegiline (2)			
210	Placebo for Selegiline (2)			
211	Selegiline (2)			
212	Selegiline (2)			
213	Placebo for Selegiline (2)			
214	Selegiline (2)			
215	Selegiline (2)			
216	Selegiline (2)			
217	Placebo for Selegiline (2)			
218	Placebo for Selegiline (2)			
219	Selegiline (2)			
220	Selegiline (2)			
221	Placebo for Selegiline (2)			
222	Selegiline (2)			
224	Selegiline (2)			
301	Placebo for 1mg Rasagiline (3)			
302	1mg Rasagiline (3)			
303	1mg Rasagiline (3)			
304	1mg Rasagiline (3)			
305	1mg Rasagiline (3)			
306	Placebo for 1mg Rasagiline (3)			
307	Placebo for 1mg Rasagiline (3)			
309	1mg Rasagiline (3)			
310	Placebo for 1mg Rasagiline (3)			
311	1mg Rasagiline (3)			
312	1mg Rasagiline (3)			
313	1mg Rasagiline (3)			
314	1mg Rasagiline (3)			
315	Placebo for 1mg Rasagiline (3)			
316	1mg Rasagiline (3)			
317	1mg Rasagiline (3)			
318	1mg Rasagiline (3)			
319	1mg Rasagiline (3)			
320	Placebo for 1mg Rasagiline (3)			
321	1mg Rasagiline (3)			
322	1mg Rasagiline (3)			
323	1mg Rasagiline (3)			
325	Placebo for 1mg Rasagiline (3)			
401	Placebo for 2mg Rasagiline (4a)			
402	Placebo for 2mg Rasagiline (4a)			
403	2mg Rasagiline (4a)			

b(4)

Listing of Tyramine Threshold Pressor Doses in Periods 1 and 3 and TSF for Individual Subjects According to Treatment (Continued)

404	2mg Rasagiline (4a)
405	Placebo for 2mg Rasagiline (4a)
407	2mg Rasagiline (4a)
408	2mg Rasagiline (4a)
409	Placebo for 2mg Rasagiline (4a)
410	2mg Rasagiline (4a)
412	2mg Rasagiline (4a)
413	2mg Rasagiline (4a)
414	Placebo for 2mg Rasagiline (4a)
417	2mg Rasagiline (4a)
418	Placebo for 2mg Rasagiline (4a)
419	2mg Rasagiline (4a)
420	Placebo for 2mg Rasagiline (4a)
421	2mg Rasagiline (4a)
422	2mg Rasagiline (4a)
423	2mg Rasagiline (4a)
424	2mg Rasagiline (4a)
425	Placebo for 2mg Rasagiline (4a)
426	2mg Rasagiline (4a)
427	Placebo for 2mg Rasagiline (4a)
428	2mg Rasagiline (4a)
450	2mg Rasagiline (4b)
451	2mg Rasagiline (4b)
455	Placebo for 2mg Rasagiline (4b)
456	Placebo for 2mg Rasagiline (4b)
457	2mg Rasagiline (4b)
458	2mg Rasagiline (4b)
459	Placebo for 2mg Rasagiline (4b)
460	2mg Rasagiline (4b)
461	2mg Rasagiline (4b)
462	Placebo for 2mg Rasagiline (4b)
463	2mg Rasagiline (4b)
464	2mg Rasagiline (4b)
465	Placebo for 2mg Rasagiline (4b)
466	2mg Rasagiline (4b)
467	2mg Rasagiline (4b)
468	Placebo for 2mg Rasagiline (4b)
469	2mg Rasagiline (4b)
470	Placebo for 2mg Rasagiline (4b)
471	2mg Rasagiline (4b)
474	Placebo for 2mg Rasagiline (4b)
475	2mg Rasagiline (4b)
476	2mg Rasagiline (4b)
478	Placebo for 2mg Rasagiline (4b)
501	4mg Rasagiline (5)
502	4mg Rasagiline (5)
503	Placebo for 4mg Rasagiline (5)
504	Placebo for 4mg Rasagiline (5)
505	4mg Rasagiline (5)
506	4mg Rasagiline (5)
507	4mg Rasagiline (5)
508	Placebo for 4mg Rasagiline (5)
509	4mg Rasagiline (5)
510	4mg Rasagiline (5)
512	4mg Rasagiline (5)
514	4mg Rasagiline (5)
515	4mg Rasagiline (5)
516	4mg Rasagiline (5)
517	Placebo for 4mg Rasagiline (5)
518	4mg Rasagiline (5)
519	4mg Rasagiline (5)
520	Placebo for 4mg Rasagiline (5)
521	4mg Rasagiline (5)
522	Placebo for 4mg Rasagiline (5)

b(4)

Listing of Tyramine Threshold Pressor Doses in Periods 1 and 3 and TSF for Individual Subjects According to Treatment (Continued)

524	4mg Rasagiline (5)
525	4mg Rasagiline (5)
526	Placebo for 4mg Rasagiline (5)
527	4mg Rasagiline (5)
601	6mg Rasagiline (6)
602	6mg Rasagiline (6)
603	6mg Rasagiline (6)
604	Placebo for 6mg Rasagiline (6)
605	Placebo for 6mg Rasagiline (6)
607	6mg Rasagiline (6)
608	6mg Rasagiline (6)
609	Placebo for 6mg Rasagiline (6)
612	Placebo for 6mg Rasagiline (6)
613	6mg Rasagiline (6)
615	6mg Rasagiline (6)
616	6mg Rasagiline (6)
617	6mg Rasagiline (6)
618	Placebo for 6mg Rasagiline (6)
619	6mg Rasagiline (6)
620	Placebo for 6mg Rasagiline (6)
621	6mg Rasagiline (6)
622	Placebo for 6mg Rasagiline (6)
623	Placebo for 6mg Rasagiline (6)
624	Placebo for 6mg Rasagiline (6)
625	6mg Rasagiline (6)
626	6mg Rasagiline (6)
627	6mg Rasagiline (6)
629	6mg Rasagiline (6)

b(4)

Reviewer Comments

- Listing 17.2.6-6 below shows individual results for very high TSF (> 20). Although most of these subjects were in the phenelzine group, 5 subjects were also in the 4 or 6 mg rasagiline group. **Of significant interest, there was one subject in the 1 and 2 mg rasagiline groups, one subject in the selegiline group, and three subjects in the placebo group. This observation further emphasizes the critical importance of characterizing tyramine sensitivity with placebo subjects under double-blinded conditions.**

Listing 17.2.6-6 List of Subjects with TSF>10

subject number	Treatment Group	TSF
104	Phenelzine (1)	
110	Phenelzine (1)	
603	6mg Rasagiline (6)	
108	Phenelzine (1)	
117	Phenelzine (1)	
105	Phenelzine (1)	
114	Phenelzine (1)	
109	Phenelzine (1)	
309	1mg Rasagiline (3)	
107	Phenelzine (1)	
112	Phenelzine (1)	
115	Phenelzine (1)	
116	Phenelzine (1)	
220	Selegiline (2)	
428	2mg Rasagiline (4a)	
456	Placebo for 2mg Rasagiline (4b)	
509	4mg Rasagiline (5)	
102	Phenelzine (1)	
519	4mg Rasagiline (5)	
621	6mg Rasagiline (6)	
521	4mg Rasagiline (5)	
103	Phenelzine (1)	
310	Placebo for 1mg Rasagiline (3)	
427	Placebo for 2mg Rasagiline (4a)	

b(4)

3.2.4 Sensitivity Analyses For Characterizing TSF by TYR30 Threshold Pressor Responses

Sensitivity Analyses of TYR 30/TSF Ratios with Different Criteria for Threshold Response

Based upon DNP recommendations, the sponsor conducted various sensitivity analyses of the TYR30/TSF) ratios. Not infrequently, a single elevation of SBP to ≥ 30 mm Hg above the pre-treatment SBP might be considered to be a tyramine threshold, pressor response. However, the DNP has been concerned that a single threshold increment might be a non-specific increase for some unknown reason and has thought that a more sustained increase to the threshold value or above it ought to represent a more specific response to tyramine. In addition, previous DNP experience has shown the requiring a more sustained SBP increase to determine a threshold, pressor response provides more reliable TSF data.

The following sensitivity analyses show data comparisons for different tyramine pressor thresholds requiring : 1) three consecutive SBP threshold increases (≥ 30 mm Hg above the mean pre-treatment value) 5 minutes apart (Table 15); 2) two consecutive SBP threshold increases 5 minutes apart (Table 18); and 3) a single SBP threshold increase (Table 19).

Table 15 Summary Table of $TYR30_3$ Ratios

	Arithmetic Mean	Geometric Mean	Median
Phenelzine (1)	20.14	17.32	17
Selegiline (2)	3.87	2.47	2
1 mg Rasagiline (3)	2.98	2.03	2
2 mg Rasagiline (4a)	4.67	3.33	4
2 mg Rasagiline (4b)	2.79	2.45	3
4 mg Rasagiline (5)	8.22	4.50	4
6 mg Rasagiline (6)	7.31	5.10	5
Pooled Placebo (4a,2,3,5,6)	4.98	1.50	1

Table 18 Summary Table of $TYR30_2$ Ratios

	Arithmetic Mean	Geometric Mean	Median
Phenelzine (1)	18.25	14.20	18
Selegiline (2)	3.58	2.52	2
1 mg Rasagiline (3)	3.10	2.15	2
2 mg Rasagiline (4a)	4.50	3.12	3
2 mg Rasagiline (4b)	2.67	2.31	2
4 mg Rasagiline (5)	9.39	4.95	4
6 mg Rasagiline (6)	8.73	5.46	5
Pooled Placebo (4a,2,3,5,6)	5.96	1.61	1

Table 19 Summary Table of $TYR30_1$ Ratios

	Arithmetic Mean	Geometric Mean	Median
Phenelzine (1)	15.34	11.37	16
Selegiline (2)	5.37	2.76	2
1 mg Rasagiline (3)	4.84	2.16	2
2 mg Rasagiline (4a)	7.12	4.07	3
2 mg Rasagiline (4b)	5.4	2.45	3
4 mg Rasagiline (5)	6.12	2.67	3
6 mg Rasagiline (6)	11.82	5.12	5
Pooled Placebo (4a,2,3,5,6)	6.01	2.16	1

Reviewer Comments

- I have created Table C which integrates results of Table 15, 18, and 19 and allows a comparison of geometric mean, arithmetic mean, and median for each treatment according to the three different tyramine pressor thresholds.

- Table C shows results for $TYR30_3$ (i.e., TSF based upon at least 3 consecutive SBP increases of 30 mm Hg or more at 5 minute intervals) (e.g., a sustained increase for a least 10 minutes) for different presentations of central tendency (e.g., arithmetic mean, geometric mean, and median). In this comparative analysis, results for geometric mean and median appear to make more scientific sense than results for arithmetic mean. The lowest ratio is observed for pooled placebo and the highest ratio is for phenelzine as would be expected/predicted. Results further show that the 1 mg rasagiline ratio is numerically greater than placebo and that the ratios dose-dependently, and progressively increase such that the highest rasagiline ratio is observed at the 6 mg dose. In contrast,

comparison of arithmetic means does not make as much scientific sense because pooled placebo is numerically greater than several active drug treatments and the 4 mg rasagiline ratio is greater than that for 6 mg. Geometric mean and arithmetic mean for 1 mg rasagiline is somewhat less than that for selegiline but median TSF is similar for both drugs.

- Table C also shows results for $TYR30_2$ (i.e., TSF based upon at least 2 consecutive SBP increases of 30 mm Hg or more at 5 minute intervals) (e.g., a sustained increase for a least 5 minutes) for different presentations of central tendency (e.g., arithmetic mean, geometric mean, and median). In this comparative analysis, results for geometric mean and median appear to make more scientific sense than results for arithmetic mean. The lowest ratio is observed for pooled placebo and the highest ratio is for phenelzine as would be expected/predicted. Results further show that the 1 mg rasagiline ratio is numerically greater than placebo and that the ratios dose-dependently, and progressively increase such that the highest rasagiline ratio is observed at the 6 mg dose. In contrast, comparison of arithmetic means does not make as much scientific sense because pooled placebo is numerically greater than several active drug treatments and the 4 mg rasagiline ratio is greater than that for 6 mg. Geometric mean and arithmetic mean for 1 mg rasagiline is somewhat less than that for selegiline but median TSF is similar for both drugs.

