

MEMORANDUM

DATE: July 1, 2004

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

TO: File, NDA 21-641

SUBJECT: Recommendation for action on NDA 21-641, for the use of Agilect (rasagiline mesylate) in patients with Parkinson's Disease

NDA 21-641, for the use of Agilect (rasagiline mesylate), a presumably selective MAO-B inhibitor, in patients with Parkinson's Disease (PD), was submitted by Teva Neuroscience, Inc., on 9/5/03. The application contains the results of three randomized controlled trials, one in patients recently diagnosed not receiving concomitant L-dopa (TEMPO), and two in patients with late PD experiencing "Off" episodes (PRESTO, LARGO). In addition, safety data and the requisite pre-clinical, CMC, and clinical pharmacology data have been submitted.

The application has been reviewed by Dr. Len Kapcala, medical officer, neurology team (review dated 6/25/04), Dr. Lisa Jones, medical officer, safety team, Dr. Judy Racoosin, safety team leader (memo dated 6/25/04), Dr. Sharon Yan, statistician (review dated 6/2/04), Dr. Andre Jackson, Office of Clinical Pharmacology and Biopharmaceutics (review dated 5/13/04), Dr. William Timmer, chemist (review dated 5/14/04), Dr. Paul Roney, pharmacologist, Dr. Lois Freed, pharmacology team leader, Dr. Tristan Massie, statistician (animal carcinogenicity; review dated 2/9/04), Carol Holquist, Division of Medication Errors and Technical Support (review dated 1/21/04), Dr. Ni Khin, Division of Scientific Investigations (review dated 4/8/04), and Dr. John Feeney, Neurology Team Leader (memo dated 6/25/04). The review team recommends that the application be considered Approvable. I will briefly review the relevant data, and offer the division's recommendations for action on the application.

EFFICACY

As noted above, the sponsor has submitted the results of three controlled trials in patients with PD. I will briefly describe the results of these trials.

TEMPO

This was a randomized, parallel group double-blind trial in which patients with early PD (Modified Hoehn and Yahr Score of less than or equal to 3) who had not been treated with levodopa or dopamine agonists for at least 6 weeks prior to their enrollment into the study were randomized to receive either rasagiline 1

mg/day, 2 mg/day, or placebo. The study was 26 weeks in duration, and was performed in 28 US centers and 4 Canadian centers. The primary endpoint was the change from baseline in the total UPDRS score (consisting of measures of ADL, Motor Function, and Mentation). Patients were evaluated at baseline and Weeks 4, 8, 14, 20, and 26. Secondary outcomes included scores on the individual UPDRS sub-scales, Hoehn and Yahr Stage, and Schwab and England ADL. The time to requiring levodopa therapy was also examined. The following chart describes patient flow in the trial:

| | Ras 1 mg | Ras 2 mg | Placebo |
|---|----------|----------|---------|
| Randomized | 134 | 132 | 138 |
| Completed (without needing additional tx) | 111 | 105 | 112 |

The following chart displays the efficacy results:

Mean Total UPDRS Scores and Change From Baseline

| Drug | Mean | Change | P-value (vs placebo) |
|------------------|-------|--------|----------------------|
| Ras 1 (N=134) | 24.75 | .06 | .0001 |
| Ras 2 (N=132) | 26.61 | .72 | .0001 |
| Pbo (N=138) | 28.44 | 3.91 | |

Statistically significant drug-placebo differences emerged (and persisted to endpoint) at Week 4 for the 2 mg group, and at Week 8 for the 1 mg group.

Secondary Outcomes

Nominally significant drug-placebo differences were seen on the individual sub-scales (Mentation, ADL, Motor Score) for both doses, save for a non-significant difference for the 1 mg group on the Mentation sub-scale; the estimate of the treatment effect on the Motor Score was greater for the 1 mg group than for the 2 mg group (this order was reversed for the ADL score; see Dr. Yan's Table 8, page 10 of her review).

Too few patients required the addition of levodopa therapy, so this outcome was not analyzed.

LARGO

This was a randomized, parallel group, double blind trial in patients with late-stage PD who were receiving levodopa and a dopa decarboxylase inhibitor and who were experiencing "Off" episodes. In this trial, patients were randomized to receive either rasagiline 1 mg, entacapone 200 mg with each dose of l-dopa, or placebo. This study was 18 weeks in duration (a 6 week l-dopa dose adjustment phase followed by a 12 week l-dopa dose maintenance phase), and the primary outcome was the change from baseline in the total daily "Off" time (as recorded by patients in diaries).

Secondary outcomes (to be analyzed sequentially in the following order) were:

Global Improvement (7 point scale, centered at 0=No Change)
Change From Baseline in UPDRS-ADL during the "Off" state
Change From Baseline in UPDRS-Motor Score during the "On" state

This study was performed in Israel, Argentina, and Europe.

The following chart displays patient flow through the study:

| | Ras | Enta | Placebo |
|------------|-----|------|---------|
| Randomized | 231 | 227 | 229 |
| Completed | 208 | 197 | 194 |

The following chart displays the results of the primary outcome measure:

Mean Total Daily "Off" Time, and Change from Baseline

| Drug | Mean (Hrs) | Change | P-value (vs placebo) |
|---------------------|------------|--------|----------------------|
| Ras 1 mg (N=222) | 5.58 | -1.17 | .0001 |
| Enta (N=218) | 5.58 | -1.19 | .0001 |
| Placebo (N=218) | 5.54 | -.35 | |

Secondary Outcome

| Drug | CGE | Change ADL (Off) | Change Motor (On) |
|----------|-------|------------------|-------------------|
| Ras 1 mg | -.93 | -2.61 | -3.87 |
| P-value | <.001 | .0001 | .0001 |
| Enta | -.79 | -2.28 | -3.51 |
| P-value | <.001 | .0012 | .0006 |
| Placebo | -.44 | -.89 | -.82 |

PRESTO

This was a randomized, parallel group, double-blind trial in patients similar in design to the LARGO study. In this study, patients were randomized to receive either rasagiline 0.5 mg, 1 mg, or placebo. The study was 26 weeks in duration, and the primary outcome was, as in LARGO, the change in total daily "Off" time. Secondary outcomes were as in LARGO. This study was conducted in the US and Canada.

The following chart displays patient flow through the study:

| | Ras .5 | Ras 1 | Placebo |
|------------|--------|-------|---------|
| Randomized | 164 | 149 | 159 |
| Completed | 142 | 132 | 140 |

The following chart displays the results of the primary outcome measure:

Mean Total Daily "Off" Time, and Change from Baseline

| Drug | Mean (Hrs) | Change | P-value (vs placebo) |
|----------------------|------------|--------|----------------------|
| Ras .5 mg (N=157) | 6.01 | -1.38 | .02 |
| Ras 1 mg (N=142) | 6.25 | -1.85 | .0001 |
| Placebo (N=152) | 5.98 | -.88 | |

Secondary Outcome

| Drug | CGE | Change ADL (Off) | Change Motor (On) |
|-----------|-------|------------------|-------------------|
| Ras .5 mg | -.40 | -.60 | -1.43 |
| P-value | .003 | .007 | .001 |
| Ras 1 mg | -.66 | -.68 | -1.30 |
| P-value | .0001 | .0034 | .0008 |
| Placebo | -.02 | .68 | 1.21 |

Demographic Subgroups

According to Dr. Yan, results did not differ between men and women and patients above and below 65 year old, with one possible exception.

In the PRESTO study, on the primary outcome measure (total daily "Off" time), at the 0.5 mg dose, men (N=295) had a -1.49 hour change from baseline (p=.02 compared to placebo) and women (N=156) had a -1.12 hour change from baseline (p=.67 compared to placebo).

SAFETY

A total of 1537 subjects/patients were exposed to at least one dose of rasagiline during development. A total of 1028 patients have been exposed for at least 6 months, and 674 patients have been exposed for at least one year.

The sponsor has divided the patients into various safety cohorts. Cohort 1 consists of placebo controlled monotherapy studies (2 studies, TEMPO, 26 weeks, and TV-1012/231, 10 weeks), Cohort 2 consists of placebo controlled adjunctive PD studies (PRESTO, LARGO), and Cohort 9 consists of all PD patients treated with rasagiline (Cohorts 3-8 consist of various other cohorts derived from the various studies; see Dr. Jones's review, pages 23-24 for their definitions).

In Cohort 1, the median duration of exposure for each of the dose groups (1 mg and 2 mg/day) was about 180 days (149 and 146 patients, respectively). In Cohort 2, the median duration of exposure to rasagiline 1 mg/day was 129 days (a total of 380 patients). About 54% received this treatment for between 18-26 weeks, with another 17% exposed for between 26-30 weeks. In Cohort 9, a total

of 1360 patients were exposed (see Dr. Jones's Table 9, page 27 for the distribution of patients by dose).

Deaths in PD Patients (Cohort 9)

A total of 32 patients in Cohort 9 died; 21 treated with rasagiline. Six rasagiline patients died of CVAs (one CVA death in each of the entacapone and placebo groups), 4 of cancer, 2 of pneumonia, 3 were "sudden" death, and 3 due to unknown causes (the other 4 were clearly not drug related). The deaths were not obviously drug related. No deaths occurred in Cohort 1, and 4 rasagiline and 4 placebo patients died in Cohort 2 (in Cohort 2, 2 rasagiline patients died in PRESTO; 1 in each dose group, both of CVAs; no placebo patients died in PRESTO).

Serious Adverse Events

A total of 5% of rasagiline patients in Cohort 1 experienced an SAE (4% at 1 mg, 6% at 2 mg) compared to 2.6% of placebo patients. In the 1 mg group, 4/6 patients with SAEs had cardiac related events and in the 2 mg group, the largest number of SAEs in any one body system was 4/9 patients with an SAE in the category Body as a Whole.

In Cohort 2, 8% of rasagiline and placebo patients experienced an SAE.

In Cohort 9, 14 patients reported accidental injury, and 14 patients reported angina. A total of 16 patients experience syncope, but, as Dr. Jones points out, these cases generally occurred after prolonged exposure to the drug.

Discontinuations

In Cohort 1, 5 rasagiline 1 mg patients, 2 rasagiline 2 mg patients, and one placebo patient discontinued treatment due to an adverse event. Only hallucinations occurred in more than one patient (3 in the 1 mg group). In Cohort 2, 4.2% of rasagiline and 4.9% of placebo patients discontinued for an adverse event. In Cohort 9, about 10% of patients discontinued secondary to an ADR. Nervous system events accounted for 4% of the discontinuations, then about 3% for CV events, and 2% for GI events.

In all controlled trials, 6 rasagiline and one placebo patient discontinued due to hallucinations. In Cohort 9, 14 patients discontinued due to hallucinations.

Adverse Events

Below is a table of common adverse events that occurred at least twice as frequently on drug than on placebo in Cohort 1:

| Event | Rasagiline 1 mg | Placebo |
|----------------|-----------------|---------|
| Flu Syndrome | 6% | 0.7% |
| Depression | 5.4% | 2% |
| Rhinitis | 2.7% | 1.3% |
| Conjunctivitis | 2.7% | 0.7% |
| Vertigo | 2% | 0.7% |
| Malaise | 2% | 0% |
| Neck Pain | 2% | 0% |
| Neoplasm | 2% | 0% |
| Arthritis | 2% | 0.7% |

The following adverse events appeared to be dose related:

| Event | Ras 2 mg | Ras 1 mg | Placebo |
|-----------------|----------|----------|---------|
| Abnormal Dreams | 3.4% | 0.7% | 0% |
| Sleep Disorder | 2.7% | 1.3% | 0.7% |
| Somnolence | 2.7 | 1.3 | 0.7 |
| Ataxia | 2.7 | 1.3 | 0.7 |
| Flatulence | 2.7 | 1.3 | 0.7 |
| Vomiting | 2.7 | 1.3 | 0.7 |

The following Adverse Events were seen in Cohort 2:

| Event | Ras 1 mg | Placebo |
|----------------------|----------|---------|
| Postural Hypotension | 4.7% | 1.3% |
| Weight Loss | 4.2% | 1.5% |
| Constipation | 4.2% | 2.1% |
| Abdominal Pain | 3.9% | 1.3% |
| Vomiting | 3.4% | 1% |
| Arthralgia | 3.2% | 1.3% |
| Dystonia | 2.4% | 0.8% |
| Anorexia | 2.1% | 0.5% |
| Abnormal Dreams | 2.1% | 0.8% |

In Cohort 9, the following adverse events were reported:

| Event | Incidence |
|----------------------|-----------|
| Accidental Injury | 17.6% |
| Infection | 17.7% |
| Dizziness | 12.8% |
| Nausea | 12.4% |
| Sleep Disorder | 11.8% |
| Dyskinesia | 10.7% |
| Arthralgia | 10.7% |
| Headache | 10.3% |
| Pain | 9.9% |
| Postural Hypotension | 7.8% |

Labs

There were no systematic abnormalities on any routine laboratory test that appeared to be of clinical significance.

EKG

As noted by Drs. Jones and Racoosin, only in the Cohort 2 patients were data on mean change and outlier analyses presented for EKG intervals; in this cohort, no important abnormalities were seen. However, the data were simply reported as "normal" or "abnormal" for Cohort 1.

Tyramine studies

Although rasagiline is supposedly a selective MAO-B inhibitor (at least at 1 mg), the sponsor evaluated its potential to inhibit MAO-A by assessing patients' responses to ingestion of tyramine before and after treatment in four separate studies. I will briefly present the results of these studies.

Paris Study

A total of 29 normal healthy males between the ages of 18-40 were entered into this study. In period 1, they received 10 days of treatment with placebo; on Days 8, 9, and 10, they received the following treatments (fasted) in addition:

Day 8- tyramine 50 mg, one-half hour after placebo

Day 9-tyramine 100 mg, one-half hour after placebo, followed by tyramine 200 mg 3 1/2 hours after this

Day 10-tyramine 400 mg, one-half hour after placebo, followed by tyramine 800 mg 3 1/2 hours later.

After Period 1, the patients were assigned to receive the following doses for the next 10 days, in Period 2:

- Rasagiline 1 mg (N=6)
- Rasagiline 2 mg (N=6)
- Deprenyl 10 mg (N=6)
- Placebo (N=9)

(The investigator treated an additional 3 patients with placebo outside of the protocol).

As in Period 1, the subjects received the same tyramine doses as previously described on Days 8, 9, 10. After each dose of tyramine (periods 1 and 2), blood pressure was monitored frequently for several hours. When the subject experienced a systolic blood pressure increase of at least 30 mm Hg, no further doses of tyramine were given (up to a maximum dose of 800 mg). The ratio of the dose giving such a response at baseline (Period 1) to the tyramine dose giving a blood pressure response on treatment with study drug (Period 2), the so-called "pressor ratio", is a measure of the sensitivity to tyramine (an indirect measure of MAO-A inhibition).

Although 29 patients were treated in this study, 8 of these subjects did not experience a pressor response at the maximum dose of 800 in Period 1, and 4 others did not reach a pressor response at 800 mg in Period 2. In addition, another 11 subjects reached a pressor response at 800 mg in Period 1, and 6 subjects reached a pressor response at 800 mg in Period 2 (some reached a response at 800 mg in both periods).

The following chart displays the tyramine pressor ratios in those patients who reached a pressor response in both periods:

| | |
|-----------------------|-----|
| Deprenyl (N=3) | 4.3 |
| Rasagiline 2 mg (N=5) | 2.8 |
| Rasagiline 1 mg (N=4) | 1.3 |
| Placebo (N=5) | 1.1 |

(These results differ only slightly from those calculated by the sponsor using data from all 29 subjects; in their calculations, if a pressor response was not achieved, they added 50 mg to the maximum dose reached [e.g., if a pressor response was not reached at 800 mg of tyramine, they assigned a dose of 850 mg as giving a pressor response]).

Tyramine levels seemed to increase in the presence of active drug treatment (see Dr. Kapcala's review, pages 51-2).

Study TV 1012/132

This study was designed to assess the tyramine response in patients with PD receiving treatment with levodopa, in addition to other anti-PD treatments. Patients were given a dose of 75 mg of tyramine on Day -7 (baseline) and then treated on an out-patient basis with either rasagiline 1 mg (N=7), rasagiline 2 mg (N=7), or placebo (N=6) for 3 weeks on a restricted tyramine diet, with BP to be recorded by the patient (caregiver) twice a day, 1 hour after the morning medication, and after dinner. On Days 22, 23, and 24, the patients were given a dose of tyramine 25 mg, 50 mg, and 75 mg in applesauce, respectively, about 5-10 minutes before a standardized meal, and then had their blood pressure monitored frequently. They were then sent home on an unrestricted diet for the next 7 weeks, and then evaluated on Days 42, 56, and 70 (tyramine 75 mg was again given on Day 70). The sponsor documented maximum MAO-B inhibition by Day 22, which persisted up to Day 70.