- Table C finally shows results for $TYR30_1$ (i.e., TSF based upon at least a single SBP increase of 30 mm Hg or more) for different presentations of central tendency (e.g., arithmetic mean, geometric mean, and median). In this comparative analysis, geometric mean is similar for placebo and rasagiline 1 mg and all higher doses (2-6 mg) are numerically greater than that for 1 mg. However, geometric mean TSF for 2 mg (4.1) is numerically greater than that for 4 mg (2.7) but less than that for 6 mg (5.1). Median TSF for 1 mg rasagiline is greater than placebo and all higher doses (2-6 mg) are greater than that for 1 mg. Whereas median TSF is similar for 2 and 4 mg, median TSF is highest for 6 mg. Median TSF for phenelzine is greatest among all treatments and similar for 1 mg rasagiline and selegiline. Results for arithmetic mean were not very discriminating. Arithmetic mean for placebo was greater than that for selegiline and 1 mg and 2 mg rasagiline and quite similar for 4 mg rasagiline but less than that for 6 mg. Not surprisingly, arithmetic mean for phenelzine was greatest among all treatments.

  Overall, geometric and arithmetic mean results were not sensitive for showing that 1 mg rasagiline increased TSF compared to placebo. Neither did arithmetic mean TSF make scientific sense nor provide much useful information because TSF for active drugs was frequently less than that for placebo despite that facts that many other analyses suggest that rasagiline and selegiline increase tyramine sensitivity.

Table C (Reviewer Table) **Comparative Sensitivity Analyses for Tyramine Sensitivity Factor (TSF = Pre-Treatment Tyramine Threshold Dose/Post-Treatment Tyramine Threshold Dose) for Various Central Tendency Presentations and Various Criteria for Determining Tyramine Threshold Dose for ≥ 30 mm Hg SBP Increase**

Various TSF Central Tendency Presentations and Criteria for Determining TYR30 Threshold Dose	TREATMENT							
	Pooled Placebo	Selegiline	Rasagiline 1 mg	Rasagiline 2 mg (14 days)	Rasagiline 2 mg (30 days)	Rasagiline 4 mg	Rasagiline 6 mg	Phenelzine
Geometric Mean								
$TYR30_3$ TSF	1.5	2.5	2.0	3.3	2.5	4.5	5.1	17.3
$TYR30_2$ TSF	1.6	2.5	2.2	3.1	2.3	5.0	5.5	14.2
$TYR30_1$ TSF	2.2	2.8	2.2	4.1	2.5	2.7	5.1	11.4
Arithmetic Mean								
$TYR30_3$ TSF	5.0	3.9	3.0	4.7	2.8	8.2	7.3	20.1
$TYR30_2$ TSF	6.0	3.6	3.1	4.5	2.7	9.4	8.7	18.3
$TYR30_1$ TSF	6.0	5.4	4.8	7.1	5.4	6.1	11.8	15.3
Median								
$TYR30_3$ TSF	1	2	2	4	3	4	5	17
$TYR30_2$ TSF	1	2	2	3	2	4	5	18
$TYR30_1$ TSF	1	2	2	3	3	3	5	16

$TYR30_3$ = Tyramine threshold dose based upon 3 consecutive increments (compared to pre-tyramine) of SBP of ≥ 30 mm Hg at BP measurements at 5 minute intervals (i.e., sustained SBP for at least 10 minutes)
$TYR30_2$ = Tyramine threshold dose based upon 2 consecutive increments (compared to pre-tyramine) of SBP of ≥ 30 mm Hg at BP measurements at 5 minute intervals (i.e., sustained SBP for at least 5 minutes)
$TYR30_1$ = Tyramine threshold dose based upon SINGLE increment (compared to pre-tyramine) of SBP of ≥ 30 mm Hg at BP measurements at 5 minute intervals (i.e., sustained SBP for at least 10 minutes)

Table 15.2-26 compares results for statistical comparisons of active drug treatments with placebo (matching placebo and pooled placebo) for TSFs based upon the different TYR30 thresholds (e.g., $TYR30_3$ = TYR30, $TYR30_2$, $TYR30_1$). All comparisons with each rasagiline dose vs either matching placebo or pooled placebo were statistically different (i.e., $p < 0.05$) for $TYR30_3$/TYR30, and $TYR30_2$. Based upon $TYR30_1$, 6 mg rasagiline was the only rasagiline dose that was statistically different from either matching placebo or pooled placebo. Selegiline was statistically different from placebo only when $TYR30_3$/TYR30, and $TYR30_2$ threshold criteria were applied and only for pooled placebo but not matching placebo.

Table 15.2-26. Comparison Of Statistical Analyses Between TYR30 Threshold Doses Of Each Group Vs. Matching And Pooled Placebo

		THR30 Threshold		
		$TYR30_1$	$TYR30_2$	TYR30
		*P-Value	*P-Value	*P-Value
Active Treatment vs Matching Placebo	Active Treatment			
	Selegiline (2)	0.830576	0.62032	0.322748
	1mg Rasagiline (3)	0.914877	0.015519	0.021931
	2mg Rasagiline (4a)	0.460958	0.07471	0.069151
	4mg Rasagiline (5)	0.111323	0.000736	0.001141
	6mg Rasagiline (6)	0.017534	0.000137	0.000187
Active Treatment vs Pooled Placebo	Phenelzine (1)	0.000121	0.0001	<0.0001
	Selegiline (2)	0.193266	0.002811	0.008553
	1mg Rasagiline (3)	0.382709	0.002081	0.002641
	2mg Rasagiline (4a)	0.059286	0.000627	0.000267
	4mg Rasagiline (5)	0.421087	0.000044	0.000026
	6mg Rasagiline (6)	0.030563	0.000128	0.000083

*Wilcoxon Rank Test

Reviewer Conclusions/Comments

- $TYR30_3$/TSF for all central tendency assessments seems to provide the best characterization of TSF.
- $TYR30_3$/TSF is a much better and more rigorous criterion than the less rigorous criterion of $TYR30_1$ but only seems to be marginally better than $TYR30_2$.
- $TYR30_2$/TSF appears to be a reasonably good minimal standard criterion but may not be quite as good as $TYR30_3$/TSF.
- $TYR30_1$/TSF does not appear to be a good method for accurately characterizing TSF.
- Geometric mean or median for TSF (based upon $TYR30_3$, $TYR30_2$, or $TYR30_1$) provides better characterization of TSF than arithmetic mean.

low pressor dose was obtained in non-treated subjects (placebo and Period 1) subjects, or for the large intrasubject pressor dose variability seen in placebo subjects. **Nevertheless, these observations in placebo subjects clearly underscore the necessity of incorporating placebo subjects in a double-blind study design after randomization for characterizing a drug's tyramine sensitivity accurately and adequately.**

For the non-selective comparator phenelzine, the geometric mean and median pressor doses required to achieve pressor endpoint at baseline were 463.4 mg and 450 mg respectively. Following 14 days of dosing with phenelzine (Period 3), the geometric mean and median pressor doses required to achieve pressor endpoint were reduced to 27.0 mg and 25 mg, respectively (Table 16). There was a clear dichotomy of tyramine pressor doses between Periods 1 and 3. The minimum pressor dose went from 300 mg in Period 1 to 5 mg in Period 3.

The geometric mean and median pressor doses required to achieve pressor endpoint for 1 mg rasagiline at baseline were 441.6 mg and 400 mg respectively. Following 14 days of dosing with 1 mg rasagiline, the geometric mean and median pressor doses required to achieve pressor endpoint were reduced to 218.6 mg and 200 mg, respectively (Table 16). The minimum pressor dose went from 300 mg in Period 1 to 25 mg in Period 3 which is within the variability range seen for placebo subjects.

A negative association or inverse correlation was evident between rasagiline dose and geometric mean pressor dose in Period 3. There was no association between rasagiline dose and minimum pressor dose.

As described above, in Period 3 several individual subjects (both on placebo and on treatment with selegiline and rasagiline) reached potentiation at surprisingly low tyramine doses or with unexpectedly high TSF values. There is no clear explanation for this high variability in response but this reflects the variability of TYR30 in the study.

As described above, in Period 3 several individual subjects (both on placebo and on treatment with selegiline and rasagiline) reached tyramine threshold pressor potentiation at surprisingly low tyramine doses or with unexpectedly high TSF values. There is no clear explanation for this high variability in response but this reflects the variability of TYR30 in the study.

Reviewer Comments

- In a very general sense, various central tendency representations (e.g., geometric mean, arithmetic mean, median) reflected various increases in tyramine sensitivity in Pediod 3 after the different treatments including 1 mg rasagiline and all higher rasagiline doses, selegiline, and phenelzine (Table 16). Geometric and arithmetic mean doses allowed discrimination of the dose-dependent increase in tyramine sensitivity induced by all doses of rasagiline and these mean doses were inversely related to the increase in tyramine sensitivity. However, representation of median doses did not exhibit this dose-dependent

- Although median TSF appears to be a reasonable method for characterizing central tendency, geometric mean appears to be the best central tendency characterization presentation for TSF and appears to be a more sensitive and more discriminating method than that based upon median TSF.

3.2.5 Tyramine Pressor Doses

Table 16 summarizes information about mean and median tyramine threshold, pressor doses for Periods 1 and 3 according to treatment. Table 17 summarizes minimum pressor doses in each period according to treatment.

Table 16 Summary Table of Mean and Median Pressor Doses (mg)

	Period 1			Period 3		
	Arithmetic Mean	Geometric Mean	Median	Arithmetic Mean	Geometric Mean	Median
Phenelzine (1)	481.3	463.4	450	31.0	27.0	25
Selegiline (2)	398.7	331.3	400	182.5	134.0	200
1mg Rasagiline (3)	456.3	441.6	400	248.3	218.6	200
2mg Rasagiline (4a)	486.7	445.6	500	174.0	135.9	200
2mg Rasagiline (4b)	492.9	474.4	450	207.1	193.6	200
4mg Rasagiline (5)	511.8	480.4	500	144.1	106.7	200
6mg Rasagiline (6)	450.0	397.8	400	118.3	89.9	100
Pooled Placebo (4a,2,3,5,6)	505.1	473.2	500	415.8	314.0	400

Source: Table 15.2-1, Table 15.2-2

Table 17 Summary Table of Minimum Pressor Doses (mg)

	Period 1	Period 3
Phenelzine (1)	300.0	5.0
Selegiline (2)	50.0	12.5
1mg Rasagiline (3)	300.0	25.0
2mg Rasagiline (4a)	100.0	12.5
2mg Rasagiline (4b)	300.0	100.0
4mg Rasagiline (5)	200.0	12.5
6mg Rasagiline (6)	50.0	12.5
Pooled Placebo (4a,2,3,5,6)	200	12.5

Source: Table 15.2-1, Table 15.2-2

For the pooled placebo group, the geometric mean and median pressor doses required to achieve pressor endpoint at baseline were 473.2 mg and 500 mg, respectively. Following 14 days of dosing with placebo (Period 3), the geometric mean and median pressor doses required to achieve pressor endpoint were reduced to 314.0 mg and 400 mg, respectively (Table 16). The minimum pressor dose went from 200 mg in Period 1 to 12.5 mg in Period 3 (Table 17). **Moreover, one subject in Period 1 (baseline/pre-treatment) reached potentiation at 25 mg tyramine, but this subject was not randomized into the study.** Three placebo subjects had a minimum pressor dose of 12.5 mg in Period 3. There is no clear explanation as to why such a

Table 15.2-27. Maximal Increment in SBP – P1 and P3 Phenelzine

TVP-1012-120-TYR	Study Period							
	Period 1				Period 3			
	SBP Max Increment				SBP Max Increment			
	AS IS		LOCF		AS IS		LOCF	
	N	Mean	N	Mean	N	Mean	N	Mean
Tyramine Dose								
5.0	.	.	.	.	16	17.69	16	17.69
15.0	.	.	.	.	15	25.07	16	27.63
25.0	16	16.38	16	16.38	14	46.07	16	47.13
35.0	.	.	.	.	7	37.00	16	51.50
45.0	.	.	.	.	3	49.33	16	56.13
50.0	16	17.50	16	17.50	.	.	.	.
55.0	.	.	.	.	1	27.00	16	56.19
65.0	.	.	.	.	1	26.00	16	56.13
75.0	.	.	.	.	1	85.00	16	59.81
85.0	.	.	.	.	0	.	16	59.81
95.0	.	.	.	.	0	.	16	59.81
100.0	16	19.25	16	19.25	.	.	.	.
105.0	.	.	.	.	0	.	16	59.81
200.0	16	17.00	16	17.00	.	.	.	.
300.0	16	27.06	16	27.06	.	.	.	.
400.0	13	41.15	16	43.81	.	.	.	.
500.0	8	32.25	16	43.94	.	.	.	.
600.0	7	54.71	16	54.88	.	.	.	.
700.0	1	66.00	16	56.56	.	.	.	.
800.0	0	.	16	56.56	.	.	.	.