In this study, there were no systematic changes in blood pressure noted after treatment with tyramine, either in the patients' home diaries, or on formal testing. Two patients met formal criteria for a pressor response (systolic elevation of at least 30 mm Hg for three readings (q 5 minutes), both in the 2 mg rasagiline group, one at 25 and 50 mg, one at 75 mg. Both patients were asymptomatic (see Dr. Kapcala's review, pages 90-96 for details of these cases).

TEMPO Sub-study

In this study, a sub-set of the patients in the TEMPO study received a tyramine challenge at the end of their participation in TEMPO. Here, they received a 75 mg dose of tyramine in applesauce within 1 hour of a low tyramine meal, after which their blood pressure was monitored carefully. In this study, 19 patients received rasagiline 1 mg, 19 patients received rasagiline 2 mg, and 17 patients received placebo.

There were no systematic blood pressure changes, and although no patients reached the criteria (three consecutive systolic BP increases of at least 30 mm Hg) for a pressor response, two patients in the rasagiline 2 mg group had elevations of blood pressure that almost qualified (i.e., had one BP reading that was minimally below the criterion and the surrounding measurements met the criterion).

PRESTO Sub-study

This study followed essentially the same design as the TEMPO sub-study, although in this study, a tyramine dose of 50 mg was added to a dessert at the

end of the PRESTO study. Here, 22 patients received rasagiline 0.5 mg, 12 patients received rasagiline 1 mg, and 21 patients received placebo.

There were no systematic changes in blood pressure, although 3 patients in the rasagiline 0.5 mg group and 1 placebo patient met pressor criteria (an additional 2 placebo patients had two consecutive BP measurements that met criteria).

Melanoma

During the course of development of rasagiline, a number of cases of melanoma were detected. As a result, the sponsor instituted systematic monitoring of patients for the emergence of melanomas. Specifically, after the detection of the sixth case, all patients underwent dermatologic examination every three months. After this monitoring program was instituted, an additional 14 cases were detected. The first 6 cases were detected in the first 3 1/2 years of development; the additional 14 cases were detected in the next 1 1/4 years. Therefore, a total of 20 cases of melanoma (in 19 patients) were detected during the development of rasagiline. About 42-44% of patients had a baseline evaluation for melanomas, and a total of about 83% patients had at least one on-treatment examination.

Most of the cases were detected in the open-label extensions of the controlled trials. A total of 5 cases occurred during the controlled trials (the following chart is adopted from Dr. Racoosin's Table):

| | Rasagiline | | Placebo | |
|--------|------------|------|---------|------|
| | Cases | Rate | Cases | Rate |
| TEMPO | 1 | 8.3 | 0 | 0 |
| PRESTO | 3 | 20.6 | 0 | 0 |
| LARGO | 0 | 0 | 1 | 13.6 |

Rate is expressed in cases/1000 pt-yrs, and the number of pt-yrs on rasagiline in TEMPO and PRESTO is about twice that on placebo (each study had two rasagiline groups).

A total of 16/19 patients in whom melanoma was diagnosed were in TEMPO and PRESTO (8 in each); these studies were performed in North America, while LARGO was performed in Europe, Argentina, and Israel.

Three of the cases were diagnosed prior to the initiation of any treatment.

Of the 16 melanomas that occurred in (15) rasagiline treated patients, 7 were invasive and 9 were in situ at the time of diagnosis. In these patients, the range of duration of treatment at the time of diagnosis was 2.5-55 months, with a

median duration of 13 months and a mean duration of 21 months. A total of 7 cases were diagnosed within 9 months of the initiation of treatment.

Because almost all cases were diagnosed in patients in open-label, uncontrolled studies, efforts were made to compare the incidence seen in the development program with appropriate comparator groups. The comparator groups evaluated by Dr. Jones were SEER, American Academy of Dermatology Screening Program, and other PD drug NDA datasets.

SEER

The Surveillance, Epidemiology, and End Results (SEER) program is administered by the National Cancer Institute. It collects cancer incidence data and outcome (survival) from 11 population based registries and 3 additional registries. According to Dr. Jones, these registries collectively include about 14% of the US population. SEER calculates rates for invasive melanoma only, although it collects data on in situ tumors as well. Dr. Jones describes that, based on conversations she has had with personnel at the SEER central registry as well as with personnel at some of the registries, SEER collects information from private laboratories as well as hospitals, and makes efforts to collect information on cases from private practitioners. Nonetheless, various literature reports suggest that up to about 20% of melanomas may not be reported to SEER. SEER does not collect cases derived from an active screening program (that is, patients represented in this database are not specifically actively screened for tumors).

Accordingly, Dr. Jones has calculated whether or not the rate of invasive melanoma seen in the NDA database is greater than that in the SEER database, with various assumptions about the degree of underreporting (we expect that the rate of underreporting for invasive tumors would in general be less than that for in situ tumors):

The rate of invasive melanoma in the SEER database is 24/100,000 pt-yrs in males and 16.2/100,000 pt-yrs for females. The exposure to rasagiline was 2030 patient-years. With these rates and exposures, the following expected number of cases would be (taken from Dr. Jones's Table 60, page 128 of her review):

| Expected Number of Cases | Obs/Exp | 95% CI |
|--------------------------|---------|-----------|
| 0.9 (SEER rate) | 7.8 | 3.1, 16 |
| 1.3 (1.5 x SEER rate) | 6.2 | 2.2, 11.1 |
| 1.8 (2 x SEER rate) | 3.9 | 1.6, 8.0 |
| 2.7 (3 x SEER rate) | 2.6 | 1.04, 5.3 |

American Academy of Dermatology (AAD) Screening Data

This database collects data in a voluntary screening program that solicits participation through local public service announcements. According to Dr. Jones, in this database, "...pathologic confirmation on all suspicious lesions identified by screening.", is sought. Based on the AAD rates of melanoma, Dr. Jones has calculated the number of cases that would be expected in the NDA database:

| Number of Cases Expected | # Observed | Obs/Exp | 95% CI |
|--------------------------|------------|---------|-----------|
| Invasive 1.5 | 4 | 2.6 | .72, 6.7 |
| In Situ 0.59 | 6 | 10.2 | 3.7, 22.1 |

Because patients in the AAD database were screened only once, and patients in the NDA database were screened frequently, Dr. Jones calculated the above rates using only those tumors detected at the first screening:

| Number of Cases Expected | # Observed | Obs/Exp | 95% CI |
|--------------------------|------------|---------|------------|
| Invasive 1.5 | 2 | 1.3 | .16, 4.75 |
| In Situ 0.59 | 3 | 5.1 | 1.05, 14.9 |

Combining the invasive and in situ tumors in this latter analysis yields an observed/expected ratio of about 2.4.

PD NDA Databases

As noted above, we asked the sponsors of recently approved anti-PD therapies to supply us with data on the occurrence of melanoma in their development programs. As far as I know, none of these programs ever actively screened or examined patients for melanoma (the numbers in this table were calculated using all cases described in the appropriate database, not just cases that occurred in the PD drug-treated patients):

| Drug | Pt-Yrs | Cases/1000 Pt-yrs |
|-------------|--------|-------------------|
| Pramipexole | 6909 | 1.6 |
| Ropinerole | 3377 | 0.3 |
| Entacapone | 2486 | 0 |
| Tolcapone | 3200 | 0.3 |
| Rasagiline | 2450 | 8.2 |

(Including only those tumors in the rasagiline group that were detected prior to active screening gives a rate of about 5.3 cases/1000 pt-yrs).

The sponsor claims that there may be an increased incidence of melanoma in PD patients, and that the higher rate of melanoma seen in the North American studies (TEMPO, PRESTO) is consistent with patients in North America having a greater number of melanoma risk factors than patients in Argentina, Europe, or Israel (the sites of LARGO).

With regard to rates of melanoma by region, Dr. Jones has documented that indeed the rates of melanoma are higher in the countries in which the TEMPO and PRESTO studies were done compared to those in the LARGO countries.

Regarding the (presumed) association between melanoma and PD, the sponsor has initiated two studies to address this question.

In one study, a cohort of PD patients is being followed in Israel. In this study, patients are referred by neurologists for dermatologic screening. As of 7/03, 1207 PD patients had been evaluated and data from 1146 were available. There were 8 cases of melanoma (7 in situ, 1 invasive). The sponsor concludes that this rate is about 10 times the background rate seen in Israel.

Another study is examining a North American cohort that shows a rate of 1/143 patients. The sponsor states that this is higher than background rates reported in the literature. Dr. Jones discusses three studies from the literature that describe an increase in the incidence of melanoma in PD patients compared to the general population (see Dr. Jones's review, pages 123-124).

Dr. Jones's Figure 5, page 126 also provides interesting data on the melanoma rate/100 patient-years in the NDA database. As she shows, the rate shows no particular pattern:

| Duration | Cases | Rate/100 Pt-yrs |
|------------------------|-------|-----------------|
| 0-0.5 yrs of exposure | 2 | 0.3 |
| 0.5-1 year of exposure | 5 | 1.3 |
| 1-2 years of exposure | 3 | 0.9 |
| 2-3 years of exposure | 1 | 0.4 |
| 3+ years of exposure | 4 | 1.3 |

Other issues

CMC

Although the chemistry reviewer notes no comments in his review, the compound is a mesylate salt, and, as such, the synthesis may produce multiple impurities that are either known, or suspected, mutagens. According to current Agency practice, we will ask the sponsor to decrease the limits of these compounds to below 10^{-6} , or to demonstrate in adequate studies that they are not genotoxic.

Pre-clinical

Rasagiline is associated with a statistically significant increase in combined lung adenoma and adenocarcinoma in the mouse. The ratio of the AUC at the low effect dose to the AUC at human doses is about 170, but the ratio of the AUC at the no effect dose to the human AUC is only about 5. Further, rasagiline is positive in 3 chromosomal aberration assays and in the mouse lymphoma assay. The report of the rat carcinogenicity study was inadequate, as histopathologic examination was performed only on the high dose group, which was greater than the MTD.

A rat segment III study was performed at a company $—$, that is known to the Agency to have produced unacceptable reproduction studies at that time (1997), related to the employment of a particular individual (see Dr. Freed's memo); all such studies done at that time are apparently considered invalid.

OCPB

The primary route of metabolism of rasagiline is via CYP 1A2; the concomitant administration of ciprofloxacin doubled the AUC of rasagiline. The co-administration of l-dopa and rasagiline increases the AUC of rasagiline by about 30%. In patients with moderate hepatic impairment, the AUC of rasagiline is increased about 7 fold; in patients with mild hepatic impairment, the AUC is increased about 2 fold.

Rasagiline does not inhibit CYP enzymes (at least at concentrations 3 times those achieved with a 1 mg dose). The half-life of the parent is between 2-3.5 hours, and the half-life of the primary metabolite (1-Aminoindan; AI), which accounts for about 20% of an administered dose, is about 10-12 hours. Only about 0.5% of an administered dose is recovered in the urine unchanged.

COMMENTS

The sponsor has submitted the results of three controlled trials designed to demonstrate the effectiveness of rasagiline in the treatment of early and late PD. These studies clearly demonstrate the effectiveness of rasagiline alone (with positive effects on the UPDRS, a standard scale that assesses the fundamental clinical deficits of PD), and in the presence of levodopa in more advanced patients (with significant effects on the amount of time spent "Off"). In the TEMPO study (monotherapy), both 1 and 2 mg/day were effective, but there seemed to be no advantage of the 2 mg dose. Similarly, in the PRESTO (late stage) study, 0.5 and 1 mg/day were effective, and although the 1 mg dose was numerically superior to the 0.5 mg dose on the primary, and some secondary outcomes, the 0.5 mg dose is clearly an effective dose, including on all the critical secondary outcomes (I would not make much of the lack of significance, and apparent small treatment effect, of the 0.5 mg dose in women; there is no obvious reason to believe women do not respond similarly to men at this dose, they do respond similarly to men at 1 mg, and women do not have a decreased exposure to rasagiline, at a given dose, than men. I believe that this "finding" is merely an artifact of the multiple sub-groups examined in these analyses).

There are no obvious clinical adverse events that would preclude approval, although the sponsor has not provided complete data on several questions (for example, they have not provided an adequate description of EKG intervals in the monotherapy setting, they need to further evaluate the occurrence of a "flu syndrome" that occurred in 4.7% of rasagiline patients in Cohort 1 and in 0.7% of placebo patients, and for about 7% of patients who discontinued due to adverse events the specific events responsible for the discontinuation were not adequately defined). However, there remain two clinical safety issues that require additional discussion.

The sponsor has presented the results of four studies examining rasagiline treated patients' sensitivity to tyramine. These studies are designed to examine whether or not, and at what dose, rasagiline loses its selectivity for MAO-B. If rasagiline were to be associated with appreciable sensitivity to tyramine (lose selectivity) at therapeutic doses, we would be concerned about the occurrence of hypertensive adverse events when patients ingested meals/foods rich in tyramine. In such a case, if the drug were to be approved, labeling would need to warn prescribers that patients would need to restrict their diets to low tyramine foods.

The best designed study was the Paris study, which did not detect any appreciable sensitivity to tyramine at the 1 mg dose, although the 2 mg dose did demonstrate a mean increase in the pressor ratio; depending upon the analyses done, the pressor ratio at the 2 mg dose was close to that of a single 10 mg dose of selegiline (although the approved dosing regimen for selegiline is 5 mg BID).

However, Dr. Kapcala has numerous concerns about the conduct of the study, and hence its interpretation.

First, he notes that the population studied, healthy young men, may not adequately reflect the sensitivities of the older population for whom this drug would be indicated. He also notes the small number of patients studied.

Further, standard studies of this type define a pressor response as 3 consecutive systolic elevations, closely spaced (usually about 5 minutes apart). In this study, patients were considered to have achieved a response on the basis of a single elevated systolic reading.

He is particularly concerned that many subjects (either in Period 1 and/or Period 2) either met the pressor criteria only at 800 mg of tyramine, or not at all. In his experience (he has reviewed many such studies in multiple NDA submissions), this is highly unusual. That is, most patients reach a pressor response at considerably lower doses, and this observation makes him question the bioperformance of the particular tyramine product used, at least in this study. It is important to note that the supplier of the tyramine in this study was the supplier of the tyramine for the other studies as well.

Further, in those cases in which the patient did not reach a pressor response, the sponsor assigned a dose of 50 mg more to the maximum dose given, and considered the resultant dose as the dose used in the calculation of the pressor ratio for that subject. As he notes, this can produce underestimates of the pressor ratios. As I described earlier, he re-calculated the ratios, using only those patients in whom this maneuver was not employed. This increased the mean pressor ratios for drug treated patients (including that for the 1 mg dose) but it further decreased the sample size.

He also notes that the lowest tyramine dose the sponsor used was 50 mg, whereas in many such studies, tyramine titration begins with 25 mg. This too could have resulted in a lack of sensitivity of the assay.

In Study TV1012/132, again there were no systematic increases in BP in patients with PD who were receiving concomitant anti-PD medications, either as assessed by home monitoring or on formal testing in response to increasing single doses of tyramine given close in time to a meal. However, in this study, two patients receiving rasagiline 2 mg did meet pressor criteria.

Dr. Kapcala has reservations about this study as well.

We have little experience with the administration of tyramine with (or close in time to) a meal. Typically, these studies are done in the fasted state; as Dr. Kapcala notes, giving tyramine with a meal typically delays the absorption of the tyramine, and may blunt the effect. Further, blood pressure increases may be

delayed in time due to the delayed absorption tyramine, but the frequency of the BP monitoring typically decreases after 2-3 hours of tyramine ingestion in these studies, so any potential pressor response may be missed.

In the PRESTO sub-study, again no major systematic BP changes were noted, but many of the same questions raised about the previously described study apply here as well (the kinetics of tyramine given with food, decreased late monitoring of BP, performance of the tyramine). It is also interesting to note that three patients who received 0.5 mg rasagiline met pressor criteria, as did one placebo patient (2 other placebo patients had 2 consecutive systolic increases of at least 30 mm Hg).

Finally, in the TEMPO sub-study, although there were no major systematic BP changes, two patients at the 2 mg dose had 2 consecutive BP readings that met criteria with an adjacent reading that missed the criterion by a few mm Hg (and a subsequent reading that did meet criteria). Again, the same concerns expressed about the last two studies apply here as well.