Reviewer Comments

- Table 15.2-27 shows that phenelzine treatment (Period 3) facilitated low tyramine doses (5-45 mg) to produce a significant mean maximal SBP increase (18-49 mm Hg). Table 15.2-29 further shows the marked mean, maximal SBP potentiation by phenelzine when a single common low dose of tyramine (25 mg) produced a mean 46 mm Hg increase compared to only 16 mm Hg for placebo for "AS IS" data (i.e., actual, observed data).

Table 15.2-29. Maximal Increment in SBP – P3 Phenelzine vs P3 Pooled Placebo

TVP-1012-120-TYR	SBP Max Increment									
	AS IS					LOCF				
	Pooled Placebo (4s,2,3,5,6)		Phenelzine (1)			Pooled Placebo (4s,2,3,5,6)		Phenelzine (1)		
	N	Mean	N	Mean	*P-value	N	Mean	N	Mean	*P-value
Tyramine Dose										
5.0	.	.	16	17.69	.	.	.	16	17.69	.
12.5	39	17.15	.	.	.	39	17.15	.	.	.
15.0	.	.	15	25.07	.	.	.	16	27.63	.
25.0	37	16.68	14	46.07	<.0001	39	19.13	16	47.13	<.0001
35.0	.	.	7	37.00	.	.	.	16	51.50	.
45.0	.	.	3	49.33	.	.	.	16	56.13	.
50.0	36	14.58	.	.	.	39	17.69	.	.	.
55.0	.	.	1	27.00	.	.	.	16	56.19	.
65.0	.	.	1	26.00	.	.	.	16	56.13	.
75.0	.	.	1	85.00	.	.	.	16	59.81	.
85.0	.	.	0	.	.	.	.	16	59.81	.
95.0	.	.	0	.	.	.	.	16	59.81	.
100.0	35	17.60	.	.	.	39	21.33	.	.	.
105.0	.	.	0	.	.	.	.	16	59.81	.
200.0	34	21.41	.	.	.	39	25.92	.	.	.
300.0	33	27.94	.	.	.	39	32.82	.	.	.
400.0	27	32.15	.	.	.	39	39.03	.	.	.
500.0	19	40.58	.	.	.	39	47.03	.	.	.
600.0	9	45.22	.	.	.	39	51.95	.	.	.
700.0	3	38.67	.	.	.	39	53.51	.	.	.
800.0	2	50.50	.	.	.	39	54.49	.	.	.

*Two Sample T-Test

effect because median doses for 1, 2, and 4 mg rasagiline were similar at 200 mg despite the fact that rasagiline dose-dependently increase tyramine sensitivity.

- All central tendency representations of pooled placebo tyramine threshold, pressor dose were lower in Period 3 (than in Period 1), presumably indicating a "placebo effect" after subjects had been randomized and studied under double-blinded conditions. Although one might expect that determining/characterizing tyramine threshold dose might be purely objective and not susceptible to a placebo effect and subjective influences, it would appear that there might be some subjective influences involved in this characterization. However, it is not possible to discern how subjective influences may precisely play in making this determination.

- Minimum tyramine threshold, pressor doses after treatment in Period 3 were not helpful in discriminating the extent or magnitude of increased tyramine sensitivity. The minimum tyramine threshold dose was quite low at 12.5 mg and similar for many treatments including 2, 4, and 6 mg rasagiline, selegiline, and even placebo.

3.2.6 Evaluation of Maximal Increments From Pre-Tyramine Dose Systolic Blood Pressure (SBP)

As a result of DNP requests/recommendations, the sponsor conducted and submitted various analyses of the maximal increase blood pressure (systolic-SBP and diastolic-DBP) with various tyramine doses in Periods 1 (pre-treatment) and 3 (after treatment). Various analyses of maximal increase in SBP according to treatment are shown in the following tables. Tabular results show the effects of treatment on maximal SBP increases to various tyramine doses in Period 3 (vs Period 1) and in Period 3 (vs Placebo). Data analyses for only SBP are presented here because they appeared to provide better discrimination of an increase in tyramine sensitivity than data analyses for DBP which showed less pronounced effects than those on SBP. Analyses of active drug vs placebo in each period are presented for actual, observed data and also according to the principle of last observation carried forward (LOCF) in which missing data at a specific tyramine dose are imputed. Based upon my past experience with actual observed data appearing to provide more useful information, my review will focus on results of actual observed data indicated in the tables by the terms "AS IS."

The various analyses of TSF previously presented indicate whether treatment produces an increase in tyramine sensitivity and the extent or magnitude of the increased tyramine sensitivity. However, these various analyses of the effect of treatment on maximal SBP increase provide a different perspective and useful insight into the specific effect and potential of different tyramine doses to increase blood pressure after treatment.

Table 15.2-33. Maximal Increment in SBP – P3 Selegiline vs P1 Selegiline

TVP-1012-120-TYR	SBP Max Increment													
	AS IS							LOCF						
	SBP Max Increment at Period 1 (P1)		SBP Max Increment at Period 3 (P3)		SBP Difference P3-P1			SBP Max Increment at Period 1 (P1)		SBP Max Increment at Period 3 (P3)		SBP Difference P3-P1		
	N	Mean	N	Mean	N	Mean	*P-Value	N	Mean	N	Mean	N	Mean	*P-Value
Tyramine Dose														
12.5	0	.	15	23.27	0	.	.	0	.	15	23.27	0	.	.
25.0	15	18.13	14	21.57	14	4.71	0.3372	15	18.13	15	24.00	15	5.87	0.2184
50.0	15	16.33	13	25.46	13	10.31	0.0065	15	16.33	15	30.40	15	14.07	0.0035
100.0	14	19.93	13	34.15	13	14.08	0.0080	15	20.93	15	37.93	15	17.00	0.0020
200.0	13	21.85	8	39.13	8	20.13	0.0207	15	24.53	15	47.47	15	22.93	0.0006
300.0	12	31.83	5	43.80	5	13.00	0.2511	15	35.20	15	52.13	15	16.93	0.0265
400.0	9	34.89	1	61.00	0	.	.	15	43.93	15	54.60	15	10.67	0.0765
500.0	6	44.33	0	.	0	.	.	15	51.13	15	54.60	15	3.47	0.4765
600.0	3	43.33	0	.	0	.	.	15	52.73	15	54.60	15	1.87	0.6887
700.0	2	68.00	0	.	0	.	.	15	56.27	15	54.60	15	-1.67	0.7469
800.0	0	.	0	.	0	.	.	15	56.27	15	54.60	15	-1.67	0.7469

*Paired T-Test

Reviewer Comments

- Table 15.2-33 shows that selegiline treatment (Period 3) potentiated lower tyramine doses (50-200 mg) to produce statistically greater mean maximal SBP increases (10-20 mm Hg, "AS IS") than in untreated Period 1. Table 15.2-35 shows that selegiline treatment potentiated lower tyramine doses (50-300 mg) to produce statistically significant or borderline significant mean maximal SBP increases that were 10-18 mm Hg greater than placebo for actual observed data (i.e., "AS IS").

Table 15.2-35. Maximal Increment in SBP – P3 Selegiline vs P3 Pooled Placebo

TVP-1012-120-TYR	SBP Max Increment									
	AS IS					LOCF				
	Pooled Placebo (4a,2,3,5,6)		Selegiline (2)			Pooled Placebo (4a,2,3,5,6)		Selegiline (2)		
	N	Mean	N	Mean	*P-value	N	Mean	N	Mean	*P-value
Tyramine Dose										
12.5	39	17.15	15	23.27	0.1521	39	17.15	15	23.27	0.1521
25.0	37	16.68	14	21.57	0.1573	39	19.13	15	24.00	0.2895
50.0	36	14.58	13	25.46	0.0048	39	17.69	15	30.40	0.0133
100.0	35	17.60	13	34.15	0.0007	39	21.33	15	37.93	0.0031
200.0	34	21.41	8	39.13	0.0027	39	25.92	15	47.47	0.0002
300.0	33	27.94	5	43.80	0.0532	39	32.82	15	52.13	0.0010
400.0	27	32.15	1	61.00	0.0836	39	39.03	15	54.60	0.0028
500.0	19	40.58	0	.	.	39	47.03	15	54.60	0.1360
600.0	9	45.22	0	.	.	39	51.95	15	54.60	0.5550
700.0	3	38.67	0	.	.	39	53.51	15	54.60	0.7838
800.0	2	50.50	0	.	.	39	54.49	15	54.60	0.9758

*Two Sample T-Test

Reviewer Comments

- Table 15-2-36 shows that the placebo treatment in the placebo-matched group for 1 mg rasagiline did not potentiate any tyramine doses to produce statistically significant and greater mean, maximal SBP increases in Period 3 compared to those in untreated Period 1. This result serves as a negative control for active drug treatment that potentiated tyramine doses to produce statistically greater mean, maximal SBP increases in Period 3 compared to responses in Period 1 or to effects of placebo treatment in Period 3.

Table 15.2-36. Maximal Increment in SBP – P3 Placebo[Rasagiline1 mg] vs P1 Placebo[Rasagiline1 mg]

TVP-1012-120-TYR	SBP Max Increment													
	AS IS							LOCF						
	SBP Max Increment at Period 1 (P1)		SBP Max Increment at Period 3 (P3)		SBP Difference P3-P1			SBP Max Increment at Period 1 (P1)		SBP Max Increment at Period 3 (P3)		SBP Difference P3-P1		
	N	Mean	N	Mean	N	Mean	*P-Value	N	Mean	N	Mean	N	Mean	*P-Value
Tyramine Dose														
12.5	0	.	7	21.14	0	.	.	0	.	7	21.14	0	.	.
25.0	7	16.00	6	22.33	6	8.17	0.0429	7	16.00	7	26.57	7	10.57	0.0237
50.0	7	16.00	6	15.67	6	-1.67	0.7144	7	16.00	7	20.86	7	4.86	0.5396
100.0	7	14.43	6	21.67	6	7.00	0.3818	7	14.43	7	26.00	7	11.57	0.1826
200.0	7	23.71	6	14.33	6	-9.67	0.2327	7	23.71	7	19.71	7	-4.00	0.6456
300.0	6	29.83	6	28.17	5	-1.80	0.8510	7	34.14	7	31.57	7	-2.57	0.7446
400.0	5	31.00	6	43.83	4	12.25	0.3017	7	36.57	7	45.00	7	8.43	0.1890
500.0	4	43.25	2	50.50	2	5.00	0.8440	7	47.14	7	49.71	7	2.57	0.6575
600.0	3	42.00	1	51.00	1	8.00	.	7	51.71	7	51.71	7	0.00	1.0000
700.0	1	33.00	0	.	0	.	.	7	51.00	7	51.71	7	0.71	0.8804
800.0	1	69.00	0	.	0	.	.	7	56.14	7	51.71	7	-4.43	0.3079

*Paired T-Test

Table 15.2-39. Maximal Increment in SBP – P3 Rasagiline 1 mg vs P1 Rasagiline 1 mg

TVP-1012-120-TYR	SBP Max Increment													
	AS IS							LOCF						
	SBP Max Increment at Period 1 (P1)		SBP Max Increment at Period 3 (P3)		SBP Difference P3-P1			SBP Max Increment at Period 1 (P1)		SBP Max Increment at Period 3 (P3)		SBP Difference P3-P1		
	N	Mean	N	Mean	N	Mean	*P-Value	N	Mean	N	Mean	N	Mean	*P-Value
Tyramine Dose														
12.5	0	.	16	13.13	0	.	.	0	.	16	13.13	0	.	.
25.0	16	15.50	15	17.53	15	2.53	0.4740	16	15.50	16	17.19	16	1.69	0.6197
50.0	16	18.94	14	14.50	14	-4.14	0.0725	16	18.94	16	16.88	16	-2.06	0.5006
100.0	16	14.44	14	17.86	14	3.29	0.2275	16	14.44	16	19.81	16	5.38	0.1230
200.0	16	17.13	14	38.43	14	21.57	0.0009	16	17.13	16	37.81	16	20.69	0.0007
300.0	16	27.88	7	58.14	7	35.43	0.0041	16	27.88	16	53.88	16	26.00	0.0002
400.0	13	39.69	2	62.50	2	44.50	0.2629	16	42.69	16	56.56	16	13.88	0.1139
500.0	7	38.57	0	.	0	.	.	16	50.13	16	56.56	16	6.44	0.3781
600.0	4	50.25	0	.	0	.	.	16	57.50	16	56.56	16	-0.94	0.8469
700.0	1	42.00	0	.	0	.	.	16	57.31	16	56.56	16	-0.75	0.8778
800.0	0	.	0	.	0	.	.	16	57.31	16	56.56	16	-0.75	0.8778

*Paired T-Test

Reviewer Comments

- Table 15.2-39 shows that **1 mg rasagiline treatment** (Period 3) potentiated tyramine doses (200-400 mg) to produce statistically greater mean maximal SBP increases (22-45 mm Hg, "AS IS") than in untreated Period 1. Table 15.2-41 shows that **1 mg rasagiline treatment** potentiated tyramine doses (200-400 mg) to produce statistically significant mean maximal SBP increases that were 17-30 mm Hg greater than placebo for actual observed data (i.e., "AS IS").

Table 15.2-41. Maximal Increment in SBP – P3 Rasagiline 1 mg vs P3 Pooled Placebo

TVP-1012-120-TYR	SBP Max Increment									
	AS IS					LOCF				
	Pooled Placebo (4a,2,3,5,6)		1mg Rasagiline (3)		*P-value	Pooled Placebo (4a,2,3,5,6)		1mg Rasagiline (3)		*P-value
	N	Mean	N	Mean		N	Mean	N	Mean	
Tyramine Dose										
12.5	39	17.15	16	13.13	0.2967	39	17.15	16	13.13	0.2967
25.0	37	16.68	15	17.53	0.7809	39	19.13	16	17.19	0.6310
50.0	36	14.58	14	14.50	0.9785	39	17.69	16	16.88	0.8525
100.0	35	17.60	14	17.86	0.9443	39	21.33	16	19.81	0.7474
200.0	34	21.41	14	38.43	0.0021	39	25.92	16	37.81	0.0433
300.0	33	27.94	7	58.14	<.0001	39	32.82	16	53.88	0.0005
400.0	27	32.15	2	62.50	0.0140	39	39.03	16	56.56	0.0016
500.0	19	40.58	0	.	.	39	47.03	16	56.56	0.0779
600.0	9	45.22	0	.	.	39	51.95	16	56.56	0.3440
700.0	3	38.67	0	.	.	39	53.51	16	56.56	0.4903
800.0	2	50.50	0	.	.	39	54.49	16	56.56	0.6218

*Two Sample T-Test

Table 15.2-45. Maximal Increment in SBP – P3 Rasagiline 2 mg (4a) vs P1 Rasagiline 2 mg (4a)

TVP-1012-120-TYR	SBP Max Increment													
	AS IS							LOCF						
	SBP Max Increment at Period 1 (P1)		SBP Max Increment at Period 3 (P3)		SBP Difference P3-P1			SBP Max Increment at Period 1 (P1)		SBP Max Increment at Period 3 (P3)		SBP Difference P3-P1		
	N	Mean	N	Mean	N	Mean	*P-Value	N	Mean	N	Mean	N	Mean	*P-Value
Tyramine Dose														
12.5	0	.	14	17.71	0	.	.	0	.	14	17.71	0	.	.
25.0	15	15.60	13	19.08	13	4.15	0.3863	15	15.60	14	20.50	14	5.64	0.2348
50.0	15	17.80	13	19.77	13	1.85	0.5860	15	17.80	14	21.14	14	3.57	0.3272
100.0	15	19.07	11	25.91	11	11.91	0.0218	15	19.07	14	28.29	14	10.21	0.0382
200.0	14	19.07	8	50.00	8	31.85	0.0001	15	22.67	14	45.43	14	23.21	0.0005
300.0	14	31.00	3	59.00	3	42.67	0.0026	15	33.80	14	50.79	14	17.43	0.0215
400.0	13	37.15	0	.	0	.	.	15	40.00	14	50.79	14	11.93	0.1300
500.0	8	31.38	0	.	0	.	.	15	44.40	14	50.79	14	7.21	0.3846
600.0	5	43.40	0	.	0	.	.	15	51.80	14	50.79	14	-0.71	0.9177
700.0	3	50.67	0	.	0	.	.	15	56.93	14	50.79	14	-6.21	0.2843
800.0	1	39.00	0	.	0	.	.	15	58.60	14	50.79	14	-8.00	0.1338

*Paired T-Test

Reviewer Comments

- Table 15.2-45 shows that 2 mg rasagiline treatment (14 days, Period 3) potentiated tyramine doses (100-300 mg) to produce statistically greater mean maximal SBP increases (12-43 mm Hg, "AS IS") than in untreated Period 1. Table 15.2-47 shows that 2 mg rasagiline treatment potentiated tyramine doses (200-300 mg) to produce statistically significant mean maximal SBP increases that were 29-31 mm Hg greater than placebo for actual observed data (i.e., "AS IS"). This treatment also potentiated a nearly statistically significant (p=0.0644) mean maximal SBP increase vs placebo after 100 mg tyramine.

Table 15.2-47. Maximal Increment in SBP – P3 Rasagiline 2 mg (4a) vs P3 Pooled Placebo

TVP-1012-120-TYR	SBP Max Increment									
	AS IS					LOCF				
	Pooled Placebo (4a,2,3,5,6)		2mg Rasagiline (4a)			Pooled Placebo (4a,2,3,5,6)		2mg Rasagiline (4a)		
	N	Mean	N	Mean	*P-value	N	Mean	N	Mean	*P-value
Tyramine Dose										
12.5	39	17.15	14	17.71	0.8939	39	17.15	14	17.71	0.8939
25.0	37	16.68	13	19.08	0.4933	39	19.13	14	20.50	0.7614
50.0	36	14.58	13	19.77	0.1752	39	17.69	14	21.14	0.4753
100.0	35	17.60	11	25.91	0.0644	39	21.33	14	28.29	0.1761
200.0	34	21.41	8	50.00	<.0001	39	25.92	14	45.43	0.0010
300.0	33	27.94	3	59.00	0.0027	39	32.82	14	50.79	0.0037
400.0	27	32.15	0	.	.	39	39.03	14	50.79	0.0372
500.0	19	40.58	0	.	.	39	47.03	14	50.79	0.5005
600.0	9	45.22	0	.	.	39	51.95	14	50.79	0.8179
700.0	3	38.67	0	.	.	39	53.51	14	50.79	0.5502
800.0	2	50.50	0	.	.	39	54.49	14	50.79	0.3939

*Two Sample T-Test

Table 15.2-51. Maximal Increment in SBP – P3 Rasagiline 2 mg (4b) vs P1 Rasagiline 2 mg (4b)

TVP-1012-120-TYR	SBP Max Increment													
	AS IS							LOCF						
	SBP Max Increment at Period 1 (P1)		SBP Max Increment at Period 3 (P3)		SBP Difference P3-P1			SBP Max Increment at Period 1 (P1)		SBP Max Increment at Period 3 (P3)		SBP Difference P3-P1		
	N	Mean	N	Mean	N	Mean	*P-Value	N	Mean	N	Mean	N	Mean	*P-Value
Tyramine Dose														
12.5	0	.	14	17.71	0	.	.	0	.	14	17.71	0	.	.
25.0	14	16.36	14	16.71	14	0.36	0.9132	14	16.36	14	16.71	14	0.36	0.9132
50.0	15	16.27	15	23.40	15	7.13	0.0901	15	16.27	15	23.40	15	7.13	0.0901
100.0	14	18.79	14	30.93	14	12.14	0.0150	14	18.79	14	30.93	14	12.14	0.0150
200.0	14	19.64	11	46.55	11	27.55	0.0010	14	19.64	14	48.93	14	29.29	<.0001
300.0	14	30.07	4	70.00	4	29.00	0.1352	14	30.07	14	63.14	14	33.07	0.0001
400.0	12	41.67	0	.	0	.	.	14	43.29	14	63.14	14	19.86	0.0016
500.0	7	39.14	0	.	0	.	.	14	47.14	14	63.14	14	16.00	0.0093
600.0	6	48.33	0	.	0	.	.	14	55.07	14	63.14	14	8.07	0.1159
700.0	2	59.00	0	.	0	.	.	14	58.79	14	63.14	14	4.36	0.4010
800.0	0	.	0	.	0	.	.	14	58.79	14	63.14	14	4.36	0.4010

*Paired T-Test

Reviewer Comments

Table 15.2-51 shows that 2 mg rasagiline treatment (30 days, Period 3) potentiated tyramine doses (100-200 mg) to produce statistically greater mean maximal SBP increases (12-28 mm Hg, "AS IS") than in untreated Period 1. This treatment also potentiated a trending statistically significant (p=0.0901) mean maximal SBP increase after 50 mg tyramine. Table 15.2-49 shows that 2 mg rasagiline treatment potentiated tyramine doses (200-300 mg) to produce statistically significant mean maximal SBP increases that were 24-36 mm Hg greater than placebo (i.e., matching placebo x 30 days) for actual observed, "AS IS") data. Mean maximal SBP increases after lower tyramine doses (50-100 mg) were numerically greater (vs placebo) and nearly statistically significant. **Overall, 2 mg rasagiline-induced increased tyramine sensitivity was similar for 14 vs 30 days treatment relative to stimulating mean maximal SBP increases.**

Table 15.2-49. Maximal Increment in SBP – P3 Rasagiline 2 mg (4b) vs P3 Placebo[Rasagiline 2 mg] (4b)

TVP-1012-120-TYR	SBP Max Increment									
	AS IS					LOCF				
	Placebo for 2mg Rasagiline (4b)		2mg Rasagiline (4b)			Placebo for 2mg Rasagiline (4b)		2mg Rasagiline (4b)		
	N	Mean	N	Mean	*P-value	N	Mean	N	Mean	*P-value
Tyramine Dose										
12.5	9	21.67	14	17.71	0.4467	9	21.67	14	17.71	0.4467
25.0	8	10.75	14	16.71	0.0757	9	16.11	14	16.71	0.9036
50.0	8	13.88	15	23.40	0.0564	9	18.89	15	23.40	0.4495
100.0	8	20.50	14	30.93	0.0997	9	24.78	14	30.93	0.3630
200.0	8	23.13	11	46.55	0.0261	9	27.11	14	48.93	0.0224
300.0	6	34.33	4	70.00	0.0188	9	39.11	14	63.14	0.0016
400.0	5	41.20	0	.	.	9	46.78	14	63.14	0.0152
500.0	2	30.50	0	.	.	9	47.22	14	63.14	0.0169
600.0	2	47.00	0	.	.	9	50.89	14	63.14	0.0415
700.0	0	.	0	.	.	9	50.89	14	63.14	0.0415
800.0	0	.	0	.	.	9	50.89	14	63.14	0.0415