One could argue that if the primary clinical concern relates to the sensitivity to tyramine in the face of a high tyramine meal, giving a capsule of tyramine with food (the condition in these studies giving rise to concerns about the absorption of tyramine), might be an ecologically valid methodology to employ. Unfortunately, we do not know if administering a capsule of tyramine with a meal results in the same absorption of tyramine as would result from a *meal* with the same amount of tyramine, especially given the different sorts of foods that may contain tyramine (e.g., cheese, wine, etc.).

It is true that, in the entire database, there is no particular evidence that there were significant problems related to hypertension, and, in particular, frequent BP monitoring at home by patients did not reveal any systematic elevations of BP. However, we have no knowledge about the temporal relationship between BP monitoring and meals (although patients in TV 1012/132 were to monitor BP "after dinner"), nor do we have information about the content of the meals. Similarly, throughout the development program, although there were no important signals of hypertension, we do not have information about the timing of the measurements in relation to meals, nor do we know the content of any meals. In this regard, however, it is interesting to note that there were a number of CVAs including several deaths due to CVA) in rasagiline treated patients (of course, it is impossible to attribute these unambiguously to drug)

Although there does not appear to be a signal of tyramine sensitivity at 1 mg of rasagiline, the deficiencies in the studies described raise significant concerns about the results obtained. In particular, the large number of subjects in the Paris study who either reached a pressor response only at 800 mg of tyramine or who did not reach a response even at that dose, the small numbers studied and the healthy population enrolled, and the administration of the tyramine in the

other studies with food (and resultant questions about its kinetics and the appropriateness of less frequent monitoring further out in time) are particularly problematic aspects of the studies. Further, the studies, taken as a whole, and however, flawed, do suggest a loss of sensitivity at the 2 mg dose, at least in some patients. Certainly, if this is true, there is not a large margin between what would be the recommended dose (1 mg) and the dose showing a tyramine effect. Further, there will undoubtedly be patients who receive 1 mg of rasagiline who will be exposed to levels of rasagiline that may approach those typically seen at 2 mg (for example, patients with co-administered CYP 1A2 inhibitors). I believe that, for all the reasons given above, the sponsor should perform an adequate tyramine challenge study in the appropriate population (such a study should examine a wide dose range and perhaps employ a positive control). In the absence of definitive data on this question, I would recommend that, if approved, labeling inform prescribers that patients' intake of tyramine should be limited.

The other potentially significant safety concern relates to the issue of melanoma.

A total of 15 patients treated with rasagiline were noted to have a melanoma during the development program. Because most occurred in open label uncontrolled studies, it is difficult to determine causality. In an attempt to do so, the Division has compared the rates in this NDA with those in several databases; SEER, AAD Screening Program, and other NDAs for anti-PD treatments.

The sponsor suggests that cases are underreported to SEER (especially in situ tumors), and that because SEER does not assess patients who have been actively examined for melanoma, it is an inappropriate comparator for their drug, given the active surveillance employed in their studies.

Dr. Jones has attempted to address these concerns. She calculated the number of cases expected in the NDA population under various assumptions about underreporting in SEER. Even with assumptions about underreporting more conservative than those published in the literature, she still finds an excess number of invasive melanomas in the NDA database.

Because SEER patients were not actively screened, she compared the rasagiline rates to those determined in the AAD Screening project. Even when considering only those cases in the NDA detected on first dermatological examination (because patients in the AAD database were only screened once), she still detected an excess of cases in the NDA in in situ tumors.

Finally, Dr. Jones examined the rates of melanoma in other relevant NDAs. The rate in the rasagiline NDA was considerably greater than that seen in three other NDAs, although if we restrict our consideration to only those rasagiline cases detected prior to the initiation of active screening, the rate is about 5/1000 pt-yrs. We do not have data for several other NDAs (including selegiline), and in none of the NDAs were patients actively monitored for melanoma.

The sponsor argues that patients with PD have a higher rate of melanoma than the general public, and that patients in North America (where most of the NDA tumors were seen) have greater risk factors for melanoma. They present data of varying quality to support these views.

My view is that even if these observations are true, they do not allay my concerns about the potential of rasagiline to either cause and/or promote the growth of melanoma.

Even though some studies may have demonstrated that PD patients have a higher rate of melanoma than the general public, these studies have examined patients being treated with dopaminergic therapies. It is quite possible that all of these therapies may be associated with an increase in melanoma; therefore, I do not believe that these studies are capable of assessing the (potential) inherent risk of melanoma associated with PD itself. Also, although the rates of melanoma are presumably greater in North America than in other geographic regions, I do not see how this addresses the question of the risk of rasagiline (recall that rasagiline has arguably been shown to increase the risk compared to the SEER and AAD databases, both US databases).

The sponsor also argues that the latency to tumor formation with rasagiline is too short to be biologically plausible. I have no way of knowing if this is true (it is true that one case was detected about 2 ½ months after treatment initiation), but most cases did occur after 6 months (the median time to detection was 13 months; mean 21 months), so I would not rule out the possibility on these grounds (especially if it was acting as a promoter). It is, however, interesting to note, as Dr. Feeney does, that 4/6 in situ tumors in rasagiline treated patients included in the original AAD comparisons occurred within 5-9 months of treatment initiation. Although I would agree that many would consider this duration of treatment extremely unlikely to be sufficient to cause tumors (or, I suppose, even promote tumor growth), in my view it does not rule out the possibility that these tumors are related to treatment with rasagiline (although the short latency does raise questions about causality).

In my view, the data on this question are not definitive. Comparisons to epidemiologic databases are not without problems (and, depending upon various assumptions, the relative risk of rasagiline to the patients in the two comparator databases was not uniformly large), and detection of the tumors in the trials was not without flaws (for example, many patients did not have baseline evaluations). Further, although the risk with rasagiline appears large compared to three recently approved treatments, patients in those other development programs were not actively screened, and, in addition, the risk with rasagiline appears somewhat less than that for tolcapone (although, again, we are investigating this further).

Taken as whole, then, I cannot rule out the possibility that rasagiline use is associated with either the onset or exacerbation/promotion of melanoma. However, I also do not believe that I can reach this conclusion definitively at this time. Drs. Jones and Racoosin have recommended a large simple trial in which patients treated with rasagiline are compared (with appropriately frequent monitoring) to PD patients treated with other therapies (although probably not selegiline). This seems to me to be an appropriate approach to obtaining a definitive answer, at least to the question of whether or not rasagiline increases the risk of melanoma beyond that imposed by other anti-PD therapies. Such a study will not answer the question of whether or not treatment with rasagiline increases the rate of melanoma above that intrinsic to PD, or above that of the rate in the general public (although this latter question could be addressed prospectively as well).

I should note that the drug is considered to be genotoxic, and to have caused an increase in adenoma and adenocarcinoma of the lung in the mouse (statistically significant in the male, almost significant in the female, significant combined). These findings, of course, increase my concern, not just related to melanoma, but to other tumor formation as well. As I noted above, the rat carcinogenicity study has been inadequately reported, and we will ask for the results of histopathologic examination of the low and high dose groups. However, the melanoma issue aside, I believe that this issue can be adequately handled in labeling for this drug intended for this serious disease in this population (of course, the results of the rat study may have an important impact on the ultimate approvability of the application).

In summary, rasagiline is an effective treatment for patients with PD, either as monotherapy or as adjunctive therapy. If approved, it would be the only MAO-B inhibitor approved for use in monotherapy of PD (although selegiline is used off-label as monotherapy, on the basis of the results of the DATATOP study). Its use, however, may be associated with several significant safety concerns. First, I do not believe that we know yet whether, or at what dose, rasagiline loses its selectivity for inhibiting MAO-B and begins to inhibit MAO-A. If it does lose selectivity at doses close to 1 mg, the label would, in my view, need to inform prescribers/patients that they should limit their dietary intake of tyramine containing foods. Until the sponsor performs a definitive study to examine this question, labeling should include such a statement recommending dietary restrictions.

Second, rasagiline use may be associated with an increased risk for melanoma. The comparisons to epidemiologic databases are certainly suggestive, but not, in my view, definitive. The results of the mouse carcinogenicity study and the genotoxicity studies are also worrisome in this regard (these studies obviously raise concerns about cancers other than melanoma as well, of course). I believe additional work needs to be done to further address this question, but that the application can be approved before the definitive answer is obtained (which is

likely to be at least several years), if labeling adequately informs the prescriber about this potential risk.

Also, I note that Ms. Holquist states that DDMAC objects to the sponsor's proposed name Agilect, presumably because —

— I have no objection to the name.

Finally, we have several other requests and questions for the sponsor.

For the reasons given above, then, I recommend that the sponsor be sent the attached Approvable letter.

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/s/

Russell Katz
7/1/04 07:22:10 AM
MEDICAL OFFICER

Clinical NDA Review of Efficacy and Pharmacodynamic Effects on Tyramine Sensitivity

Brand Name: AGILECT

Generic Name: rasagiline

Sponsor: TEVA Pharmaceuticals

Indication: monotherapy for early Parkinson's Disease and adjunctive treatment of advanced Parkinson's Disease

NDA Number: 21641

Original Receipt Date: 9/9/03

Clinical Reviewer: Leonard P. Kapcala, M.D.

Review Author: Leonard P. Kapcala, M.D.

Review Completed: 6/18/04

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1. EXECUTIVE SUMMARY

This NDA submission provides information and data to support the approval of rasagiline for the indication of treatment of “early” Parkinson's Disease patients as monotherapy and the adjunctive treatment of “advanced” Parkinson's Disease patients on levodopa (LD) treatment. Rasagiline is a “selective” inhibitor of monoamine oxidase (MAO) B. The NDA contains 3 pivotal studies for the treatment of Parkinson's disease: TEMPO for mono-therapy; LARGO and PRESTO for adjunctive therapy. All three studies were randomized, double-blinded, placebo-controlled, and parallel group in design.

Efficacy

Study TVP 1012/232 (TEMPO)

Study Objectives

The objectives of this study were to assess the efficacy, tolerability and safety of two doses of rasagiline in early PD patients who were not receiving or did not require levodopa-LD/carbidopa therapy.

Study Design

Study TVP 1012/232 (TEMPO) was a North American, multicenter (32 centers: 28 US and 4 Canadian centers), randomized, double-blind, parallel group, phase 3 clinical study conducted in “early” Parkinson's Disease patients. The study consisted of a 26-week, placebo-controlled treatment phase followed by a 26-week active-treatment phase.

Patients were randomized in equal numbers to one of two (1 or 2 mg/day) dosages of rasagiline or to placebo. A one-week titration period was followed by a 25-week maintenance period during the placebo-controlled phase.

The second phase of the study was a 26-week active-treatment phase in which investigators and patients remained blinded to treatment assignment. Patients were transferred to the active-treatment phase if additional therapy was required before completing the 26-week placebo-controlled phase.

To be included in the study, patients were required to have idiopathic PD with a severity of ≤ 3 in USA or < 3 in Canada on the Modified Hoehn and Yahr scale. For at least six weeks prior to baseline, patients could not be treated with LD or dopaminergic agonists.

Primary Efficacy Endpoint and Analysis

The efficacy evaluation was based on the 26-week placebo-controlled phase. The primary efficacy endpoint for the placebo-controlled phase was the change in “Total” UPDRS (sum of parts I-mental + II-ADL + III-motor) from baseline to the termination visit. UPDRS was

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measured at Weeks 0 (baseline), 4, 8, 14, 20, and 26 (termination). Patients that needed LD therapy before the 26-week visit and any others who terminated prematurely from the study had their last observation carried forward (LOCF). Missing items in the UPDRS scale were replaced according to the LOCF rule.

The baseline adjusted analysis of covariance was to be used for comparing the adjusted mean differences between the changes observed in each of the active drug groups versus placebo (two contrasts) incorporating terms for treatment and center. Baseline UPDRS was to be included in the model as a covariate. A treatment-by-center interaction term was to be included in the model if it was significant ($p < .05$).

Primary Efficacy Endpoint Results

The primary efficacy endpoint was the change in "Total" UPDRS (sum of parts I + II + III) from baseline to the end of the placebo-controlled phase (26 weeks). Results for the primary efficacy endpoint are shown in Table 1. Mean baseline "Total" UPDRS was 24.54, 24.69, and 25.89 for placebo, 1 mg, and 2 mg rasagiline, respectively. These results indicated that both 1 and 2 mg daily rasagiline produced highly statistically significant beneficial effects on the primary efficacy endpoint.

Table 1 Summary of Pivotal Studies with Mean Changes in the Primary Efficacy Endpoint

| Study/ Protocol # | Indication | Duration | Primary Endpoint | Treatment Group Mean (SD) | | | | |
|---|------------|----------|---|------------------------------|------------------|-----------------|------------------|---------|
| | | | | 0.5 mg | 1 mg | 2 mg | Entacap | Placebo |
| TEMPO (232) (North America) | Mono | 26 weeks | Change in "Total" UPDRS | N/A | 0.06 p=.0001 | 0.72 p=.0001 | N/A | 3.91 |
| LARGO (122) (EU, Israel, Argentina) | Adjunct | 18 weeks | Change in daily "Off" time (hour) | N/A | -1.17 p=.0001 | N/A | -1.19 p=.0001 | -3.5 |
| PRESTO (North America) | Adjunct | 26 weeks | Change in daily "Off" time (hour) | -1.38 p=.0199 | -1.85 p=.0001 | N/A | N/A | -8.8 |

The sponsor conducted a double-blinded, active treatment phase (up to 26 weeks) that followed the randomized, double-blind, placebo-controlled phase (up to 26 weeks) and that involved a delayed start of 2 mg/day rasagiline in patients previously treated with placebo in the first study phase. Patients who had been treated with 2 mg/day rasagiline for up to 12 months appeared to show a statistically significant lower change of "total" UPDRS (i.e. part I + II + III) from baseline than patients who had been treated with placebo for up to 26 weeks in the first phase and with rasagiline 2 mg/day for up to 26 weeks in the second, active treatment phase. The sponsor interpreted its analysis of "total" UPDRS change from baseline to the end of the active treatment phase as suggesting a delay in the progression of Parkinson's Disease by 2 mg/day rasagiline. It should be recalled that all efficacy data included in the analyses would have been collected without addition of any dopaminergic therapy or prior to the addition of any dopaminergic and carrying forward the last efficacy data collected before of such treatment.

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Although I would agree that the efficacy data collected are somewhat suggestive of a delay in the progression of Parkinson's Disease, I believe that there are many concerns with the design and analysis of this study that make these data at best, only suggestive of an effect of rasagiline on progression of Parkinson's Disease.

Reviewer's Conclusions

- Rasagiline showed a robust therapeutic effect on the primary efficacy outcome measure, change of "total" UPDRS (i.e. sum of parts I-Mental + II-ADL + III-Motor) from baseline to termination (up to 26 weeks) of the placebo-controlled phase and indicates that rasagiline is effective as monotherapy in "early" patients with Parkinson's Disease who are not taking concomitant dopaminergic therapy.
- Both doses (1 and 2 mg/day) of rasagiline were therapeutically effective and 2 mg/day did not suggest any additional therapeutic over that produced by 1 mg/day.
- There does not appear to be any clear effect of gender or age (≥ 65 years old) on the efficacy of rasagiline.
- Although the sponsor's analyses showed nominally statistically significant, beneficial effects of rasagiline on multiple secondary efficacy endpoint in both study phases, I cannot draw serious conclusions about the efficacy on these endpoints because of issues of multiplicity whereby the sponsor did not make statistically appropriate adjustments for these multiple comparisons.
- Based upon exploratory analyses, rasagiline "monotherapy" may have the potential to exert a beneficial effect on slowing/delaying disease progression of patients with "early" Parkinson's Disease but this effect should be investigated in studies that are carefully, and appropriately designed and statistically analyzed.

Study TVP 1012/133 (PRESTO)

Study Objectives

The objectives of the study were to evaluate the efficacy, tolerability and safety of two dosages of rasagiline (0.5 or 1 mg/day) compared to placebo in Parkinson's Disease subjects with motor fluctuations on LD therapy.

Study Design

This was a multi-center, double-blind, randomized, placebo-controlled study that was conducted in 3 parallel groups of PD subjects in North America. It was designed to assess the efficacy and safety of rasagiline as adjunct therapy to LD/DDI. On entering the study subjects were being treated chronically with LD/DDI therapy and were experiencing motor fluctuations.