*Two Sample T-Test

Table 15.2-55. Maximal Increment in SBP – P3 Rasagiline 4 mg vs P1 Rasagiline 4 mg

TVP-1012-120-TYR	SBP Max Increment												
	AS IS							LOCF					
	SBP Max Increment at Period 1 (P1)		SBP Max Increment at Period 3 (P3)		SBP Difference P3-P1			SBP Max Increment at Period 1 (P1)		SBP Max Increment at Period 3 (P3)		SBP Difference P3-P1	
	N	Mean	N	Mean	N	Mean	*P-Value	N	Mean	N	Mean	N	Mean	*P-Value
Tyramine Dose														
12.5	0	.	17	21.47	0	.	.	0	.	17	21.47	0	.	.
25.0	17	17.29	15	16.87	15	0.47	0.8739	17	17.29	17	22.12	17	4.82	0.2366
50.0	17	14.65	14	21.64	14	7.21	0.0068	17	14.65	17	28.12	17	13.47	0.0053
100.0	17	15.06	14	41.79	14	26.36	0.0086	17	15.06	17	44.71	17	29.65	0.0009
200.0	17	20.88	9	58.22	9	40.89	0.0008	17	20.88	17	64.06	17	43.18	<.0001
300.0	16	26.75	1	61.00	1	51.00	.	17	28.35	17	66.41	17	38.06	<.0001
400.0	14	29.07	0	.	0	.	.	17	33.94	17	66.41	17	32.47	<.0001
500.0	11	44.91	0	.	0	.	.	17	46.82	17	66.41	17	19.59	0.0117
600.0	5	31.40	0	.	0	.	.	17	48.29	17	66.41	17	18.12	0.0324
700.0	4	34.75	0	.	0	.	.	17	52.41	17	66.41	17	14.00	0.0873
800.0	3	65.67	0	.	0	.	.	17	58.88	17	66.41	17	7.53	0.2387

*Paired T-Test

Reviewer Comments

Table 15.2-55 shows that 4 mg rasagiline treatment (Period 3) potentiated tyramine doses (50-200 mg) to produce statistically greater mean maximal SBP increases (7-41 mm Hg, "AS IS") than in untreated Period 1. Table 15.2-57 shows that 4 mg rasagiline treatment potentiated tyramine doses (50-300 mg) to produce statistically significant mean maximal SBP increases that were 7-33 mm Hg greater than placebo for actual observed data (i.e., "AS IS").

Table 15.2-57. Maximal Increment in SBP – P3 Rasagiline 4 mg vs P3 Pooled Placebo

TVP-1012-120-TYR	SBP Max Increment									
	AS IS					LOCF				
	Pooled Placebo (4a,2,3,5,6)		4mg Rasagiline (5)			Pooled Placebo (4a,2,3,5,6)		4mg Rasagiline (5)		
	N	Mean	N	Mean	*P-value	N	Mean	N	Mean	*P-value
Tyramine Dose										
12.5	39	17.15	17	21.47	0.3511	39	17.15	17	21.47	0.3511
25.0	37	16.68	15	16.87	0.9464	39	19.13	17	22.12	0.5122
50.0	36	14.58	14	21.64	0.0283	39	17.69	17	28.12	0.0310
100.0	35	17.60	14	41.79	0.0003	39	21.33	17	44.71	0.0005
200.0	34	21.41	9	58.22	<.0001	39	25.92	17	64.06	<.0001
300.0	33	27.94	1	61.00	0.0543	39	32.82	17	66.41	<.0001
400.0	27	32.15	0	.	.	39	39.03	17	66.41	<.0001
500.0	19	40.58	0	.	.	39	47.03	17	66.41	0.0010
600.0	9	45.22	0	.	.	39	51.95	17	66.41	0.0067
700.0	3	38.67	0	.	.	39	53.51	17	66.41	0.0086
800.0	2	50.50	0	.	.	39	54.49	17	66.41	0.0114

*Two Sample T-Test

Table 15.2-61. Maximal Increment in SBP – P3 Rasagiline 6 mg vs P1 Rasagiline 6 mg

TVP-1012-120-TYR	SBP Max Increment													
	AS IS							LOCF						
	SBP Max Increment at Period 1 (P1)		SBP Max Increment at Period 3 (P3)		SBP Difference P3-P1			SBP Max Increment at Period 1 (P1)		SBP Max Increment at Period 3 (P3)		SBP Difference P3-P1		
	N	Mean	N	Mean	N	Mean	*P-Value	N	Mean	N	Mean	N	Mean	*P-Value
Tyramine Dose														
12.5	0	.	14	16.71	0	.	.	0	.	14	16.71	0	.	.
25.0	15	15.40	13	23.77	13	9.31	0.0869	15	15.40	14	25.21	14	10.57	0.0459
50.0	15	15.93	11	22.91	11	9.18	0.1265	15	15.93	14	24.93	14	9.57	0.1041
100.0	14	14.21	9	41.89	9	29.22	0.0190	15	15.93	14	41.36	14	24.50	0.0070
200.0	14	20.07	5	68.00	5	46.60	0.0244	15	21.40	14	58.43	14	36.36	0.0007
300.0	14	24.71	0	.	0	.	.	15	25.73	14	58.43	14	31.50	0.0035
400.0	12	42.50	0	.	0	.	.	15	44.60	14	58.43	14	11.93	0.3633
500.0	7	47.14	0	.	0	.	.	15	59.07	14	58.43	14	0.07	0.9948
600.0	3	26.33	0	.	0	.	.	15	60.40	14	58.43	14	-1.36	0.8988
700.0	3	49.00	0	.	0	.	.	15	64.93	14	58.43	14	-6.21	0.5050
800.0	0	.	0	.	0	.	.	15	64.93	14	58.43	14	-6.21	0.5050

*Paired T-Test

Reviewer Comments

Table 15.2-61 shows that 6 mg rasagiline treatment (Period 3) potentiated tyramine doses (100-200 mg) to produce statistically greater mean maximal SBP increases (29-47 mm Hg, "AS IS") than in untreated Period 1. This treatment also potentiated a trending statistically significant mean maximal SBP increase after 25 and 50 mg tyramine. Table 15.2-63 shows that 6 mg rasagiline treatment potentiated tyramine doses (25-200 mg) to produce statistically significant/borderline significant mean maximal SBP increases that were 7-47 mm Hg greater than placebo for actual observed data (i.e., "AS IS"). **In general, rasagiline-induced potentiation of progressively lower tyramine doses for augmenting mean maximal SBP increases was dose-related.**

Table 15.2-63. Maximal Increment in SBP – P3 Rasagiline 6 mg vs P3 Pooled Placebo

TVP-1012-120-TYR	SBP Max Increment									
	AS IS					LOCF				
	Pooled Placebo (4a,2,3,5,6)		6mg Rasagiline (6)			Pooled Placebo (4a,2,3,5,6)		6mg Rasagiline (6)		
	N	Mean	N	Mean	*P-value	N	Mean	N	Mean	*P-value
Tyramine Dose										
12.5	39	17.15	14	16.71	0.9199	39	17.15	14	16.71	0.9199
25.0	37	16.68	13	23.77	0.0491	39	19.13	14	25.21	0.1841
50.0	36	14.58	11	22.91	0.0539	39	17.69	14	24.93	0.1489
100.0	35	17.60	9	41.89	0.0004	39	21.33	14	41.36	0.0016
200.0	34	21.41	5	68.00	<.0001	39	25.92	14	58.43	<.0001
300.0	33	27.94	0	.	.	39	32.82	14	58.43	0.0002
400.0	27	32.15	0	.	.	39	39.03	14	58.43	0.0022
500.0	19	40.58	0	.	.	39	47.03	14	58.43	0.0656
600.0	9	45.22	0	.	.	39	51.95	14	58.43	0.2518
700.0	3	38.67	0	.	.	39	53.51	14	58.43	0.3447
800.0	2	50.50	0	.	.	39	54.49	14	58.43	0.4299

*Two Sample T-Test

3.2.7 Secondary Endpoint – Orthostatic Hypotension

The sponsor conducted and presented various analyses (mean absolute values and mean change) of orthostatic vital signs (VS) for supine and standing systolic and diastolic blood pressure and pulse.

The sponsor noted that post-baseline differences between the treatment groups in the descriptive statistics of vital sign parameters seemed random, and without evidence of a consistent pattern or dose response. The sponsor also noted that increments of SBP $\geq$ 20 mmHg seemed to occur with a higher incidence in the 4 mg and 6 mg rasagiline treatment groups compared to the lower dose groups of 1 and 2 mg rasagiline, and compared to placebo.

With respect to the secondary endpoint, the sponsor did not that there was evidence of higher orthostatism/orthostatic hypotension in rasagiline-treated subjects compared to placebo subjects, nor for a dose response.

Additional Vital Sign Analyses

The DNP requested additional VS outlier analyses to assess the effects on VS change, VS increase above certain absolute levels (on one or two consecutive occasions), and orthostatic VS and the treatment difference/effect (i.e., rasagiline % - placebo %) of these analyses.

Table 5 shows the incidence of orthostatic hypotension at baseline and after treatment (end of treatment Period 2).

Table 5: Frequency of Orthostatic Hypotension (OH) at Any Time Post Dose

TVP-1012-120-TYR		Pooled Placebo (4a,2,3,5,6)			Rasagiline															
					1mg Rasagiline (3)			2mg Rasagiline (4a)			4mg Rasagiline (5)			6mg Rasagiline (6)			All Rasagiline		
		N	#OH/ #Total Tested (%)	#OH/ #Baseline OH(%)	N	#OH/ #Total Tested (%)	#OH/ #Baseline OH(%)	N	#OH/ #Total Tested (%)	#OH/ #Baseline OH(%)	N	#OH/ #Total Tested (%)	#OH/ #Baseline OH(%)	N	#OH/ #Total Tested (%)	#OH/ #Baseline OH(%)	N	#OH/ #Total Tested (%)	#OH/ #Baseline OH(%)
Baseline	SBP OH >= 20 mmHg	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.
	SBP OH >= 40 mmHg	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.
	DBP OH >= 10 mmHg	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.
	DBP OH >= 20 mmHg	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.
	SBP OH >= 20 mmHg and DBP OH >= 10 mmHg	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.
	SBP OH >= 40 mmHg and DBP OH >= 20 mmHg	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.
Any Time Point On Treatment	SBP OH >= 20 mmHg	0	0.0	.	2	12.5	.	0	0.0	.	2	11.8	.	1	6.7	.	5	8.1	.
	SBP OH >= 40 mmHg	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.
	DBP OH >= 10 mmHg	1	3.1	.	1	6.3	.	0	0.0	.	1	5.9	.	0	0.0	.	2	3.2	.
	DBP OH >= 20 mmHg	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.
	SBP OH >= 20 mmHg and DBP OH >= 10 mmHg	0	0.0	.	0	0.0	.	0	0.0	.	1	5.9	.	0	0.0	.	1	1.6	.
	SBP OH >= 40 mmHg and DBP OH >= 20 mmHg	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.	0	0.0	.

Any patient with the categorical abnormality can be counted at each time point and thus can be counted across many time points when abnormal.

Orthostatic Hypotension (OH) = SBP or DBP decrease to at least a certain defined level while changing from supine to standing position and is calculated as follows : standing BP – supine BP

Reviewer Comments

- There were few instances of specific blood pressure outliers (as shown in Table 5) indicating orthostatic hypotension for any treatment while changing from a supine to standing position. There was no clear effect of rasagiline on the incidence of orthostatic hypotension for systolic or diastolic blood pressure, nor a suggestion of dose-dependence.

Table 1 below here shows the incidence of various threshold blood pressure increments or decrements. Table 7 shows the incidence of the treatment difference/effect (rasagiline % - placebo %) for the incidence values shown in Table 1.

Table 1: Incidence of Threshold Blood Pressure Changes at Any Time Post Dose: Change of Blood Pressure (BP) Parameters Relative to Baseline/Pre-treatment BP

TVP-1012-120-TYR				Rasagiline									
		Pooled Placebo (4a,2,3,5,6)		1mg Rasagiline (3)		2mg Rasagiline (4a)		4mg Rasagiline (5)		6mg Rasagiline (6)		All Rasagiline	
		N	%	N	%	N	%	N	%	N	%	N	%
Supine	SBP increment >= 20 mmHg	1	3.1	1	6.3	0	0.0	1	5.9	4	26.7	6	9.7
	SBP increment >= 40 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	SBP decrement >= 20 mmHg	0	0.0	2	12.5	0	0.0	1	5.9	0	0.0	3	4.8
	SBP decrement >= 40 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	DBP increment >= 10 mmHg	4	12.5	2	12.5	0	0.0	4	23.5	2	13.3	8	12.9
	DBP increment >= 20 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	DBP decrement >= 10 mmHg	2	6.3	5	31.3	2	14.3	3	17.6	2	13.3	12	19.4
	DBP decrement >= 20 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Standing	SBP increment >= 20 mmHg	6	18.8	3	18.8	2	14.3	7	41.2	5	33.3	17	27.4
	SBP increment >= 40 mmHg	0	0.0	1	6.3	0	0.0	0	0.0	0	0.0	1	1.6
	SBP decrement >= 20 mmHg	0	0.0	0	0.0	0	0.0	2	11.8	0	0.0	2	3.2
	SBP decrement >= 40 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	DBP increment >= 10 mmHg	7	21.9	6	37.5	4	28.6	5	29.4	3	20.0	18	29.0
	DBP increment >= 20 mmHg	0	0.0	1	6.3	0	0.0	0	0.0	0	0.0	1	1.6
	DBP decrement >= 10 mmHg	3	9.4	5	31.3	1	7.1	3	17.6	1	6.7	10	16.1
	DBP decrement >= 20 mmHg	0	0.0	1	6.3	0	0.0	1	5.9	0	0.0	2	3.2
Change from Supine to Standing	SBP increment >= 20 mmHg	10	31.3	3	18.8	1	7.1	4	23.5	4	26.7	12	19.4
	SBP increment >= 40 mmHg	0	0.0	1	6.3	0	0.0	0	0.0	0	0.0	1	1.6
	SBP decrement >= 20 mmHg	1	3.1	0	0.0	2	14.3	2	11.8	1	6.7	5	8.1
	SBP decrement >= 40 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	DBP increment >= 10 mmHg	7	21.9	5	31.3	4	28.6	8	47.1	1	6.7	18	29.0
	DBP increment >= 20 mmHg	1	3.1	1	6.3	0	0.0	0	0.0	0	0.0	1	1.6
	DBP decrement >= 10 mmHg	6	18.8	5	31.3	3	21.4	4	23.5	3	20.0	15	24.2
	DBP decrement >= 20 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Table 7: Incidence of the Treatment Difference/Effect (Active Drug % - Placebo %) for Threshold Blood Pressure Changes at Any Time Post Dose

TVP-1012-120-TYR		1mg Rasagiline (3)	2mg Rasagiline (4a)	4mg Rasagiline (5)	6mg Rasagiline (6)	All Rasagiline
		% Diff	% Diff	% Diff	% Diff	% Diff
Supine	SBP increment >= 20 mmHg	3.1	-3.1	2.8	23.5	6.6
	SBP increment >= 40 mmHg	0.0	0.0	0.0	0.0	0.0
	SBP decrement >= 20 mmHg	12.5	0.0	5.9	0.0	4.8
	SBP decrement >= 40 mmHg	0.0	0.0	0.0	0.0	0.0
	DBP increment >= 10 mmHg	0.0	-13	11.0	0.8	0.4
	DBP increment >= 20 mmHg	0.0	0.0	0.0	0.0	0.0
	DBP decrement >= 10 mmHg	25.0	8.0	11.4	7.1	13.1
	DBP decrement >= 20 mmHg	0.0	0.0	0.0	0.0	0.0
Standing	SBP increment >= 20 mmHg	0.0	-4.5	22.4	14.6	8.7
	SBP increment >= 40 mmHg	6.3	0.0	0.0	0.0	1.6
	SBP decrement >= 20 mmHg	0.0	0.0	11.8	0.0	3.2
	SBP decrement >= 40 mmHg	0.0	0.0	0.0	0.0	0.0
	DBP increment >= 10 mmHg	15.6	6.7	7.5	-1.9	7.2
	DBP increment >= 20 mmHg	6.3	0.0	0.0	0.0	1.6
	DBP decrement >= 10 mmHg	21.9	-2.2	8.3	-2.7	6.8
	DBP decrement >= 20 mmHg	6.3	0.0	5.9	0.0	3.2
Change from Supine to Standing	SBP increment >= 20 mmHg	-13	-24	-7.7	-4.6	-12
	SBP increment >= 40 mmHg	6.3	0.0	0.0	0.0	1.6
	SBP decrement >= 20 mmHg	-3.1	11.2	8.6	3.5	4.9
	SBP decrement >= 40 mmHg	0.0	0.0	0.0	0.0	0.0
	DBP increment >= 10 mmHg	9.4	6.7	25.2	-15	7.2
	DBP increment >= 20 mmHg	3.1	-3.1	-3.1	-3.1	-1.5
	DBP decrement >= 10 mmHg	12.5	2.7	4.8	1.3	5.4
	DBP decrement >= 20 mmHg	0.0	0.0	0.0	0.0	0.0

% diff =% of subjects with BP change relative to baseline on any rasagiline dose – % of subjects with BP change relative to baseline on placebo

Reviewer Comments

- The most notable effects appeared to be an increased incidence of mild-moderate increase in SBP while supine for the 6 mg dose and an increased incidence of mild-moderate increase in SBP while standing for the 4 and 6 mg doses. There was no apparent effect on these outlier thresholds for the approved rasagiline dose (1 mg).

Table 3 below here shows the incidence of increased blood pressure at or above certain increased thresholds. Table 9 shows the incidence of the treatment difference/effect (rasagiline % - placebo %) for the incidence values shown in Table 3.

Table 3: Incidence of Threshold BP Parameters at Any Time Post Dose

TVP-1012-120-TYR			Pooled Placebo (4a,2,3,5,6)		1mg Rasagiline (3)		2mg Rasagiline (4a)		4mg Rasagiline (5)		6mg Rasagiline (6)		All Rasagiline	
			N	%	N	%	N	%	N	%	N	%	N	%
At Least One Occurrence	Supine	SBP >= 140 mmHg	0	0.0	0	0.0	2	14.3	2	11.8	1	6.7	5	8.1
		SBP >= 180 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		SBP >= 140 mmHg or DBP >= 90 mmHg	1	3.1	0	0.0	2	14.3	2	11.8	1	6.7	5	8.1
		SBP >= 140 mmHg and DBP >= 90 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	1	6.7	1	1.6
		DBP >= 90 mmHg	1	3.1	0	0.0	0	0.0	0	0.0	1	6.7	1	1.6
		DBP >= 110 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		SBP >= 180 mmHg or DBP >= 110 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		SBP >= 180 mmHg and DBP >= 110 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Standing	SBP >= 140 mmHg	5	15.6	2	12.5	4	28.6	3	17.6	1	6.7	10	16.1
		SBP >= 180 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		SBP >= 140 mmHg or DBP >= 90 mmHg	7	21.9	2	12.5	5	35.7	6	35.3	1	6.7	14	22.6
		SBP >= 140 mmHg and DBP >= 90 mmHg	2	6.3	0	0.0	2	14.3	2	11.8	1	6.7	5	8.1
		DBP >= 90 mmHg	4	12.5	0	0.0	3	21.4	5	29.4	1	6.7	9	14.5
		DBP >= 110 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		SBP >= 180 mmHg or DBP >= 110 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		SBP >= 180 mmHg and DBP >= 110 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
At Least two Consecutive Occurrences on Different Time Points	Supine	SBP >= 140 mmHg	0	0.0	0	0.0	1	7.1	0	0.0	0	0.0	1	1.6
		SBP >= 180 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		SBP >= 140 mmHg or DBP >= 90 mmHg	0	0.0	0	0.0	1	7.1	0	0.0	0	0.0	1	1.6
		SBP >= 140 mmHg and DBP >= 90 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		DBP >= 90 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		DBP >= 110 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		SBP >= 180 mmHg or DBP >= 110 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		SBP >= 180 mmHg and DBP >= 110 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Standing	SBP >= 140 mmHg	0	0.0	0	0.0	2	14.3	1	5.9	0	0.0	3	4.8
		SBP >= 180 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		SBP >= 140 mmHg or DBP >= 90 mmHg	2	6.3	0	0.0	3	21.4	3	17.6	1	6.7	7	11.3
		SBP >= 140 mmHg and DBP >= 90 mmHg	0	0.0	0	0.0	1	7.1	0	0.0	0	0.0	1	1.6
		DBP >= 90 mmHg	2	6.3	0	0.0	2	14.3	3	17.6	1	6.7	6	9.7
		DBP >= 110 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		SBP >= 180 mmHg or DBP >= 110 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		SBP >= 180 mmHg and DBP >= 110 mmHg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Table 9: Threshold Blood Pressure (BP) Parameters: Incidence of the Treatment Difference/Effect (Active Drug % - Pooled Placebo %) for Threshold Blood Pressure at Any Time Post Dose

TVP-1012-120-TYR			1mg Rasagiline (3)	2mg Rasagiline (4a)	4mg Rasagiline (5)	6mg Rasagiline (6)	All Rasagiline
			% Diff	% Diff	% Diff	% Diff	% Diff
At Least One Occurrence	Supine	SBP >= 140 mmHg	0.0	14.3	11.8	6.7	8.1
		SBP >= 180 mmHg	0.0	0.0	0.0	0.0	0.0
		SBP >= 140 mmHg or DBP >= 90 mmHg	-3.1	11.2	8.6	3.5	4.9
		SBP >= 140 mmHg and DBP >= 90 mmHg	0.0	0.0	0.0	6.7	1.6
		DBP >= 90 mmHg	-3.1	-3.1	-3.1	3.5	-1.5
		DBP >= 110 mmHg	0.0	0.0	0.0	0.0	0.0
		SBP >= 180 mmHg or DBP >= 110 mmHg	0.0	0.0	0.0	0.0	0.0
		SBP >= 180 mmHg and DBP >= 110 mmHg	0.0	0.0	0.0	0.0	0.0
	Standing	SBP >= 140 mmHg	-3.1	12.9	2.0	-9.0	0.5
		SBP >= 180 mmHg	0.0	0.0	0.0	0.0	0.0
		SBP >= 140 mmHg or DBP >= 90 mmHg	-9.4	13.8	13.4	-15	0.7
		SBP >= 140 mmHg and DBP >= 90 mmHg	-6.3	8.0	5.5	0.4	1.8
		DBP >= 90 mmHg	-13	8.9	16.9	-5.8	2.0
		DBP >= 110 mmHg	0.0	0.0	0.0	0.0	0.0
		SBP >= 180 mmHg or DBP >= 110 mmHg	0.0	0.0	0.0	0.0	0.0
		SBP >= 180 mmHg and DBP >= 110 mmHg	0.0	0.0	0.0	0.0	0.0
At Least two Consecutive Occurrences on Different Time Points	Supine	SBP >= 140 mmHg	0.0	7.1	0.0	0.0	1.6
		SBP >= 180 mmHg	0.0	0.0	0.0	0.0	0.0
		SBP >= 140 mmHg or DBP >= 90 mmHg	0.0	7.1	0.0	0.0	1.6
		SBP >= 140 mmHg and DBP >= 90 mmHg	0.0	0.0	0.0	0.0	0.0
		DBP >= 90 mmHg	0.0	0.0	0.0	0.0	0.0
		DBP >= 110 mmHg	0.0	0.0	0.0	0.0	0.0
		SBP >= 180 mmHg or DBP >= 110 mmHg	0.0	0.0	0.0	0.0	0.0
		SBP >= 180 mmHg and DBP >= 110 mmHg	0.0	0.0	0.0	0.0	0.0
	Standing	SBP >= 140 mmHg	0.0	14.3	5.9	0.0	4.8
		SBP >= 180 mmHg	0.0	0.0	0.0	0.0	0.0
		SBP >= 140 mmHg or DBP >= 90 mmHg	-6.3	15.2	11.4	0.4	5.0
		SBP >= 140 mmHg and DBP >= 90 mmHg	0.0	7.1	0.0	0.0	1.6
		DBP >= 90 mmHg	-6.3	8.0	11.4	0.4	3.4
		DBP >= 110 mmHg	0.0	0.0	0.0	0.0	0.0
		SBP >= 180 mmHg or DBP >= 110 mmHg	0.0	0.0	0.0	0.0	0.0
		SBP >= 180 mmHg and DBP >= 110 mmHg	0.0	0.0	0.0	0.0	0.0

% diff = % of subjects with threshold BP on any rasagiline dose – % of subjects with threshold BP on placebo

Reviewer Comments

- The most notable effects appeared to be an increased incidence of increased SBP (≥ 140 mm Hg) while supine for 2, 4, and 6 mg and an increased incidence of increased DBP (≥ 90 mm Hg) while supine for 6 mg rasagiline (Table 9). There was no apparent effect on these outlier thresholds for the approved rasagiline dose (1 mg).