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The double-blind treatment phase consisted of a 26-week period divided into an initial 6-week levodopa dose adjustment phase and a subsequent 20-week levodopa dose maintenance phase. Following a screening visit, subjects were randomly assigned in a 1:1:1 ratio to one of the 3 treatment groups: 0.5 mg /day rasagiline, 1 mg/day rasagiline and placebo. In case of intolerability the levodopa dosage could be decreased for the first 6 weeks of the study period at the discretion of the investigator but had to remain constant for the last 20 weeks.

Post-randomization visits were conducted at the end of weeks 3, 6, 10, 14, 20 and 26 weeks for efficacy and/or safety evaluations.

Primary Efficacy Endpoint and Analysis

The primary efficacy endpoint for this trial was the change from baseline to treatment in the mean total daily "Off" time.

The total daily "Off" time was measured through 3 subject daily diaries prior to randomization (baseline measurement), and 9 subject daily diaries during treatment: 3 diaries prior to week 6, 3 diaries prior to week 14, and 3 diaries prior to week 26 (termination visit).

The principal statistical analysis of the primary endpoint was an Analysis of Covariance (ANCOVA) adjusting for baseline mean total daily "Off" time. The adjusted means of the changes observed in each of the active drug groups (two contrasts) were to be compared with placebo. The model was to include the fixed effects of treatment group, center and baseline mean total daily "Off" time. The treatment-by-center interaction was to be included in the model if it is found to be statistically significant (i.e., if $p < 0.10$).

The Hochberg's Step-up modification to Bonferroni method was to be used to protect from inflation in type I error due to multiple comparisons.

Primary Efficacy Endpoint Results

The principal analysis for the primary efficacy parameter, change from baseline to treatment in the total daily "Off" time, was an ANCOVA model with factors of treatment and center, and covariate of baseline total daily "Off" time.

At the baseline, the mean total daily "OFF" time was ~ 6 hours for all treatment groups. During the treatment period, a mean decrease of "Off" time was observed in all three treatment groups: 1.38 hours for the 0.5 mg rasagiline group, 1.85 hours for the 1.0 mg rasagiline group, and 0.88 hour for the placebo group (Table 1). The improvement observed in both rasagiline treatment groups were statistically significantly larger than the improvement observed in the placebo group, with a p-value of 0.0199 in the comparison of 0.5 mg rasagiline versus placebo and a p-value of 0.0001 in the comparison of 1.0 rasagiline versus placebo.

Reviewer's Conclusions

- Rasagiline showed a therapeutic effect on the primary efficacy outcome measure, change of

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total “OFF” time from baseline during treatment and indicates that rasagiline is effective as adjunctive therapy in patients with Parkinson's Disease who are experiencing motor fluctuations despite at least LD treatment.

- Both doses (0.5 and 1 mg/day) of rasagiline were therapeutically effective but 1 mg/day showed a numerically greater treatment effect (rasagiline – placebo) that was nearly twice as great as that associated with the lower dose.
- There does not appear to be any clear effect of gender or age (≥ 65 years old) on the efficacy of rasagiline.
- There is a suggestion of efficacy on of rasagiline on some secondary efficacy endpoints. Both doses of rasagiline exerted a statistically significant benefit on the first 3 (Change from Baseline in UPDRS ADL “OFF”, Change from Baseline in UPDRS ADL “OFF”, Change from Baseline in UPDRS Motor “ON”) of 4 secondary efficacy endpoints identified for a hierarchical sequence analysis at an α of 0.05.
- Although the sponsor's efficacy analyses showed many nominally statistically significant, beneficial effects of rasagiline on multiple efficacy endpoint in both study

Study TVP 1012/122 (LARGO)

Study Objectives

The objectives of the study were to evaluate the efficacy, tolerability and safety of rasagiline mesylate versus placebo in PD subjects with motor fluctuations on LD/peripheral dopa decarboxylase inhibitor (DDI, i.e. carbidopa or benserazide) therapy.

Study Design

This was a multicenter, double-blind, double-dummy, randomized, placebo and entacapone-controlled study that was conducted in 3 parallel groups of PD subjects in Europe, Argentina and Israel. It was designed to assess the efficacy and safety of rasagiline mesylate as an adjunctive therapy to LD/DDI. On entering the study, subjects were being treated chronically with LD/DDI therapy and were experiencing motor fluctuations.

The double-blind treatment phase consisted of an 18-week period divided into an initial 6-week levodopa dose adjustment phase and a subsequent 12-week levodopa dose maintenance phase.

Following a screening visit to ensure study eligibility, subjects entered a 2 to 4 week placebo “run-in” phase during which a subject's individual LD/DDI dosage regimen was optimized. After being optimized, the dosage regimen had to remain stable for at least 2 weeks before the subject underwent randomization at visit 0 (baseline).

Subjects were randomized based on a 1:1:1 assignment ratio into one of the following treatment groups:

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- 1) Rasagiline mesylate 1 mg once daily
- 2) Placebo
- 3) Entacapone 200 mg with each LD dose

The LD dosage could be decreased for the first 6 weeks of the study period at the discretion of the investigator but had to remain constant for the last 12 weeks.

Post-randomization visits were conducted at the end of week 3/visit 1, week 6/visit 2, week 10/visit 3, week 14/visit 4 and week 18/visit 5.

The primary study objective and a number of other endpoints were assessed from data recorded by subjects in the "24-hour" diary in which subjects rated themselves as "ON without dyskinesia or without troublesome dyskinesia", "ON with troublesome dyskinesias", "OFF", or "asleep". Subjects were instructed on how to complete the diary at the screening visit and thereafter completed it during the 3 consecutive days immediately prior to baseline, and during the 3 consecutive days immediately prior to visits 2, 3, 4, and 5.

Primary Efficacy Endpoint and Analysis

The primary efficacy endpoint for this trial was the change from baseline to treatment in the mean total daily "OFF" time.

The mean total daily "Off" time during treatment was based on averaging measurements from Week 6 through Week 18 (12 daily diaries). Baseline measurement for an individual subject was the mean value of total daily "Off" time recorded in 3 diaries completed before randomization.

The principal statistical analysis of the primary endpoint was an Analysis of Covariance (ANCOVA) comparing the adjusted means of the changes observed in the rasagiline 1mg/day treatment group to placebo by performing a single degree of freedom comparison (contrast) in a model that includes the 3 treatment groups. The model includes the effects of treatment group, center and baseline mean total daily "OFF" time as a covariate. The treatment-by-center interaction was to be included in the model if it is found to be statistically significant ($p < 0.10$).

Primary Efficacy Endpoint Results

The primary endpoint for this trial was the change from baseline during treatment in the mean total daily "OFF" time.

At the baseline, the mean total daily "Off" time was ~ 5.5 hours for all treatment groups. Although all treatment groups had a decrease in the mean total daily "Off" time during the treatment period, the analysis (Table 1) showed that subjects in both rasagiline and entacapone groups had significantly larger improvement in the total daily "Off" time than subjects in the placebo group.

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Reviewer's Conclusions

- Rasagiline (1 mg/day) showed a therapeutic effect on the primary efficacy outcome measure, change of total "OFF" time from baseline during treatment and indicates that rasagiline is effective as adjunctive therapy in patients with Parkinson's Disease who are experiencing motor fluctuations despite at least LD treatment.
- There does not appear to be any clear effect of gender or age (≥ 65 years old) on the efficacy of rasagiline.
- There is a suggestion of efficacy on of rasagiline on some secondary efficacy endpoints. Both doses of rasagiline exerted a statistically significant benefit on the first 3 (Change from Baseline in UPDRS ADL "OFF", Change from Baseline in UPDRS ADL "OFF", Change from Baseline in UPDRS Motor "ON") of 4 secondary efficacy endpoints identified for a hierarchical sequence analysis at an α of 0.05.
- Although the sponsor's efficacy analyses showed many nominally statistically significant, beneficial effects of rasagiline on multiple efficacy endpoint in both study phases, I cannot draw serious conclusions about the efficacy on these endpoints because of issues of multiplicity whereby the sponsor did not make statistically appropriate adjustments for these multiple comparisons.
- Although there was no formal comparison of the efficacy of rasagiline with entacapone (both of which were investigated in this study), in general the benefit of rasagiline in general appeared to be similar to that of entacapone.

Safety

The Safety Review was conducted by Dr. Lisa Jones and is provided in her separate review.

Preclinical Pharmacology / Toxicology

The review of Dr. Paul Roney deals with these issues.

Pharmacokinetics

The review of Dr. Andre Jackson deals with these issues.

Statistics

The review of Dr. Sharon Yan deals with these issues.

Chemistry

The review of Dr. William Timmer deals with these issues.

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Summary of Tyramine / Pharmacodynamic Study Results

Study P94159 Tyramine Challenge in Healthy Young Males

This double-blind placebo-controlled study assessed tyramine sensitivity (regarding blood pressure) pre- and post-treatment in young, healthy males during dietary tyramine restriction. Three groups (group 1 – rasagiline 1 mg QD; group 2 – rasagiline 2 mg QD; group 3 – selegiline 10 mg QD) of subjects were studied sequentially and randomized to placebo (n = 3) or active drug (n = 6). Beginning on day 8 of treatment, subjects were administered increasing doses of tyramine (in capsule, 50 – 800 mg) once or twice daily and blood pressure was monitored for a protocol-defined tyramine threshold pressor response (≥ 30 mm Hg systolic blood pressure above pre-tyramine value; TYR30). Subjects were also studied with increasing tyramine doses before treatment. Tyramine sensitivity factor (TSF) was determined by comparing tyramine threshold doses in Period 1 (pre-treatment) / Period 2 (post-treatment).

Main Results

Table 2 shows TSFs only for subjects who demonstrated a protocol defined pressor response of tyramine in both periods. In 18 out of 29 subjects, 800 mg tyramine was required to show a threshold pressor response or there was no such response at any dose up to 800 mg.

Table 1 Mean TSF Ratio Based Upon Actually Meeting Protocol Specified Criterion (≥ 30 mm Hg SBP Increment)

| Protocol P94159 | Tyramine Sensitivity Factor (Period1/Period2) (Per Protocol) | | | | |
|--|--|-------------|----------|-------------|-------------|
| | Mean | Std | N | Min | Max |
| Treatment Group | | | | | |
| DEPRENYL (Selegiline) 10mg QD | 4.33 | 3.51 | 3 | 1.00 | 8.00 |
| PLACEBO | 1.10 | 0.55 | 5 | 0.50 | 2.00 |
| TVP-1012 1mg QD | 1.25 | 0.50 | 4 | 1.00 | 2.00 |
| TVP-1012 2mg QD | 2.80 | 1.10 | 5 | 2.00 | 4.00 |

Plasma tyramine levels of subjects treated with each dose of rasagiline and selegiline typically showed increased (relative to placebo) ratios of Period 2/ Period 1 plasma tyramine suggesting some inhibition of MAO-A after treatment. In most instances there was a suggestion of dose-dependence because the 2 mg group ratio was usually higher than that for the 1 mg group.

Study 132 Tyramine Challenge in Parkinson's Disease Patients on LD

This double-blind placebo-controlled study assessed tyramine sensitivity (regarding blood pressure) pre- and post-treatment in Parkinson's Disease patients (on stable dose of LD/CD).

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Two groups (group 1 – rasagiline 1 mg QD; group 2 – rasagiline 2 mg QD) of subjects were studied sequentially and randomized to placebo (n = 3) or active drug (n = 6). Patients were studied for tyramine-induced pressor response to 75 mg tyramine pre-treatment and to increasing doses of tyramine (up to 75 mg) post-treatment according to the study design shown in Figure 1. The rasagiline groups included 7 patients /group and the placebo group included 6 patients.

The subject was to take his/her assigned study medication and LD/CD dose and 30 minutes later, the patient was to be served a standardized morning meal in which tyramine has been mixed in applesauce and vital signs (blood pressure and pulse) were recorded at 5 minute intervals over the first 2 hours and at 15 minute intervals over the last 2 hours. The maximal systolic blood pressure and increment after tyramine were to be assessed and compared.

Figure 1 Study 132 Design

| Visit | Screening | Screening | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|-----------|-----------|---|---|----|-------|-------|-------|----|----|-------|----|----|
| Day | -2 weeks | -7 | 1 | 7 | 21 | 22 | 23 | 24 | 42 | 56 | 70 | 84 | 98 |
| Tyramine | | 75 mg | | | | 25 mg | 50 mg | 75 mg | | | 75 mg | | |
| Tyramine restricted diet for 24 days | | | | | | | | | | | | | |
| Rasagiline (1 or 2 mg/day) or placebo were administered for 70 days | | | | | | | | | | | | | |

Main Results

- Two patients (2 mg rasagiline group) were thought to have exhibited a rasagiline- tyramine interaction showing sustained systolic blood pressure increments after 50 mg and after 75 mg tyramine.
- The data did not suggest an effect of treatment on tyramine testing based upon mean maximal systolic blood pressure or mean maximal systolic blood pressure change. Mean ratios of maximal systolic blood pressure change for 75 mg tyramine at pre-treatment / day 70 did not suggest any treatment effect with mean ratios ranging between 2.1 – 2.5 for all 3 groups. Neither was there any suggestion for an increased frequency of systolic blood pressure increments of ≥ 30 mm Hg after tyramine at any of the tyramine challenges.
- Potentially clinically significant (PCS) abnormal orthostatic vital signs that occurred after tyramine and study treatment showed a highest frequency of hypertensive events (i.e. blood pressure increments > 30 mm Hg) in the 2 mg rasagiline group. Frequency of such events when occurring in the 1 mg group was typically greater than that in the placebo group.
- Review of PCS blood pressure readings from home ambulatory recordings did not suggest a clear effect of rasagiline on outlier readings, particularly for hypertensive events. Patients measured blood pressure twice daily (in am and randomly after dinner).
- Review of the adverse events (AEs) suggested that there may have been an increased frequency of AEs coded as hypertension related to rasagiline. Two patients treated with 2 mg

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rasagiline had 4 AEs, one patient treated with 1 mg rasagiline had 1 AE, and there were no such AEs in patients treated with placebo.

- There was a suggestion of increased orthostatic blood pressure measurements in rasagiline treated patients.

Tyramine Challenge Sub-Study 232 (TEMPO) “Early” Parkinson's Disease (Monotherapy)

Early Parkinson's Disease patients participating in the rasagiline monotherapy trial (232 - TEMPO) were studied for tyramine sensitivity at the end (6 months) of the randomized, double-blinded, placebo-controlled phase. Patients had been randomized to placebo (n = 17), 1 mg rasagiline (n = 19) and 2 mg rasagiline (n = 19) vital sign responses were assessed after 75 mg tyramine. The primary outcome measure was the # patients experiencing a systolic blood pressure increase of ≥ 30 mm Hg on 3 consecutive measurements compare to baseline (mean of 4 values).

After patients ate their own meal (without significant tyramine), they received 75 mg tyramine added to applesauce within an hour of the completion of their meal. The study meal was meant to simulate the subject's normal dietary habits.

Main Results

- No patients met the primary outcome measure but 2 patients (2 mg rasagiline) exhibited borderline pressor responses after tyramine that were just barely beneath the protocol-defined threshold.
- Mean maximal systolic blood pressure was 137, 148, and 153 mm Hg for placebo, 1 mg rasagiline and 2 mg rasagiline, respectively after 75 mg tyramine. Mean maximal systolic blood pressure increment was 15, 19, and 21 mm Hg for placebo, 1 mg rasagiline and 2 mg rasagiline, respectively.
- There was an increased frequency of subjects showing a systolic blood pressure increment of ≥ 30 mm Hg in 1 mg (21 %) and 2 mg (16 %) rasagiline groups compared to placebo (6 %). Only one subject (2 mg group) exhibited a systolic blood pressure increment ≥ 50 mm Hg (i.e. 51).

Tyramine Challenge Sub-Study 133 PRESTO (“Advanced” Parkinson's Disease on LD)

“Advanced” Parkinson's Disease patients participating in the rasagiline adjunctive trial (133 - PRESTO) were studied for tyramine sensitivity at the end (6 months) of the randomized, double-blinded, placebo-controlled phase. Patients had been randomized to placebo (n = 22), 0.5 mg rasagiline (n = 22) and 1 mg rasagiline (n = 13) vital sign responses were assessed after 50 mg tyramine. The primary outcome measure was the # patients experiencing a systolic blood pressure increase of ≥ 30 mm Hg on 3 consecutive measurements compare to baseline (mean of 4 values).

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This study was generally conducted similarly as Tyramine Substudy 232 (TEMPO) with a major study design difference being that 50 mg tyramine was administered immediately at the end of the meal during the dessert phase. Tyramine was also added to one of several dairy desserts instead of to applesauce as was done in the TEMPO Tyramine Substudy.

Main Results

- Four subjects (7%) had an increase in BP that met the predefined endpoint of systolic BP of > 30 mmHg above the mean baseline value for at least 3 consecutive measurements. Three of these subjects (# 4, 118, 266) had received 0.5 mg/day rasagiline and one had received placebo (# 411). None of the subjects who received 1 mg/day rasagiline had a clinically significant blood pressure increase during the tyramine challenge.
- Mean maximal systolic blood pressure was similar (141-146 mm Hg) among all treatment groups.
- Mean maximal systolic blood pressure increment above pre-tyramine baseline was higher in the 0.5 mg rasagiline group (27 mm Hg) than the mean value (21 mm Hg) for both the placebo and 1 mg rasagiline groups.
- Although the frequency of maximal systolic blood pressure increments was similar (17 – 24 %) among all treatment groups for increment \geq 30 mm Hg, there appeared to be an increased frequency of marked outlier responses \geq 60 mm Hg for the 0.5 mg rasagiline group (18 %) compared to the placebo (5 %) and 1 mg rasagiline (0 %) groups.
- Marked outlier responses in the 0.5 mg rasagiline group were exhibited by the 3 patients (patient # 4 - 69 mm Hg; patient # 118 – 78 mm Hg; patient # 266 – 69 mm Hg) who met the protocol-defined primary tyramine threshold outcome plus another patient (# 10 – 65 mm Hg) who did not. The single placebo patient (# 411) who exhibited a marked outlier increment patient (74 mm Hg) had also met the protocol-defined primary tyramine threshold outcome.

Reviewer's Overview of Tyramine Sensitivity Related to Rasagiline Treatment

- My perspective is that Study P94159 provides potentially the most useful, interpretable information on rasagiline-induced tyramine sensitivity (as a possible reflection of MAO-A inhibition). This study was conducted under fasting conditions and used a conventional approach of assessing tyramine threshold pressor dose responses (i.e. TYR30 or tyramine dose that increased systolic blood pressure by \geq 30 mm Hg) while administering increasing doses of tyramine before and after study drug treatment. However, this study was associated with numerous problems/limitations including : 1) relatively small number (N = 3-5) of subjects per treatment showing actual threshold responses; 2) extremely homogeneous study population (young healthy males) with probable bias for lowest rasagiline exposure (i.e. plasma rasagiline AUC) ; 3) concerns about the biological potency of tyramine; 4) narrow daily dose range (e.g. only 1 and 2 mg) for studying rasagiline; 5) absence of 25 mg tyramine dose that could provide more accurate assessment of TSF; and 6) DSI inspection report that

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did not document evidence assuring protocol specified fasting and dietary restrictions and appropriate measurements of blood pressure. My recommendation is that a study employing a similar approach must be conducted with an improved study design to overcome problems and limitations identified for Study P94159 prior to approval.

Study P94159 suggested a modestly increased tyramine sensitivity (i.e. TSF = 2.8) associated only with the 2 mg daily dose (and not with 1 mg; TSF = 1.3). However, plasma tyramine measurements showing higher ratios after treatment than before treatment for both doses of rasagiline vs placebo also suggested some MAO-A inhibition by the 1 mg dose. **Based upon other PK data, there is a suggestion that increased plasma rasagiline exposure occurs in females, older subjects, patients treated with LD, subjects with mild hepatic impairment and patients using drugs inhibiting CYP 1A2 (e.g. a fluoroquinolone, fluvoxamine, ticlodpine, etc.) or drugs that are substrates of CYP 1A2 (e.g. caffeine, acetaminophen, amitriptyline, naproxen, propranolol, etc.) and could act as competitive antagonists that might increase rasagiline exposure. Thus, an elderly, female with hepatic dysfunction and treated with LD and 1 mg rasagiline and one or more interacting drugs (e.g. drugs that inhibit CYP 1A2 or compete as substrates of CYP 1A2) could potentially be exposed to a much higher AUC for plasma rasagiline (than the exposure observed in young, healthy males). Correspondingly, a patient experiencing an additive effect of several of these factors influencing rasagiline PK/exposure could potentially exhibit a significantly increased sensitivity for tyramine (i.e. potential hypertensive “cheese” reaction). A more comprehensive study as suggested ought to characterize the TSF more precisely.**

- I find it difficult to interpret the results of the 3 studies assessing tyramine sensitivity (e.g. pressor responses) in which relatively low doses of tyramine (50 or 75 mg) were added to food and administered to patients with Parkinson's Disease either just before or just after other food. The main problem is that food can markedly alter the bioavailability/PK (e.g. decrease C_{max} and AUC and delay T_{max}) of tyramine. The sponsor's rationale to administer tyramine with food was to represent a more realistic situation in life whereby a patient might be exposed to a “high” amount of tyramine contained within a meal (food and/or drink). Unfortunately, this is not a common approach to assess tyramine sensitivity by administering tyramine by adding it to food. There was no “positive control” MAO-A inhibiting drug that was simultaneously studied to show that this testing approach is reasonably sensitive for demonstrating the presence or absence of tyramine sensitivity.

I am not aware of unequivocal evidence/data indicating that the bioavailability of tyramine contained within a food/drink product is similar or different from that of tyramine added to food (and also administered either just before or after other food). **The sponsor did not validate its tyramine testing approach to assure the reviewer that the absence of significant tyramine-induced pressor response was a true negative and not a false negative resulting from a significant diminishing or abolishing effect of the food on the bioavailability of tyramine and correspondingly the pressor response of this tyramine.** In addition, the decreased monitoring in the design of these studies after 2 hours of tyramine administration could also have contributed toward missing significant tyramine-induced pressor responses occurring not unexpectedly at a relatively late timepoint (e.g. after 2

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hours). Nevertheless, the data accumulated in these studies suggest some rasagiline-induced increase of tyramine sensitivity. This suggested increased in tyramine sensitivity was not only observed at the 2 mg daily dose but also at a lower dose down to 0.5 mg daily. Considering that this study design could potentially underestimate an increase in rasagiline-induced tyramine sensitivity, it seems clearly noteworthy that any patients appeared to exhibit sensitivity to tyramine given the probability that tyramine bioavailability was significantly reduced and T_{max} was significantly delayed and therefore the study design did not seem ideal for characterizing a significantly increased sensitivity to tyramine-induced pressor responses.

- I recognize that the study design of administering tyramine under fasting conditions may not mimic real-life in which patients ingest tyramine containing. Nevertheless, this is the standard investigational approach for assessing the potency of a drug for increasing tyramine pressor sensitivity as a reflection of MAO-A inhibition. The absence of the confounding effects of food on tyramine bioavailability and corresponding pressor response allows one to characterize tyramine sensitivity and calculate the TSF. Once the TSF has been well characterized for different drug doses and the shape of the dose response curve has been established, then the next challenge is to interpret and assess the risk for a hypertensive “cheese” reaction based upon the TSFs, shape of the dose-response curve, and expectation of individual variability of drug exposure related to many factors and finally decide if dietary tyramine restriction is or is not desired.

I strongly believe that characterization of TSF based upon tyramine testing under fasting conditions should be the main method for assessing tyramine sensitivity. The sponsor should conduct a randomized, double-blinded, placebo-controlled larger study of both older males and females, study a wider range of rasagiline doses (e.g. 0.5 – 4 mg), compare selegiline as used in the U.S. (e.g. 5 mg BID), include lower doses of tyramine, and add a positive control group (e.g. tranlylcyproamine, non-selective MAO inhibitor). After such data have been accumulated, one could debate the utility of conducting additional, complementary testing of assessing tyramine sensitivity to doses of tyramine added to food. However, before initiating such studies, it would seem important for the sponsor to know more about the PK of tyramine when added to food under the sponsor’s design and the pressor responses of the this tyramine in untreated subjects and in subjects treated with a known inhibitor of MAO-A.

- Although there were some individuals who seemingly exhibited significant hypertensive responses to tyramine during tyramine testing, I am not aware that any of these experiences could be classified as “hypertensive urgency, emergency or crisis” because of the absence of significant symptoms (e.g. headache, chest pain, transient ischemic attack-like symptoms. Dr. Lisa Jones, however, did bring to my attention one patient’s experience(# 808) that I do think may represent a hypertensive “cheese reaction” associated with rasagiline treatment. There was a second patient (#803) in the same study who developed hypertension and headache on a high dose of rasagiline. Patient #803 did not clearly present as a patient experiencing a hypertensive “cheese reaction.” There is no way to be certain, but patient #808 could certainly be a hypertensive “cheese reaction” related to consumption of tyramine in her food or drink and resulting from MAO-A inhibition related to the high dose of rasagiline. Both patients had participated in a small, tolerability, dose-escalation (1, 2, 5, 10 mg) rasagiline trial

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(Study TVP-1012/111). Because of cardiovascular events of these 2 patients and a third with postural hypotension, the protocol was amended to reduce rasagiline dosing to 1 mg/d. It I have presented narrative summaries of both of these cases with hypertension and headache after 10 mg daily treatment..

Patient #808 was a 58 year-old woman who participated in a dose-escalation (1, 2, 5, 10 mg) rasagiline trial (Study TVP-1012/111). This patient had a five year history of Parkinson's Disease and hypertension was not listed among her past medical history (asthma, appendectomy). At randomization the subject's medications were:LD/CD, selegiline, biperiden, bromocriptine, and alpha-tocoferol acetate.

This subject received escalating doses of rasagiline 1 mg/day (for one week), 2 mg/day (for one week), and presumably 5 mg/day in the third week as planned in the protocol. On day 22, the dose was increased to 10 mg/day in the fourth week. On day 25, the subject experienced vertigo for approximately one hour, and headache, nausea and vomiting which lasted for several days. The study medication was stopped for 48 hours beginning on day 25. **On day 28, the subject developed severe headache and hypertension (220/120).** A blood pressure "later on that day" was stated to be within normal range, without any pharmacological intervention. The subject's rasagiline dose was reduced to 2 mg/day. The events of day 28 led to the subject's hospitalization on day 29, which lasted ten days. The study drug was permanently discontinued upon her hospital admission. After admission, the subject reported headache, mild nausea and vomiting for nine days. Hypertension was reported to have been stabilized within six days of admission following treatment with captopril, which was continued for forty days. The subject then switched to methyldopa for ten days, and finally stopped all anti-hypertensive medications 52 days after the event occurred. From that time until the last follow-up visit (two months after stopping anti-hypertensive treatment), the sponsor reported the subject remained normotensive. No information was provided regarding the patient's recent diet with respect to tyramine containing foods preceding the severe hypertension. This patient's blood pressure measurements were normotensive, with standing measurements of 120/85 (Baseline), 120/80 (Week 1), 120/80 (Week 2), and 120/85 (Week 3).

Patient #803 was a 64 year-old female who had had Parkinson's Disease for 9 years. Her medical history was remarkable for suspected Raynaud phenomenon, S/P hysterectomy and oophorectomy. Her medications included LD/CD, selegiline, lorazepam, meprobamate, pravastatin, and alpha – tocoferol. Her selegiline was discontinued one month before she began taking rasagiline in the dose escalation design. She experienced localized muscle cramps/dystonia on day 1 and day 22, while being treated with rasagiline 1 mg/day and 10 mg/day, respectively. On study day 22, her rasagiline dose was raised from 5 mg/day to 10 mg/day.

On study day 28, the subject experienced headache and hypertension (160/110). Her dose was decreased to 5 mg/day, although these symptoms were reported to last for two days. The subject also reported onset of vertigo on day 28, which persisted for approximately ten days.

On study day 29, the subject experienced a syncopal episode lasting two minutes, which resulted in a one day hospitalization. During the hospitalization, "a high blood-pressure" was measured, and the subject was diagnosed with hypertrophic cardiomyopathy. The study drug was discontinued at this time. The subject's blood pressure was reported to stabilize after two days treatment with propranolol and to remain within normal range until the end of the study follow-up period.

- There were 1452 Parkinson's Disease patients and healthy subjects (not including all clinical pharmacology studies) who had been exposed to rasagiline in the entire clinical

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program with or without LD and 1858 subject years of exposure has been accumulated. The majority of the rasagiline treatment experience in patients was not associated with dietary tyramine restriction. In Parkinson's Disease patients on LD and any dose of rasagiline without dietary tyramine restriction, the exposure was ~ 660 patient years. The sponsor had also noted that some patients had been on rasagiline and LD/CD for years without dietary tyramine restriction and without evidence of a rasagiline-induced tyramine reaction. However, it is relevant to consider that there could be some selection bias here because patients prone to significant AEs from rasagiline could discontinue from study and not be exposed to rasagiline for long periods.

- The sponsor did not consider that there was any event that could be considered a result of a potential tyramine/rasagiline interaction. **However, the sponsor has never defined what is a tyramine /rasagiline interaction.** The sponsor also noted that there were 65 patients on rasagiline 0.5 mg or 1 mg with or without LD and 29 patients on rasagiline 2 mg monotherapy who participated in tyramine challenge studies. These studies assessed the potential for interaction between rasagiline and tyramine after short and long term exposure “using very high and non-physiological doses of tyramine.” The sponsor’s overall conclusion based upon the results of these studies together with the results of home monitoring of blood pressure after meals was that rasagiline at these conditions is selective for MAO-B inhibition and can be used safely without dietary restrictions as monotherapy and as add-on therapy to LD at the indicated doses.

I differ from the sponsor’s conclusion and think that some subjects treated with rasagiline and challenged with tyramine exhibited significant, asymptomatic, tyramine-induced hypertensive responses and that patient #808 (Study TVP-1012/111) may represent a classical hypertensive “cheese reaction.”

Main Conclusions

- There are many concerns, limitations, and shortcomings for the conventional tyramine study (under fasting conditions) determining tyramine sensitivity (i.e. TSF) after treatment with rasagiline.
- The 3 other studies assessing tyramine sensitivity in Parkinson's Disease patients were confounded by the study design of administering tyramine with food and also just before or after other food. There was no validation of this method to assure that results did not underestimate tyramine-induced pressor responses.
- Some data suggest rasagiline-induced tyramine sensitivity not only with the 2 mg dose but also with lower daily doses (e.g. 0.5 and 1 mg).

There is a clear need for additional study to characterize more precisely and comprehensively rasagiline-induced tyramine sensitivity mainly by studying tyramine sensitivity under fasting conditions with an aim to overcome limitations and shortcomings of the previous study. **This study must be conducted prior to approval.**

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1.1. Overall Conclusions

1. Rasagiline is effective for the treatment of the signs and symptoms of “early” Parkinson's Disease patients as monotherapy and for the signs and symptoms of “advanced ” Parkinson's Disease patients as adjunctive treatment.
2. The pharmacodynamic effect of rasagiline with respect to inhibition of MAO-A and the corresponding risk for causing a hypertensive “cheese” reaction (from ingesting dietary tyramine) has not been adequately characterized. This characterization must be conducted prior to approval.

1.2. Recommendations

Requirements for Approval

1. A randomized, double-blinded, placebo-controlled study (under fasting conditions) must be conducted to characterize the risk more precisely and comprehensively for rasagiline-induced tyramine sensitivity. Such a study should be designed to address the following concerns, problems, and limitations of the previous study :
 - 1) relatively small number (N = 3-5) of subjects per treatment showing actual threshold responses;
 - 2) extremely homogeneous study population (young healthy males) with probable bias for lowest rasagiline exposure (i.e. plasma rasagiline AUC);
 - 3) concerns about the biological potency of tyramine;
 - 4) narrow daily dose range (e.g. only 1 and 2 mg) for studying rasagiline;
 - 5) absence of 25 mg tyramine dose that could provide more accurate assessment of TSF;
 - 6) DSI inspection report that did not document evidence assuring protocol specified fasting and dietary restrictions and appropriate measurements of blood pressure.
2. Provide quantitative information of the effect of LD on rasagiline PK parameters/ exposure.

Other Recommendations (Not Required for Approval)

1. Consideration should be given about conducting validated studies that assess tyramine sensitivity in rasagiline treated subjects when administered tyramine with food.

2. INTRODUCTION AND BACKGROUND

Parkinson's Disease and Current Therapies

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the loss of melanin-containing neurons in the substantia nigra pars compacta resulting in a reduction in the striatal dopamine. The disease is clinically manifested by bradykinesia, tremor, rigidity and postural instability. The disease develops in adulthood with the peak onset at 55-60 years. The prevalence rate is approximately 300 per 100,000 and about 60,000 new cases are diagnosed annually. The cause of PD is, at the present time, unknown.