Sponsor Orthostatic Hypotension Conclusion :

- With respect to the secondary endpoint, there was no evidence of higher orthostatism in rasagiline-treated subjects compared to placebo subjects and there was no evidence of dose response.

Reviewer Comments

- This reviewer agrees with the sponsor's conclusion and in particular notes that there was no clear evidence that rasagiline treatment was associated with an increased incidence of orthostatic hypotension or any blood pressure outlier change at a particular time after dosing.

3.2.8 Sponsor and Reviewer Study Result Conclusions

Sponsor Conclusions on Primary and Secondary Endpoint Evaluation

• The geometric mean and median TYR30 ratios were highest for the non-selective comparator phenelzine and lowest for the pooled placebo group.
• The geometric mean and median TYR30 ratios for rasagiline 1 mg were 2.03 and 2, while those for pooled placebo were 1.50 and 1, respectively. These were clearly differentiated from the results for phenelzine (17.32 and 17). Even for the highest rasagiline dose of 6 mg the TYR30 ratios were lower than those of phenelzine.
• The minimum pressor dose was similar across all study groups (other than phenelzine), including placebo.
• Sensitivity analyses support the conclusions from the primary analysis.
• With respect to the secondary endpoint, there was no evidence of higher orthostatism in rasagiline-treated subjects compared to placebo subjects and there was no evidence of dose response.
• In conclusion, the primary endpoint and supportive analyses of the study provides unequivocal evidence for the MAO-B selectivity of 1 mg rasagiline and the lack of inhibition of MAO-A.

Reviewer Summary of Study Results

- **Rasagiline (1 mg daily) treatment produced increased TSF (geometric mean, median, arithmetic mean) compared to placebo treatment.**

- **Increased tyramine sensitivity of 1 mg rasagiline treatment is exhibited by :**
  1) the increased incidence of $TYR30_3$ responses to lower tyramine doses after treatment (n Period 3) compared to baseline-pre-treatment responses (in Period 3); and
  2) the increased incidence of $TYR30_3$ responses to lower tyramine doses compared to placebo treatment.

- **Rasagiline-induced increased tyramine sensitivity is dose-dependent (across daily doses of 1-6 mg) but the effect at 6 mg (highest dose studied) is numerically less than the increased tyramine sensitivity produced by phenelzine, a completely non-selective MAO inhibitor.**

- **Increased tyramine sensitivity produced by 1 mg rasagiline treatment appears to be similar to the increased tyramine sensitivity produced by 10 mg selegiline treatment.**

Reviewer Conclusions

1. **Rasagiline (1 mg daily) treatment (presently FDA approved) is a relatively selective MAO-B inhibitor**

2. **Tyramine dietary restriction is not ordinarily required with 1 mg rasagiline treatment. However caution should be exercised about ingesting large amounts of tyramine (e.g., > 150 mg tyramine, possibly in certain products such as aged cheese) because of the possibility of a hypertensive, "cheese" reaction because of the mildly increased tyramine sensitivity associated with 1 mg rasagiline treatment.**

3. **The relative selectivity of 1 mg daily rasagiline for MAO-B appears to be similar to the relative selectivity of 10 mg daily selegiline for MAO-B.**

4. **The rasagiline label (and oral swallowed selegiline label) should be revised to reflect this new information.**

3.2.9 Pharmacokinetic / Pharmacodynamic Evaluation

This reviewer also directs the reader's attention to the Clinical Pharmacology Review by Dr. Kristina Dimova.

Pharmacokinetic/Pharmacodynamic Results

Performance of Bioanalytical Methods
The drug concentration measurements of rasagiline, its metabolite 1-AI and tyramine were performed by validated methods (rasagiline: LLQ = 0.250 ng/mL, ALQ = 10 ng/mL; 1-AI: LLQ = 0.500 ng/mL, ALQ = 10.0 ng/mL; tyramine: LLQ = 0.500 ng/mL, ALQ = 50.0 ng/mL). The bioanalytical methodologies and procedures for these determinations are documented in a combined Bioanalytical Study Report, written under the supervision of Teva

Pharmaceuticals.

All study samples were analyzed within analytical runs that complied with the acceptance ranges for the quality control samples.

Pharmacokinetic Results for Tyramine

Tyramine Cmax showed a relatively high variability.

Pharmacokinetic Results for Rasagiline and 1-AI
Mean plasma concentration-time data (linear and semi-logarithmic) of rasagiline and 1-AI are shown in Figure 3 and Figure 4, respectively.

The summary statistics of PK parameters of rasagiline and 1-AI are presented in Table 22.

The mean plasma concentration-time profiles of rasagiline showed a rapid increase in plasma concentrations after drug administration, with maximum mean plasma concentrations being reached at about 30 minutes post-dose. Thereafter, an initial rapid decrease in plasma rasagiline concentrations was followed by a slower terminal elimination phase. There was a dose-dependent increase in rasagiline plasma concentrations following multiple dose administration of increasing doses of rasagiline. In addition, after treatment with 2 mg rasagiline during 13 days and 29 days, respectively, the mean rasagiline plasma concentration-time profiles were similar.

During treatment with 1 mg rasagiline (Group 3), rasagiline plasma concentrations were below LLQ during the terminal elimination phase. In addition, during treatment with 2 mg rasagiline (Groups 4a and 4b), blood samples for measurement of rasagiline plasma concentrations were taken for only up to 4 hours post-dose (since these 2 cohorts were conducted prior to Amendment No. 3), and therefore the terminal elimination phase could not be determined accurately.