Presently, pharmacological intervention in PD is symptomatic. Augmentation of impaired dopaminergic neurotransmission is the backbone of therapy. Treatment of PD includes anticholinergic drugs to reduce the relative excess of striatal cholinergic activity accompanying dopamine deficiency; MAO-B inhibitors to inhibit the breakdown of dopamine in the Central Nerve System (CNS); dopamine agonists to supplement neurotransmission at the dopamine receptor level; and amantidine, which has shown a modest effect on PD symptoms. Symptomatic relief is often transient, as neuronal loss continues or tolerance develops.

The current standard treatment is primarily based on a dopamine replacement strategy using the dopamine precursor LD. LD is converted by dopamine decarboxylase in residual nigrostriatal neurons to dopamine, and temporarily restores the depleted dopamine stores in PD patients. The combination of LD with carbidopa (a peripheral decarboxylase inhibitor) leads to a preferential elevation of the level of dopamine in the brain. LD dramatically reduces morbidity and mortality in PD. However, long term treatment is associated with involuntary movements (dyskinesia), neuropsychiatric side effects and debilitating fluctuations in motor response following a dose of LD, which are known as .ON. (good mobility) and .OFF. (impaired mobility) periods. After five years of LD treatment, about 50% of PD patients are not adequately controlled. Therefore, some specialists believe it is desirable to delay the onset of LD treatment in patients with early PD as long as possible.

Inhibition of MAO-B, the major enzyme metabolizing dopamine in the human brain, may help conserve the depleted supply of dopamine and delay the need for exogenous LD. Selegiline (deprenyl) is a site-directed, irreversible ("suicide") inhibitor of MAO-B. In a large scale clinical study, selegiline was shown to significantly delay the time to LD in patients with early PD. Other studies have demonstrated the beneficial effect of selegiline and another MAO-B inhibitor, lazabemide, in PD patients.

A proposed mechanism through which MAO-B inhibition confers neuroprotection is by preventing the conversion of dopamine to hydrogen peroxide and the activation of other potential neurotoxins. Recent experiments have shown that selegiline appears to have anti-apoptotic effects. However, adverse effects, including activation of pre-existing gastric ulcers and occasional hypertensive episodes, may accompany treatment with selegiline. Furthermore, L-selegiline is metabolized to L-methamphetamine and L-amphetamine, which may cause undesirable side effects such as anxiety, tachycardia and insomnia. Therefore, a MAO-B inhibitor without amphetamine metabolites could be useful in the treatment of Parkinson's

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Disease, both as monotherapy and as an adjunct to LD treatment. It is relevant to note that no drugs are approved in the U.S. for delaying disease progression of Parkinson's Disease.

Rasagiline (N-propargyl-R-aminoindan) is an irreversible MAO inhibitor with high selectivity towards the B form of the enzyme. It is distinctive from selegiline in several aspects. The major metabolite of rasagiline in humans, 1-R-aminoindan (AI), is devoid of amphetamine-like properties and is not likely to interfere with cardiovascular function, or to exert neurotoxic effects. On the other hand, beneficial effects of AI on restoring hypoactivity and preventing cognitive impairment were demonstrated in several experimental animal models.¹⁸ Rasagiline is five times more potent than selegiline in antagonizing MPTP-induced neurotoxicity and protects neurons from injury in a variety of experimental models, both in-vitro and in-vivo. Even without concomitant use of LD, rasagiline restores normal behavior and locomotion in experimental models of dopamine hypofunction.

Brief Summary of Major Highlights of Regulatory History of IND 45958 for Rasagiline

- IND filed: August 5, 1994
- End of Phase II Meeting: June 18, 1997
- Meeting with FDA regarding tyramine and study TVP-1012/132: December 16, 1999
- Meeting with FDA regarding tyramine and study TVP-1012/232: March 10, 2000
- Meeting with FDA regarding tyramine and future study TVP-1012/133(PRESTO): August 17 & 23, 2000
- Meeting with FDA regarding melanoma in the development program: April 6, 2001
- Meeting with FDA regarding melanoma in the development program: August 20, 2001
- Pre-NDA meeting: April 30, 2003
- NDA submitted: September 5, 2003
- 120 day safety update submitted: December 23, 2003

3. FOREIGN MARKETING HISTORY

Rasagiline is not approved anywhere. Regulatory applications for approval of rasagiline are also under review by EMEA for the European community and by the —

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4. PRECLINICAL SUMMARY

See the review of the Pharmacologist/Toxicologist (Dr. Paul Roney) for this information.

5. FINANCIAL DISCLOSURE

The sponsor has certified that there were no conflicts of interest as defined in 21 CFR 54.2 (a) for all clinical and tyramine challenge studies including the 3 pivotal studies (TEMPO, PRESTO, LARGO).

6. DATA SOURCE DESCRIPTION

The data for efficacy and tyramine stimulated pharmacodynamic effects for rasagiline (for the indication of treatment of "early" Parkinson's Disease as monotherapy and adjunctive treatment of "advanced" Parkinson's Disease with LD) in this NDA were derived from 3 randomized, double-blind, placebo-controlled, pivotal studies and 4 pharmacodynamic studies/substudies involving challenge with tyramine. Data contained in this NDA from these studies, data for the 4 Month Safety Update, and responses to reviewers' inquiries were submitted electronically to FDA at the site : [\\CDSESUB1\N21641\N 000\2003-09-05](http://CDSESUB1\N21641\N 000\2003-09-05). Subsequent submissions related to this NDA can be found at : [\\CDSESUB1\N21641\N 000](http://CDSESUB1\N21641\N 000). In addition, paper copies of selected components of this NDA were also submitted.

7. HUMAN PHARMACOKINETICS

Summary of Pharmacokinetic (PK) Conclusions of Review by Clinical Pharmacologist / Biopharmaceutical Reviewer (Dr. Andre Jackson)

Eleven Phase I studies have been conducted by Teva to describe the human pharmacology and bioavailability/bioequivalence of rasagiline and its inactive metabolite, 1-Aminoindan (AI) following oral administration. There were 2 rich sampling drug-drug interaction studies for theophylline and ciprofloxacin. Nineteen other drug-drug interactions were investigated in the PRESTO study using sparse sampling and population analysis. An additional rich sampling study was completed to assess the potential interaction of rasagiline with tyramine.

Rasagiline was rapidly absorbed following oral administration, with T_{max} occurring at 1 hour post-dose in healthy subjects. Rasagiline is 90-94% protein bound in males and 88-92% protein bound in females (binding to human albumin is 61-66%) with red cell partitioning of 0.1-1.2 over the concentration range 1-100 ng/ml. Rasagiline is rapidly metabolized in the liver. In studies with human liver microsomes rasagiline was primarily metabolized by a single cytochrome P-450 enzyme, CYP1A2. Rasagiline's main metabolite, aminoindan (AI), is found in the urine and accounts for about 20% of the dose (less than 0.5% of the administered dose is

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excreted unchanged in the urine). The absolute bioavailability is 36%. Mass balance based upon radio-labeled drug indicated 60% and 7% respectively excreted in the urine and feces in one week, for an overall recovery of 84% in 38 days. There is no interconversion from the R to the S isomer. Figure 2 and Figure 3 show phase 1 and phase 2 metabolic biotransformations of rasagiline, respectively.

Figure 2 Phase I Biotransformations of Rasagiline

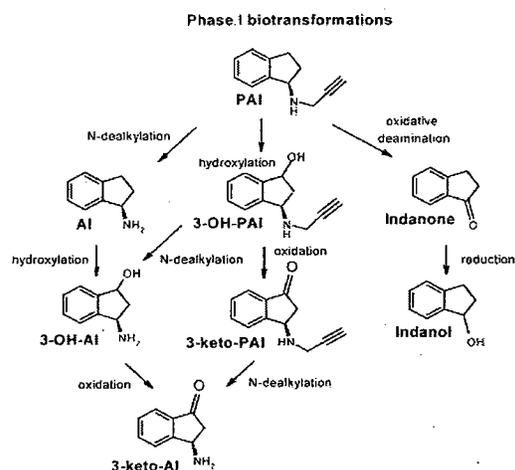
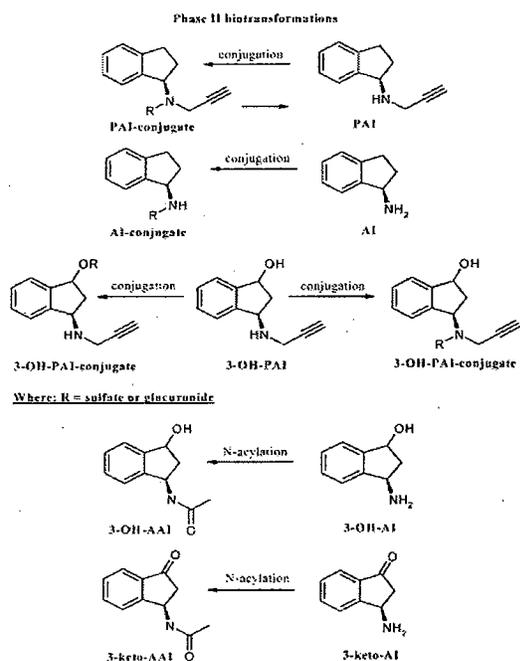


Figure 3 Phase II Biotransformations of Rasagiline



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Multiple dosing studies in PD patients not on LD showed that the pharmacokinetics were linear from 1-4 mg/day. Another study done in PD patients with rasagiline being administered as adjunct therapy to LD/carbidopa exhibited linear kinetics over the dosage range of 0.5-2 mg/day.

In a multiple increasing dose (10-day, once daily doses of 2, 5 and 10 mg) study with 24 healthy subjects, no accumulation was found for rasagiline and the metabolite AI. Rasagiline $t_{1/2}$ (half-life) is between 2.1 ± 1.1 and 3.5 ± 1.5 hours and $t_{1/2}$ of AI is between 10.4 ± 2.2 and 11.6 ± 1.3 hours. The estimate of accumulation via was 1.0, assuming a half-life of 3 hrs. Rasagiline exhibits a departure from dose proportionality above 2 mg in normals in AUC for PAI and AI following a single dose administration at the dose range of 1-20 mg and also exhibits a decrease in clearance based upon time of exposure (i.e., Clearance is lower following multiple dosing).

There were no gender differences following 1 mg once daily dosing. It should be noted that Dr. Jackson's perspective of a gender difference is > 2 fold difference between males and females. Population analysis indicated that CL/F would diminish 1% per year. CL/F increased with body weight, 0.4L/hr per kg of weight. Systemic exposure increased 7 fold for AUC_{tau} at steady-state between moderately hepatic impaired subjects and normals. Maximal exposure at steady-state was only two-fold different between mildly hepatic impaired subjects and normals. It is recommended that rasagiline should not be administered to subjects with moderate to severe hepatic impairment. Caution is advised in dosing patients with mild liver impairment. No dosage adjustment appears necessary in subjects with renal impairment since less than 0.5% of the dose is excreted unchanged in the urine.

Levodopa (LD) in the monotherapy Parkinson's Disease subjects resulted in a 31% decrease in rasagiline CL/F. However when LD was the substrate, there was no effect of rasagiline on LD.

There was an 83% increase in AUC for rasagiline in the presence of steady-state ciprofloxacin, an inhibitor of CYP1A2. There was no effect of rasagiline on theophylline or theophylline on rasagiline when they were co-administered. The results of the tyramine challenge studies indicated that rasagiline can be used safely without dietary tyramine restrictions. However several questions need to be addressed by the firm related to special populations, hepatic disease and ethnic groups. The increase in the TY30 ratio may be dangerously high in these groups and needs to be addressed by the firm due to the decrease in clearance in hepatic disease.

Rasagiline did not inhibit cytochrome P450 isoenzymes (at concentrations 3 fold higher than observed at the proposed 1 mg dose), CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP4A. These results indicate that rasagiline's therapeutic concentrations are unlikely to cause any clinically significant interference with substrates of these enzymes.

There was an increase in rasagiline clearance, at doses of 1.0 and 2 mg, of 39.1% in Parkinson's Disease subjects in the monotherapy clinical study who were currently smoking tobacco however this effect was not apparent in PD patients on chronic LD therapy that were smokers and received rasagiline 0.5 and 1 mg doses.

The concomitant intake of rasagiline with food decreased the C_{max} and AUC by 60% and 20% respectively.

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The to-be marketed 1 mg tablet was determined to be bioequivalent to the clinically studied tablet.

Rasagiline dissolution was investigated in 3 pH ranging media and a dissolution method and specifications are being set in this NDA.

8. PHARMACODYNAMICS

8.1. Background / Introduction

I have reviewed the pharmacodynamic (PD) data to support this NDA. I reviewed the sponsor's summary of PK/PD information and the final study reports for the 4 pharmacodynamic studies/substudies (1 study in healthy volunteers and 3 in patients with Parkinson's Disease) involving tyramine challenges. For greater details, see the review of the Clinical Pharmacology/Biopharmaceutical reviewer, Dr. A. Jackson who conducted the comprehensive PK/PD review and also a review of the population PK and PD results.

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

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

The WARNINGS section of the Eldepryl label notes that the selectivity of selegiline for MAO-B may not be absolute even at the recommended daily dose of 10 mg daily. This section of the label also notes that rare cases of hypertensive reactions have been associated with ingestion of tyramine-containing foods while taking the recommended daily dose of Eldepryl (5 mg BID at breakfast and lunch).

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Metabolism of various substances may be altered with inhibition of MAO-B and MAO-A. Correspondingly, changes in metabolic profiles can indirectly show these inhibitory effects. Considering that MAO-B primarily degrades dopamine and phenylethylamine (PEA), inhibition of MAO-B leads to increased dopamine and PEA and increased urinary excretion of PEA (normally PEA is not measurable in urine), a reflection of such inhibition. Along these lines, MAO-A primarily degrades serotonin (5-hydroxytryptamine-5 HT) to 5-hydroxyindoleacetic acid (5-HIAA) that is excreted in urine. MAO-A also degrades norepinephrine to dihydroxyphenylethylene glycol (DHPG or DOPEG) and 3-methoxy-4-hydroxyphenyl glycol (MHPG). Analogously, inhibition of MAO-A results in decreased plasma DHPG and MHPG and 5-HIAA as well as decreased urinary 5-HIAA.

The purpose of the main PK/PD study (P94159) was to assess MAO-B and MAO-A inhibition for 2 rasagiline doses (e.g. 1 mg and 2 mg QD) included in the pivotal efficacy trials, and compare results to those of placebo and selegiline (i.e. Eldepryl) that was taken once a day (10 mg) instead of twice daily (5 mg BID) according to the U.S. label (after breakfast and lunch). MAO-A inhibition would be assessed by evaluating changes in the sensitivity of blood pressure changes (i.e. pressor responses) to oral tyramine challenge and metabolic profiles of plasma rasagiline and its major metabolite (aminoindan) and plasma and/or urinary metabolic products/derivatives of substrates (e.g. norepinephrine and serotonin) of MAO-A. The tyramine threshold dose (i.e. TYR30 = dose of tyramine that increases systolic blood pressure ≥ 30 mm Hg above pre-treatment) was to be determined before and after drug treatment. Increments in tyramine sensitivity are determined by noting the magnitude of the lowering of the mean tyramine threshold dose after treatment, the number of subjects who exhibit threshold low tyramine doses (e.g. < 100 mg, and especially < 50 mg), and the increment in the Tyramine Sensitivity Factor (TSF). The TSF is calculated by dividing the control/pre-treatment tyramine threshold dose for each subject by the individual's post-treatment tyramine threshold dose (i.e. pre-treatment threshold dose / post-treatment threshold dose). MAO-B inhibition would be assessed by changes in platelet MAO-B activity determined by a radio enzymatic technique.

The sponsor also studied patients treated with rasagiline or placebo in 3 controlled studies to assess blood pressure and pulse responses to various, fixed, doses of tyramine administered with food and either just before or after other food. The sponsor's rationale was that a large tyramine containing ingestion challenge would be ~ 50 mg and that such testing would show whether patients treated with specific amounts of tyramine did or did not exhibit hypertensive responses and the magnitude of such responses. The sponsor's thinking was that such challenges as administered in these studies would likely be larger exposures to tyramine than would occur under a normal diet without tyramine restriction.

It is known that administration of oral tyramine can be affected significantly by eating. Previous study (Berlin et al. *Clint Pharmacology Ther*, 46 : 344 – 351, 1989) has shown that TSF can be markedly changed such that there is a 2.8 fold lower sensitivity to tyramine that is administered with a standard meal. For example, 16 healthy young volunteers showed a mean tyramine dose of 500 mg for significantly increasing blood pressure (systolic blood pressure increment ≥ 30 mm Hg or diastolic increment to > 100 mm Hg) or decreasing pulse (decrease of > 20 % relative to pre-treatment value). The tyramine threshold dose for showing these same threshold responses

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to at least one of these criteria was 1450 mg (e.g. 2.9 fold lower sensitivity by my calculation - 1450 mg/500 mg). Other publications have also commented on the observation that tyramine sensitivity is lowered when tyramine is administered with eating. This conventional testing is accomplished by assessing the blood pressure responses serially to increasing doses of tyramine in the fasting state before exposure to a drug and after exposure to a drug and determining the TSF (e.g. the tyramine dose that produces a systolic increase of ≥ 30 mm Hg before and after drug exposure at steady state). I consider this type of testing approach to be the "gold standard" for assessing tyramine sensitivity and assessing the drug-induced pharmacodynamic reflection of MAO-A inhibition via tyramine challenge testing.

In other NDAs (21336 and 21708) recently reviewed for transdermal selegiline, the sponsor conducted tyramine challenge testing under fasting conditions and found a mean TSF of 9.3 (mean tyramine threshold dose = 88 mg). The mean TSF decreased to 2.3 (mean tyramine threshold dose = 172 mg) when tyramine was administered with a meal in those same subjects. Furthermore, the sponsor has provided a recently publication (VanDenBerg et al., *J Clin Pharmacol*, 43:604-609, 2003.) that outlines the pharmacokinetics of orally administered tyramine and provides insight into results that show less sensitivity to tyramine administered with food. Eight healthy males (20-43 years) received 253 mg tyramine HCl both under fasting conditions and with a meal. There were many marked changes in PK parameters for tyramine. Mean C_{max} for tyramine with a meal was 21 % of that observed (or tyramine C_{max} was nearly 5 fold higher without food) when tyramine was administered under fasting conditions. Tyramine T_{max} administered when fasting ranged between 20 – 60 minutes and showed a mean of 30 minutes. Administering tyramine with a meal delayed T_{max} to a mean time of 75 minutes with a range of 30 to 240 minutes. Tyramine administration AUC exposure was decreased by ~ 69 % and food markedly altered the shape of the curve such that individuals who had experienced a early, significant spike of plasma tyramine now experienced a very gradual increase of plasma tyramine levels that peaked much later and the decrease of plasma tyramine was much more gradual over time. The authors concluded that a "larger amount of tyramine will be required to induce a pressor response equivalent to that following encapsulated tyramine administered in the fasting state."

Reviewer's Summary Overview of Sponsor's Tyramine Testing Approach

The sponsor conducted 4 studies to generate various data regarding tyramine challenges and to characterize the responses of normal healthy subjects and Parkinson's Disease patients to tyramine after treatment with rasagiline. The most important tyramine challenge study is TVP -P94-159 that was conducted in healthy subjects (in Paris) and used a standard tyramine testing scheme/design for assessing systolic blood pressure responses to increasing doses of tyramine administered in a fasting state. I have directed my attention in this review toward study TVP-P94159 because : 1) it employed a standard, conventional type of tyramine challenge for assessing MAO-A inhibition; and 2) subjects received tyramine and were monitored under fasting conditions and thus its results are not confounded by the effects of eating as were results of the other 3 studies that used a non-conventional approach/design associated with eating. Ingestion of food clearly has substantial effects on decreasing the bioavailability of tyramine and also decreases

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tyramine Cmax and prolongs Tmax. Such effects can clearly decrease the sensitivity to tyramine as reflected by cardiovascular responses to specific doses of tyramine.

The other 3 studies (TVP-1012/132, TVP-1012/232, TVP-1012/133) assessed cardiovascular responses (blood pressure and pulse) according to treatment groups with respect to a single or few different tyramine doses administered with food (specifically applesauce, yogurt or ice cream), and shortly before or after a meal. Study TVP-1012/132 studied tyramine responses in Parkinson's Disease patients prior to treatment and after ~ 3 weeks treatment (placebo, 1 mg/day or 2 mg/day) with increasing tyramine doses (25, 50, 75 mg) on separate days and after 10 weeks (75 mg) treatment. A third study was a sub-study of Study TVP-1012/232 that assessed the effect of monotherapy (placebo, 1 mg/day, or 2 mg/day) in patients with "early" Parkinson's Disease. In this study, 75 mg tyramine was administered with applesauce up to 60 minutes after a meal. A fourth study was a sub-study of Study TVP-1012/133 that assessed the effect of adjunctive treatment (placebo, 0.5 mg/day, or 1 mg/day) in patients with advanced Parkinson's Disease taking LD.. In this study, 50 mg was administered with yogurt or ice cream immediately after a meal.

All types of data (e.g. vital sign, adverse event, clinical efficacy, pharmacokinetic, and clinical laboratory) were collected in these various studies. **However, I have focused my review of these studies primarily to present and review cardiovascular (e.g. blood pressure) responses to tyramine challenge, and pertinent pharmacokinetic data that impact on the absence or presence (and extent) of MAO-A inhibition.** Other reviews have focused more extensively on these other types of data. The Safety Review of Dr. Lisa Jones comprehensively deals with safety issues related to rasagiline treatment, the Biopharmaceutical/Clinical Pharmacology Review of Dr. Andre Jackson comprehensively deals with pharmacokinetic /pharmacodynamic issues, and the Statistical Review of Dr. Sharon Yan, and my review of pivotal studies comprehensively deals with efficacy issues. Thus, my review in this section will not deal extensively with data that relate to these other issues (including detailed analyses of ambulatory blood pressure monitoring unrelated to tyramine challenge testing) and do not relate to inhibition of MAO-A.

8.2. Study P94159

Principal Investigator : _____

Study Site : /

8.2.1. Description of Protocol (Study, P94159)

Title of Study in Protocol : "Pharmacodynamic interacting study between TVP-1012 and oral Tyramine after repeated oral administration of 1, 2, and 4 mg/day TVP-1012 (Rasagiline) for ten days in three groups of nine normal healthy volunteers"

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Title of Study in Final Study Report : "Pharmacodynamic interacting study between TVP-1012 and oral Tyramine after repeated oral administration of 1, and 2 mg/day TVP-1012 or 10 mg/day selegiline for ten days in three groups of nine normal healthy volunteers"

Study initiation date : 10/25/94

Study completion date : 8/3/95

Objectives :

Primary : The principal objective of the study was to determine the effects of 50, 100, 200, 400, and 800 mg oral Tyramine on systolic blood pressure of healthy volunteers after repeated administration of 1, 2, and 4 mg TVP-1012 (rasagiline) daily doses for 10 days.

The pharmacodynamic end-point was the dose of tyramine that would induce an increase of systolic blood pressure of ≥ 30 mm Hg, versus the systolic blood pressure measured just before the tyramine administration.

Secondary : The secondary objective of the study is to study the extent of potential MAO-A inhibition level (taking into account the selectivity of TVP-1012) by measuring urinary VMA (vanilloyl mandelic acid), normetanephrine and MHPG (3-methoxy, 4-hydroxyphenylglycol) (as a possible index of MAO-A inhibition).

If no interaction is observed at the 4 mg TVP-1012 dose, an amendment to the protocol was to be submitted to the ethical committee to enable testing of higher doses of rasagiline.

STUDY DESIGN and SCHEDULE OF EVENTS / ASSESSMENTS :

A medical examination and tests were to be performed within two weeks before the beginning of the study, and were to include :

- a detailed medical history,
- a physical examination - including blood pressure (supine and standing), pulse rate (supine and standing) after the subject has rested comfortably for five minutes using an automatic sphygmomanometer, respiratory rate, height, weight,
- a detailed neurological examination - including cranial and motor nerve functions, reflexes, motor coordination and sensory nerve functions.
- an electrocardiogram/ECG (12 lead). Electrocardiograms were to be recorded using a cardiograph.
- a 24 hour ECG recording (ECG Holter) was to be performed.
- Clinical chemistry, and hematology tests and urinalysis

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- Qualitative recreational drug screening : amphetamine and amphetamine-like drugs, opiates, cocaine, and cannabis. If an abnormal result was observed at screening, a quantitative determination was to be performed.

The study was to be a 2-period study: - Period 1: single blind.

All subjects (27 subjects) were to receive placebo from day 1 to day 10 in period 1 under single-blind conditions to the subject. Tyramine was to be administered on day 8, 9 and 10:

- Day 8: 50 mg tyramine, 0.5 hours after placebo administration.
- Day 9: 100 mg, 0.5 hours after placebo administration and 200 mg, 3.5 hours after placebo administration.
- Day 10: 400 mg, 0.5 hours after placebo administration and 800 mg, 3.5 hours after or placebo administration.

Period 2 : double blind. Three parallel treatment groups (1, 2 and 4 mg TVP- 1012).

27 subjects were to be divided in 3 parallel groups of 9 subjects. The three groups were to be studied sequentially, starting with the low dose group. Randomization to rasagiline or placebo was to be done by TEVA.

All subjects who withdrew for reasons unrelated to the study medication were to be replaced. Replacement of subjects withdrawn because of intolerance to the study medication was supposed to be discussed with TEVA PHARMACEUTICAL INDUSTRIES LTD. In case of drop-out before any administration, the replacing subject was to be allocated the same number and treatment with a method for noting that the subject was replacing a drop-out subject.

- Group 1 : 6 subjects were to receive 1 mg/day TVP-1012 and 3 subjects were to receive placebo from day 1 to day 10.
- Group 2 : 6 subjects were to receive 2 mg/day TVP-1012 and 3 subjects were to receive placebo from day 1 to day 10.
- Group 3 : 6 subjects were to receive 4 mg/day TVP-1012 and 3 subjects were to receive placebo from day 1 to day 10.

For the three groups, tyramine was to be administered on day 8, 9 and 10 :

- Day 8 : 50 mg, 0.5 hours after TVP-1012 or placebo administration.
- Day 9 : 100 mg, 0.5 hours after TVP-1012 or placebo administration and 200 mg, 3.5 hours after TVP-1012 or placebo administration.
- Day 10: 400 mg, 0.5 hours after TVP-1012 or placebo administration and 800 mg, 3.5 hours after TVP-1012 or placebo administration.

The two periods were to be separated by a one-week wash-out.

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For each period. The primary end-point was to be the dose of tyramine that induced an increase of systolic blood pressure of ≥ 30 mm Hg, versus the blood pressure measured just before the tyramine administration.

Population: - 27 healthy male volunteers (Caucasian)

Age: 18 to 40 years.

Treatments : All TVP-1012 tablets were to be identical and placebo tablets were to match rasagiline (TVP-1012)

- TVP-1012 tablets dosed at 1 mg
- TVP-1012 tablets dosed at 2 mg
- TVP-1012 tablets dosed at 4 mg

- Tyramine capsules, dosed at 50 mg or at 200 mg.

Duration of the Study

The duration of the study in each subject was to be 41 days, consisting of a one week run-in period followed by two ten-day repeated administration periods separated by one week of wash-out, and a one-week follow-up period after the last administration.

Evaluation Criteria :

Safety Parameters :

AT EACH PERIOD :

Baseline/pre-treatment blood pressure and pulse rate were to be measured supine, after the subject has rested comfortably in supine position after 5 minutes rest and in the following minute in erect position at all times except for the period between 0.5 hours and 6.0 hours after administration on days 9 and 10. The protocol did not specify if blood pressure was to be measured by manually or with an automated device. **For these tyramine administration periods, blood pressure and pulse rate were to be measured only in supine position, every five minutes.**

- More specifically blood pressure and pulse rate were to be measured at :
 - Days 1 to 7 : 0 hr (before dosing), 1, 2, 4, 8, and 12 hours, after TVP-1012 or placebo.
 - Day 8: 0 hr (before dosing), 0.5 hours and every 5 minutes thereafter up to 3 hours, 3.5, 4, 5, 6, 8, 10, and 12 hours after TVP-1012 or placebo.
 - Days 9 and 10 : 0 hr (before dosing), 0.5 hours and every 5 minutes thereafter up

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to 6.0 hours, 6, 7, 8,10, 12 hours after TVP-1012 or placebo.

- Clinical examination on each administration day,
- Clinical laboratory tests before first dosing (between Day -7 and Day -0), before administration on day 1, 24 hours after the last administration (on day 11); and one week after the last administration,
- Urinary drug screening (opiates, cocaine, cannabis, amphetamines) before first dosing (between Day -7 and Day -0)
- Continuous 24-hour ECG recording (Holter) was to be performed at inclusion (between Day -7 and Day -0). Continuous ECG monitoring (1 lead) was also scheduled to start immediately before each tyramine administration and was to be continued until 2.5 hours thereafter. For documentation, control strips of 10 seconds duration were to be performed every 15 minutes.
- Electrocardiogram recordings :
 - Days 1 to 7: 0 hr (before dosing), 1, 2, 4, 8, and 12 hours after TVP-1012 or placebo.
 - Day 8 : 0 hr (before dosing), 0.5, 3, 3.5, 6, 8, and 12 hours after TVP-1012 or placebo.
 - Days 9 and 10: 0 hr (before dosing), 0.5, 3, 6, 6.5, 8, and 12 hours after TVP-1012 or placebo.
 - One week after the last treatment administration (post study ECG).
- Study events were to be recorded when reported spontaneously by the subject, or observed by the investigator.

Dosing Regimen

- TVP-1012 was to be administered by oral route around 7.00 a.m. on each administration day with 150 ml mineral water.
- Subjects were to be dosed in erect position for TVP-1012 (single tablet of 1 or 2 or 4 mg) or placebo (tablet) administrations and in supine position for tyramine.
- The investigator was to ask the subject to open his mouth after drug administration to check drug ingestion.
- Tyramine capsules were to be administered with 150 ml mineral water under open-label

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conditions.

- 50 mg tyramine dose = one 50 mg capsule (tyramine HCL)
 - 100 mg tyramine dose = two 50 mg capsules (tyramine HCL)
 - 200 mg tyramine dose = one 200 mg capsule (tyramine HCL)
 - 400 mg tyramine dose will be administered as two 200 mg capsules (tyramine HCL)
 - 800 mg tyramine dose = four 200 mg capsules (tyramine HCL)
- On day 8, tyramine capsule was to be administered 0.5 hours after TVP-1012 or placebo administration.
 - On Days 9 and 10, tyramine capsule(s) was to be administered 0.5 hours and 3.5 hours after TVP-1012 or placebo administration.

Pharmacokinetics (PK) :

Plasma N-propargyl-1-(R)-aminoindan (PAI) and aminoindan (AI)

- Day 1: Plasma N-propargyl-1-(R)-aminoindan (PAI) and aminoindan (AI) levels at 0 hr (before administration) and 0.5, 1, 2, 4, 8, and 12 hours after TVP-1012 or placebo administration (only on period 2),
- Day 2: Plasma PAI and AI levels at 0 (before administration) and 1 hour after TVP-1012 or placebo administration (only on period 2),
- Day 8: Plasma PAI and AI levels at 0 hr (before dosing) (only on period 2)
- Day 9: Plasma PAI and AI levels at 0 (before dosing) and 0.5, 1, 2, 4, and 8 hours after TVP-1012 or placebo administration (only on period 2),
- Day 10: Plasma PAI and AI levels at 0 (before dosing) and 0.5, 1, 2, 4, and 8 hours after TVP-1012 or placebo administration (only on period 2),

Plasma Tyramine

- On Day 8, plasma tyramine levels 0.5 (before tyramine administration) and 1.5, 3.5, 4.5, and 6.0 hours after TVP-1012 or placebo administration.
- On Day 9 and Day 10, plasma tyramine levels 0.5 (before tyramine administration) and 1.5, 3.5 (before second tyramine administration), 4.5, and 6 hours after TVP-1012 or placebo administration.

Pharmacodynamics (PD) :

- Urine samples for VMA, normetanephrine and 3-methoxy-4-hydroxyphenyl glycol (MHPG) determination were to be collected on Day 7 of each period during the following

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interval: 0-24 hours after TVP-1012 or placebo administration.

- Blood samples for platelet MAO-B activity evaluation was to be collected on Day 7, 1 hour after TVP-1012 or placebo administration.
- Blood samples for determination of dihydroxy-phenylglycol (DPGH) will be collected on Day 8, before TVP-1012 or placebo administration.