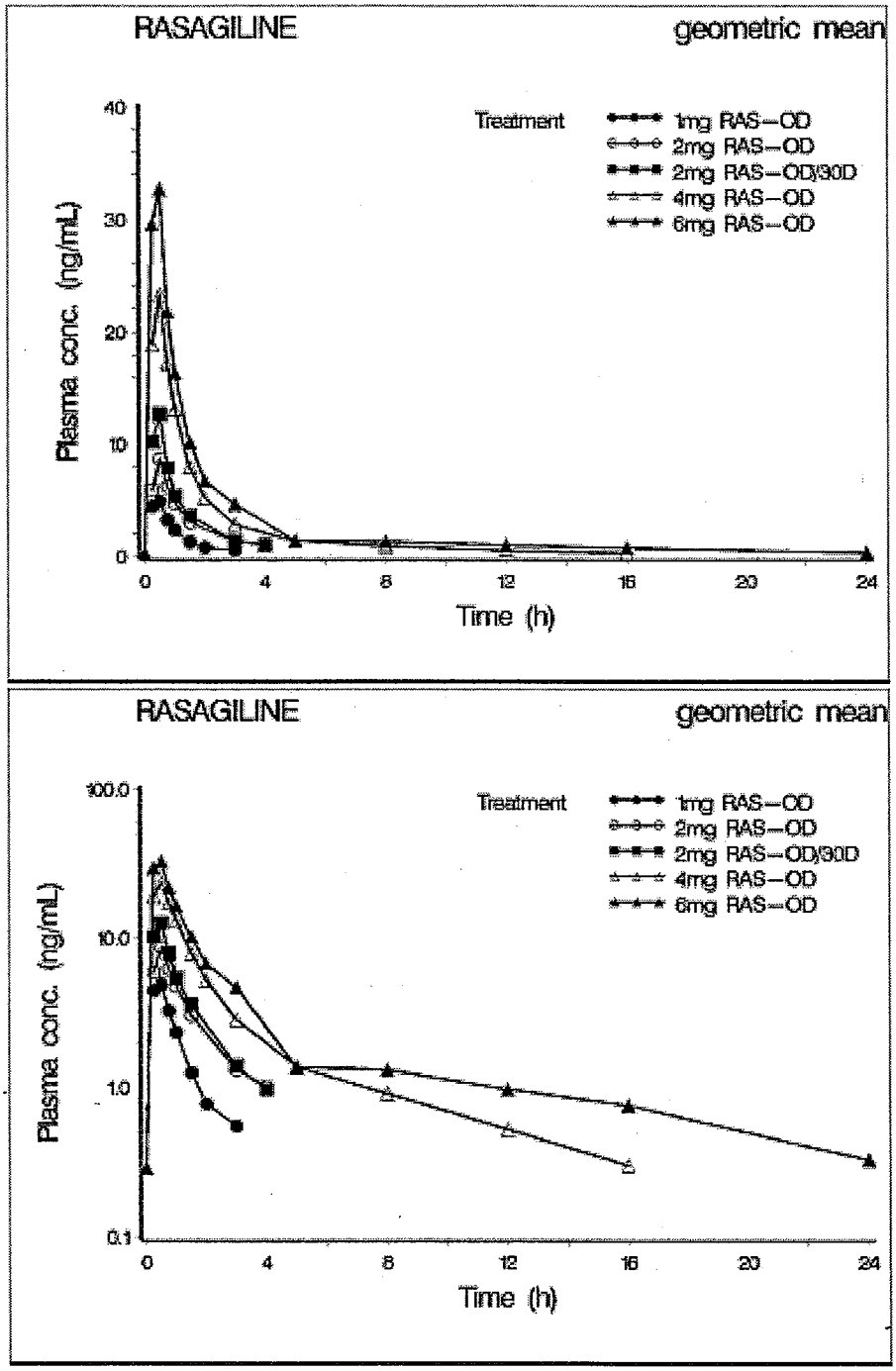


Figure 3 Mean Plasma Concentration Versus Time Profiles of Rasagiline

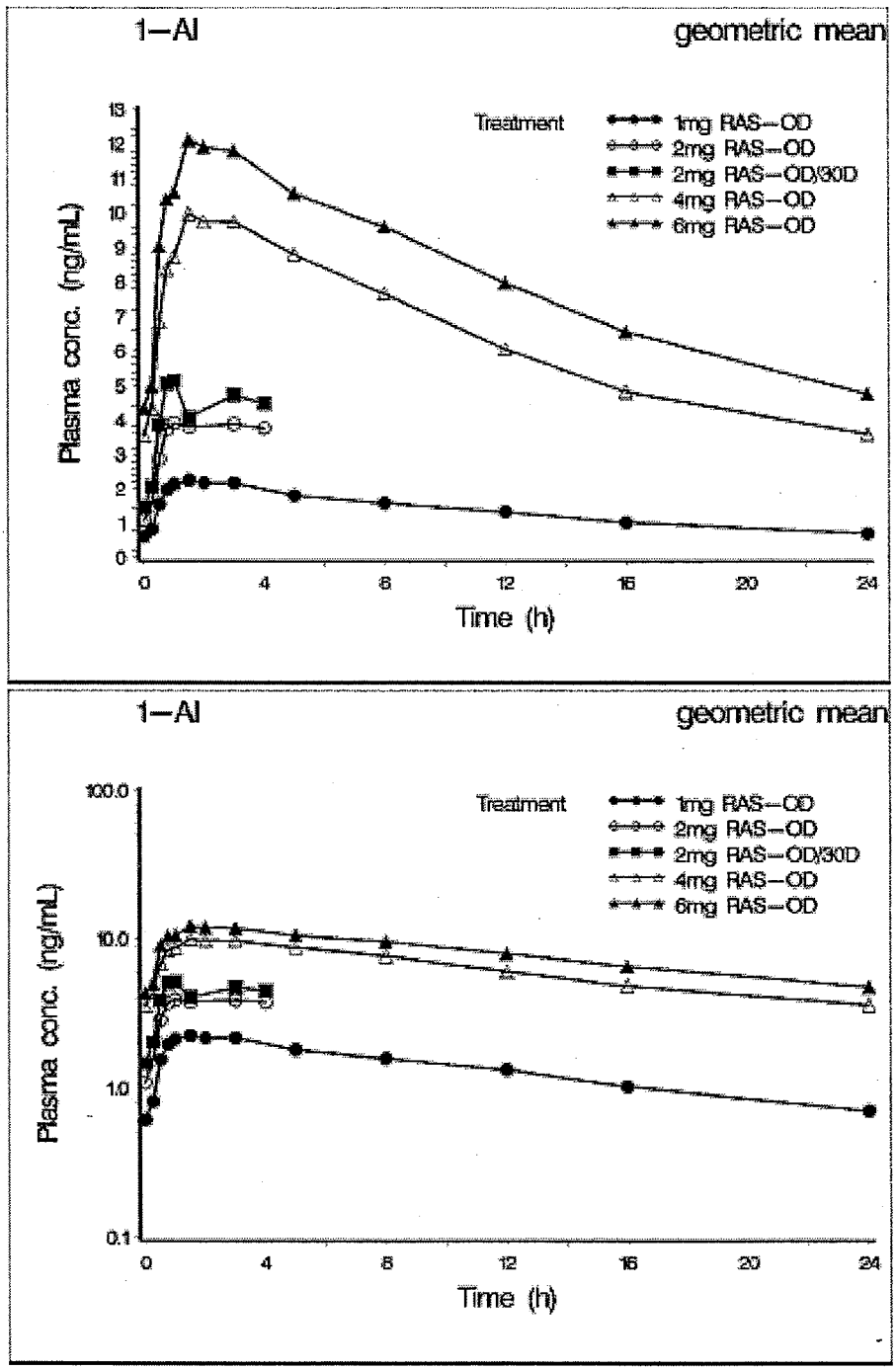


Figure 4 Mean Plasma Concentration Versus Time Profiles of 1-Al

After once daily administration of rasagiline, a dose-dependent increase in mean Cmax and AUC plasma rasagiline values was observed in the dose range of 1 mg to 6 mg rasagiline.

The median tmax for plasma rasagiline was approximately similar across the dose range studied, ranging from 0.33 h to 0.55 h. The terminal elimination half-life appeared to increase at the higher doses (4 mg and 6 mg rasagiline). The geometric mean t1/2 was between 1.19 h to 6.78 h across the dose range studied. However, it should be noted that the t1/2 of rasagiline could not be determined reliably for the 1 mg dose (Group 3) since more than half of the rasagiline plasma concentrations decreased to below LLQ within 8 hours after dosing. Similarly, the t1/2 could not be accurately estimated for Groups 4a and 4b as profiles were only sampled up to 4h post-dose. Since the half-life was underestimated for Groups 3, 4a and 4b, the AUC0-24 values were also somewhat underestimated for these groups.

The mean plasma concentration-time profiles of 1-AI showed a rapid increase in plasma concentrations after drug administration, with maximum mean plasma concentrations being reached at approximately 1-1.5 h post-dose. Thereafter, a gradual decrease in plasma 1-AI concentrations was observed. There was a dose-dependent increase in 1-AI plasma concentrations following multiple dose administration of increasing doses of rasagiline.

As for rasagiline, a dose-dependent increase in mean Cmax and AUC plasma 1-AI values was observed across the dose range studied. The median tmax for plasma 1-AI ranged from 1.07 h to 2.07 h. The geometric mean t1/2 was between 11.0 h to 15.8 h across the dose range studied. Due to the fact that for Groups 4a and 4b profiles were only sampled up to 4h post-dose, the actual terminal elimination phase could not be accurately determined. Overall the PK profile of rasagiline and 1-AI is consistent with the profile seen in previous studies.

Table 22 Summary Statistics of PK Parameters of Rasagiline and 1-AI

Treatment group	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0\text{-last}}$ (ng.h/mL)	$AUC_{0\text{-}24}$ (ng.h/mL)
			Rasagiline		
Group 3 (N=16) (1 mg RAS-OD)	5.8 (4.0–12.7)	0.39 (0.30–0.82)	1.42 (0.82-5.36)	6.39 (3.52-16.3)	7.07 (4.04-18.0)
Group 4a (N=14)# (2 mg RAS-OD)	11.3 (2.1-21.3)	0.45 (0.32-3.07)	1.19[a] (0.91-1.19)	13.7 (4.88-21.7)	16.5[a] (10.7-23.9)
Group 4b (N=14)# (2 mg RAS-OD/30D)	15.1 (7.6-24.2)	0.38 (0.25-0.57)	1.23 (0.97-1.63)	16.2 (10.1-21.0)	17.9 (12.0-23.6)
Group 5 (N=17) (4 mg RAS-OD)	27.4 (12.5-51.6)	0.55 (0.32-0.83)	4.74 (2.30-7.41)	44.5 (28.1-76.1)	46.0 (28.1-76.1)
Group 6 (N=15) (6 mg RAS-OD)	39.0 (15.1-70.5)	0.33 (0.25-0.63)	6.78 (2.51-11.1)	64.2 (20.3-96.4)	65.6 (21.2-96.5)
			1-AI		
Group 3 (N=16) (1 mg RAS-OD)	2.4 (1.7-2.9)	1.35 (0.82-3.08)	13.8 (9.25-20.4)	31.5 (15.9-48.7)	32.3 (19.1-48.8)
Group 4a (N=14)# (2 mg RAS-OD)	4.5 (2.9-8.2)	1.07 (0.82-4.07)	11.0[b] (7.12-24.3)	14.5 (9.24-25.7)	54.6[b] (34.1-90.6)
Group 4b (N=14)# (2 mg RAS-OD/30D)	5.5 (3.4-8.5)	1.08 (0.55-3.08)	13.2[c] (4.67-44.1)	18.2 (12.3-24.3)	70.8[b] (38.9-96.0)
Group 5 (N=17) (4 mg RAS-OD)	10.2 (7.4-12.7)	2.07 (0.62-3.07)	14.2 (9.83-19.2)	152 (99.5-194)	152 (99.7-194)
Group 6 (N=15) (6 mg RAS-OD)	13.1 (4.8-18.7)	1.57 (0.50-8.07)	15.8 (11.9-24.9)	190 (59.9-275)	194 (60.1-275)

For C_{max}, $t_{1/2}$, $AUC_{0\text{-last}}$ and $AUC_{0\text{-}24}$ the geometric mean (range) is presented; for t_{max} the median (range) is presented.
#: for Groups 4a and 4b profiles were sampled only for 4 hours post-dose.
[a]: N=13; [b]: N=8; [c]: N=12
Source: Table 15.3-8

Pharmacodynamic Parameters

Summary statistics of DHPG plasma concentrations are presented in Table 23.

Table 23 Summary Statistics of DHPG Plasma Concentrations

Treatment	DHPG plasma concentration Day 1 (pg/mL)		DHPG plasma concentration Day 24 or Day 40 (pg/mL)				% Change	
	Baseline*		0.5 h post-dose#		2.5 h post-dose#		Baseline / 0.5 h	
Placebo (N=45)	1024	(230)	1222	(378)	1293	(317)	19.2	(21.5)
15 mg phenelzine TID (N=16)	844	(257)	633	(194)	630	(232)	-21.5	(27.3)
5 mg selegiline BID (N=15)	804	(176)&	762	(176)	704	(167)	-5.9	(10.5)&
1 mg RAS-OD (N=16)	989	(356)	1147	(208)	1155	(231)	22.1	(25.9)
2 mg RAS-OD (N=14)	1036	(310)	1024	(254)	1064	(329)	0.7	(11.4)
2 mg RAS-OD/30D (N=14)	1045	(232)	916	(178)	1022	(238)	-10.6	(13.8)
4 mg RAS-OD (N=17)	942	(229)	745	(176)	765	(206)	-19.3	(17.7)
6 mg RAS-OD (N=10)	986	(293)	773	(174)	774	(211)	-18.2	(21.1)

The arithmetic mean (SD) is presented.

* prior to tyramine dosing

\# time relative to MAOI dosing; inhibition is at steady state at end of Period 2. The % change presented is calculated based on the 0.5 h post MAOI dose measurement versus the baseline measurement.

& N=14

Source: Table 15.3-9

Blood samples for the determination of DHPG (metabolite of noradrenaline produced by the action of the enzyme MAO-A) concentrations in plasma were collected on Day 1 and on Day 24 or Day 40 (Group 4b) after the rasagiline, phenelzine, selegiline or placebo administration.

For the positive control compound phenelzine and the comparator compound selegiline, a decrease in mean DHPG plasma concentration was observed at the doses studied which indicates an inhibition of MAO-A. The inhibition was stronger for phenelzine than for selegiline. Treatment with 1 mg rasagiline during 14 days impacted on mean DHPG concentrations similarly to placebo. After treatment with 4 mg and 6 mg rasagiline during 14 days, an obvious decrease was observed indicating inhibition of MAO-A. In conclusion, it seemed that rasagiline became less selective for MAO-B at doses of 4 mg rasagiline o.d. and higher.

SPONSOR'Conclusions on Pharmacokinetics and Pharmacodynamics

- After once daily multiple dose administration of rasagiline, a dose-dependent increase in mean Cmax and AUC plasma rasagiline and plasma 1-AI values was observed in the dose range of 1 mg to 6 mg rasagiline.
- Similar exposure to rasagiline and 1-AI was observed after 14 or 30 days of daily rasagiline 2 mg.
- On average, maximum rasagiline plasma concentrations were reached between 0.33 h and 0.55 h post-dose. The median tmax for 1-AI was between 1.07 h and 2.07 h post-dose.
- After multiple dosing with rasagiline, the geometric mean t1/2 across the 1-6 mg dose range was between 1.19 h to 6.78 h for rasagiline and between 11.1 h to 15.8 h for 1-AI.
- The mean DHPG plasma concentrations before and after 14 days of treatment with

rasagiline 1 mg support the conclusion from the primary endpoint that rasagiline 1 mg is selective for MAO-B. The selectivity of rasagiline seems to wane at doses of 4 mg rasagiline or higher.

3.2.10 Safety Evaluation

Extent of Exposure
In total, 179 subjects were exposed to oral doses of tyramine in Period 1 of the study. From these subjects, 156 subjects were exposed to a MAOI or placebo in Period 2. Ultimately, 154 subjects entered Period 3 and were exposed to oral doses of tyramine in combination with a MAOI or placebo.

Subjects who completed all 3 periods of the study (149 subjects) were included in the analysis of the primary endpoint. Subjects for whom the orthostatic BP and HR were measured in Period 2 (Groups 3-6 only) were included in the analysis of the secondary endpoint.

The sponsor presented data and analyses for adverse events, vital sign, ECGs, and clinical laboratory evolutions.

Sponsor Safety Conclusions

- Overall, the most frequently reported AEs were nervous system disorders (mainly headache, dizziness and somnolence), general disorders and administration site conditions (especially fatigue) and gastrointestinal disorders (especially nausea).
- There was no clear difference between rasagiline and placebo treated subjects with respect to AEs.
- There were 3 SAEs during the study, one in Period 1 (ventricular tachycardia) and two in Period 3 (intervertebral discitis and acute coronary syndrome).
- With regard to administration of study medication (rasagiline, phenelzine or selegiline), there were no findings of clinical relevance with respect to 12-lead ECG, continuous ECG monitoring, clinical laboratory and physical examination.

Reviewer Comments

- There was no clear change in the safety profile that has already been characterized for rasagiline.