Inclusion Criteria :

- healthy male subjects/volunteers
- 18 to 40 years old
- able to give written informed consent
- have a stable blood pressure
- Caucasian
- weight be within 15 % of the ideal body weight at the scale proposed by the Metropolitan Insurance Company
- certified as normal by a comprehensive clinical assessment (detailed medical history and a complete physical examination), an ECG and laboratory investigations (hematological and blood chemistry tests, urinalysis), the results of which are within the normal range for healthy subjects and/or clinically acceptable
- stable blood pressure defined as follows: subject will be lying in bed for 30 minutes. Systolic blood pressure was to be thereafter recorded at 5 minutes intervals during at least 30 minutes. Subjects could be included if three successive measurements of systolic blood pressure do not vary by > 5 mm Hg
- normal 24 hour ECG recording
- non smokers and were to have refrained from smoking for at least six months before the study and for the duration of the study
- normal eating habits
- willing to abstain from eating : cheese, herring, liver, chocolate, salami, ham, nuts, alcohol, yeast and yeast containing products, broad beans, bananas. citrus fruits, caffeine at least one week before administration. Diet was to be continued until at least two weeks after the last dose

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- to be registered with the social security in agreement with the French law (Huriet Law: n° 88.1138 – 20.12.88) on biomedical experimentation

Exclusion Criteria :

- have a history or signs of major medical/psychiatric illness or surgery which, in the judgment of the investigator, put them “at risk” or likely to modify their handling of the study drug
- suffer from any acute or chronic systemic disease or disorder
- have a history of hypersensitivity to at least one drug (abnormal drug reaction or idiosyncrasy or asthma)
- regular users of sedatives, hypnotics, tranquillizers or any other addictive agents
- have signs and symptoms, if any, and laboratory test values outside the clinically acceptable “normal range” for healthy subjects
- >1 ventricular premature beat per hour on the 24 hour ECG recording
- known to be prone to the abuse of alcohol or cannabis, opiates, cocaine (i.e. history or evidence of acute or chronic abuse), or heavy smokers
- drink excessive amounts of tea, coffee, chocolate, and/or beverages containing caffeine (> 1 cups/day or approximately 100 mg of caffeine per day)
- have a positive HIV test, and/or a positive HBs test, and/or a positive HCV test
- have received blood or plasma derivatives in the year preceding the initiation of the study
- have donated blood in the three months preceding the initiation of the study or would make blood donation during the study, or within the three months following the study completion
- have unstable blood pressure (stable blood pressure defined in inclusion criteria)
- have received any drug or treatment which could lead to induction or inhibition of hepatic microsomal enzymes within 3 months of the study start
- have participated in another clinical trial or pharmacokinetic experiment or tolerance study of any other drug or research compound in the three months immediately prior to the start of this study
- in the judgment of the investigator, is likely to be non-compliant or uncooperative during

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the study

- have forfeited their freedom by administrative or legal award or who are under guardianship
- not able to be contacted in case of emergency.

Hospitalization

Subjects were to be hospitalized the night before the first administration of each period. They were then to remain in the clinical unit under permanent medical and nursing supervision for 10.5 days. On days 8, 9 and 10 of each period, subjects were to be hospitalized in an intensive care unit.

Activity of Subjects

The clinical unit was situated within _____ Paris in a quiet environment. Subjects were allowed to read, write, watch television or play cards during the hospitalization. Subjects were requested not to take important exercise in the week preceding the start of the study, and until after the post-study tests. Subjects were not allowed to do strenuous physical exercise during the hospitalization. Subjects were to remain sitting or standing during two hours after drug intake. Afterwards, they were to be allowed to sit in chairs, lie in their beds or remain standing for the rest of the day.

Subjects were to go to bed at 11.00 p.m. and get up at 7.00 a.m. Meals were to be provided within the unit.

Diet

The subjects were to be fasted overnight (minimum of 10 hours) before the morning administration of treatment.

During the 24 hours preceding administration period and during all the study duration, subjects were supposed to abstain from smoking and drinking alcohol, coffee, tea or beverages containing cola. Subjects were to abstain from eating: cheese, yogurt, herring, liver, chocolate, salami, ham, nuts, alcohol, yeast and products containing yeast, broad beans, bananas, citrus fruits, caffeine at least one week before administration, during the whole study until two weeks after the last dose,

Meals were supposed to be well-balanced in carbohydrates, lipids and proteins.

On each day of administration from Day 1 to Day 7, breakfast was to be served 1 hour after TVP-1012 or placebo administration. Breakfast was to be composed of two croissants and mineral water.

On Day 8, Day 9 and Day 10, subjects were not have breakfast. Lunch was to be served four hour after TVP-1012 administration on days 1 to 7 and 6 hours after TVP-1012 or placebo

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administration on days 8, 9 and 10.

On each day of administration, dinner was to be served 12 hours after TVP-1012 administration.

Subjects were to be allowed thirty minutes to eat their meal. Subjects were only allowed to drink mineral water. The water supply was to be 1500 ml for each 24 hour period, as one bottle of mineral water, in order to allow the best normalization of water intake. Each bottle was labeled with the subject's code. Water was to be drunk during the 24 hours period. Control of empty bottles was to be made at the end of each period.

Concomitant Medication

No concomitant medication was permitted within the 7 days preceding as well as during the study. In case of drug-related emergency situations, appropriate medical treatment was to be performed.

Corrective Treatment

In case of an increase of systolic blood pressure > 60 mm Hg or in case of poor tolerance (particularly headache of high intensity), subjects could receive a corrective treatment. Corrective treatment would be intravenous nicardipine.

Premature withdrawal Of Subject from the study

A subject admitted to this study will be discontinued if :

- An increase of systolic blood pressure of ≥ 30 mm Hg is observed after administration of tyramine. In this case the following doses of TVP-1012 or placebo, and tyramine will not be administered. In this case, all investigations (clinical parameters and pharmacokinetics) were to be performed until 12 hours after the last TVP-1012 administration. Blood pressure was to be measured until back to normal, but not less than 12 hours after the last TVP-1012 or placebo administration. Laboratory tests were to be performed 24 hours after the last TVP-1012 administration and the post study assessments were to be done one week after the last TVP-1012 administration.

A subject admitted to this study was to be withdrawn from the study or will be considered as a drop-out if :

- an adverse reaction definitely attributable to the study medication was severe
- an hypersensitivity or allergic reaction clearly linked to the study medication occurred
- a subject became afflicted with a systemic illness (unrelated to the study medication but during the study) for which concomitant medication is required

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Study Discontinuation by the Investigator

If an unwanted effect (adverse reaction) was considered severe by the investigator, endangering the health of the subject, the affected subject was to be withdrawn from the study, considered as a drop-out, and replacement discussed with TEVA PHARMACEUTICAL INDUSTRIES LTD. monitor.

Statistical and Pharmacokinetic Analyses

Descriptive statistics of subjects' characteristics were to be performed by —
Statistical analysis of clinical tolerance parameters was to be performed by —
Pharmacokinetic analysis was to be performed by —

Safety Evaluation :

A physical examination was to be performed prior to study start and six to ten days after the last drug administration. Study events were to be recorded when reported spontaneously by the subject, or observed by the investigator. Any serious or unexpected adverse experience was required to be reported immediately to TEVA PHARMACEUTICAL INDUSTRIES LTD. by phone or telefax.

Adverse Events

A study event was any positive or negative event that a subject experienced during the study. Adverse reactions, a new intercurrent illness, and significant deviations from baseline laboratory values were considered as study events.

Study events were to be graded as follows :

- mild: no significant interference with normal activities; acceptable, disappeared without residual effect
- moderate: significant interference with study and/or normal daily activities
- severe: considered as unacceptable by the physician or requires treatment or required discontinuation from the study.

Signs and symptoms regarded or not as side effects related to the study medication were to be recorded by the investigator on the case report form (CRF). Every adverse event that was life threatening, requiring hospitalization, entailing the death or disabling was to be considered as a serious adverse event.

At all stages a critical evaluation of tolerance, development of unwanted effect and clinical laboratory and electrocardiography status of each subject was to be made by the investigator and team.

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Clinically significant abnormal laboratory value, abnormal vital sign or abnormal ECG was to be reported as an adverse event.

Post-Study Assessments

One week after the last administration:

- a clinical examination was to be performed
- blood pressure and pulse rate were to be measured
- electrocardiogram was to be recorded
- blood sample for laboratory screening, identical to inclusion test (except for HIV 1 & 2 antibodies research, hepatitis and urinary drug screening) were to be collected.

Summary of Major / Significant Protocol Amendments :

Amendment # 1 (8/2/94)

This amendment to the protocol was made before the study started.

- provided plans to quantify PAI (rasagiline), AI (aminoindan), tyramine, DOPEG (DHPG) and catecholamines (VMA, 5- HIAA, HVA, MHPG and normetanephrine) in the plasma and urine samples collected during the clinical study
- provided plans to assess the pharmacokinetics profiles of PAI, AI and tyramine.

Amendment # 2 (3/9/95)

- added selegiline (an MAO-B inhibitor) as a comparator treatment for comparison to treatment with placebo and rasagiline
- added a group of 9 subjects to receive a capsule of selegiline (10 mg/day as a single dose) (N = 6) or identically appearing capsule of placebo (N = 3) for 10 days
- this additional treatment group was to receive these treatments in Period 2 under “double-blinded” conditions after receiving a placebo capsule under single-blind conditions for 10 days in Period 1
- tyramine and associated assessments and measurements were to be performed on days 8, 9, and 10 of Period 1 and 2 as previously described for placebo and rasagiline treatment groups
- protocol did not specify that 5 mg selegiline tablets or placebo tablets were to be added to a capsule but this was described in the final study report

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Amendment # 3 (9/23/96)

- analyses of initial results from this study/protocol showed “a mild interaction” between tyramine and rasagiline (2 mg/day) suggesting MAO-A inhibition based upon an increase in the tyramine sensitivity factor after rasagiline treatment
- added another intermediate rasagiline dose group of 9 subjects to receive treatment with rasagiline (3 mg/day) (N = 6) or placebo (N = 3) for 10 days
- this additional treatment group was to receive these treatments in Period 2 under “double-blinded” conditions after receiving a placebo capsule under single-blind conditions for 10 days in Period 1
- tyramine and associated assessments and measurements were to be performed on days 8, 9, and 10 of Period 1 and 2 as previously described for placebo and rasagiline treatment groups
- added inclusion criterion for subjects to undergo exercise tolerance test at pre-study and to show a normal exercise tolerance test

Amendment # 4 (10/3/96)

- added inclusion criterion for subjects to undergo cardiac echocardiography at pre-study and to show a normal test result

8.2.2. Sponsor’s Presentation of Results of Study P94159

Most of the descriptions, summaries, tables, and figures presented here were taken from the sponsor’s electronic submission.

Patient Disposition

Twenty-seven (27) subjects were initially randomized and three other subjects (Nos. 1611, 1616 and 1622) were included to replace subjects No. 611, 616 and 622 who discontinued the study. Out of these 27 subjects, 18 received the study drug (N = 6, rasagiline 1 mg/day; N = 6, 2 mg/day; N = 6, selegiline 10 mg/day) and 9 received placebo. Twenty-seven subjects completed this study according to the protocol.

Subject Premature Discontinuation (All three subjects received placebo) :

- Subject No 611 discontinued the study on Day 10 of Period 1 for a personal reason.
- Subject No 616 discontinued the study on Day 9 of Period 1 because of acute psychotic episode. This subject received only placebo.

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- Subject No 622 discontinued the study on Day 7 of Period 1 for a personal reason.

All subjects had received at least one dose of study drug or placebo and were, therefore, considered to be available for the safety description.

Protocol Deviations

The sponsor noted in this section “Regarding endpoint determination, the Data Analysis Plan issued before code opening clarified the determination of an endpoint for a subject if clinical symptoms appeared although blood pressure was not increased and the possibility that a subject will continue treatment if no clinical symptoms appeared although an increase in blood pressure was observed.”

The Data Analysis Plan was not submitted for review.

Reviewer’s Note/Alert to Reader

The investigator deviated from the protocol and gave additional, higher tyramine doses to 3 subjects because he did not think that the protocol specified threshold (≥ 30 mm Hg systolic blood pressure increment after tyramine) was a true positive result from tyramine. The sponsor informed DNDP that these actions were “based upon the seasoned clinical judgment of an Investigator who was blinded to the study code at the time he made his decisions.” When tyramine “threshold” data from these higher doses were subsequently generated in these 3 subjects (subject # 626-selegiline; subject # 1611-placebo; subject # 607-1 mg rasagiline), these data were considered based upon “clinical criteria.” “Clinical criteria” data are data derived from protocol specified tyramine threshold data in 24 subjects and threshold data generated by protocol deviation/violation of assessing higher tyramine doses in 3 subjects. Most data presented by the sponsor were based upon “clinical criteria.”

Demographic and Other Baseline Characteristics

Thirty healthy male Caucasian subjects participated in this study and twenty-seven of them completed the study according to protocol. The descriptive statistics of the demographic characteristics are summarized below in Table 2.

Table 2 Demographic Data of Subjects (Mean \pm SD and range)

| Parameter | 1 mg TVP-1012 (n = 6) | 2 mg TVP-1012 (n = 6) | 10 mg selegiline (n = 7) | Placebo (n = 11) |
|-------------|----------------------------|-----------------------------|-----------------------------|----------------------------|
| Age (yrs) | 27.2 \pm 3.0 (24.0-31.0) | 23.0 \pm 2.4 (20.0-26.0) | 24.1 \pm 2.6 (21.0-27.0) | 25.5 \pm 4.2 (19.0-32.0) |
| Weight (kg) | 74.4 \pm 7.4 (64.2-81.6) | 69.4 \pm 10.2 (61.4-88.0) | 75.6 \pm 9.2 (66.0-89.0) | 75.7 \pm 8.5 (59.6-89.2) |
| Height (cm) | 179 \pm 4.7 (174-187) | 175 \pm 10.2 (165-190) | 180 \pm 6.5 (172-189) | 178 \pm 7.0 (168-188) |

Measurements of Treatment Compliance

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Treatment compliance was regularly checked by the Investigator or his deputy, after the study treatment was administered, by careful inspection of the mouth.

Effects on Vital Signs measurements

At study days 8 - 10 of each period the different tyramine doses were administered to investigate the effect of tyramine on systolic blood pressure in healthy subjects pre-treated with MAO-B inhibitors as compared to the effect in untreated subjects. The maximum systolic blood pressure change at endpoint for the four different treatments is depicted in Table 3, and the ratio was calculated for each individual subject and presented by treatment group for all the following tables.

Table 3 Mean (\pm SD) of Maximum Systolic Blood Pressure Change (mmHg) and R Ratio

| Treatment | Period 1 Placebo | Period 2 Study Drug | Period 2/Period 1 Ratio |
|------------------|---------------------|------------------------|----------------------------|
| Placebo | 43.0 \pm 10.4 | 45.8 \pm 12.1 | 1.2 \pm 0.4 |
| 1 mg TVP-1012 | 48.8 \pm 15.4 | 53.0 \pm 14.5 | 1.2 \pm 0.2 |
| 2 mg TVP-1012 | 49.8 \pm 9.8 | 53.5 \pm 19.7 | 1.2 \pm 0.4 |
| 10 mg selegiline | 44.0 \pm 12.5 | 49.2 \pm 14.2 | 1.3 \pm 0.2 |

These data show that there were no differences between the four different treatment groups with regard to the magnitude of the tyramine effect on systolic blood pressure. Tyramine increased the systolic blood pressure during period 2 by about 20-30% irrespective of the different treatments with MAO-B inhibitors or placebo. However, the rate of systolic blood pressure change (increase in systolic blood pressure/the time of its occurrence after tyramine dosing) appeared higher under TVP-1012 and selegiline treatment than under placebo treatment (Table 4). Whether these differences are meaningful is doubtful because this parameter has a high variability.

Table 4 Mean (\pm SD) Rate of the Systolic Blood Pressure Change (mmHg/hr) and Ratio

| Group | Period 1 Placebo | Period 2 Study Drug | Period 2/Period 1 Ratio |
|------------------|----------------------|------------------------|----------------------------|
| Placebo | 145.4 (\pm 105.9) | 161.3 (\pm 77.3) | 1.4 (\pm 0.9) |
| 1 mg TVP-1012 | 119.1 (\pm 40.3) | 173.8 (\pm 69.7) | 1.9 (\pm 1.5) |
| 2 mg TVP-1012 | 126.1 (\pm 55.2) | 184.5 (\pm 88.2) | 1.4 (\pm 0.5) |
| 10 mg selegiline | 62.4 (\pm 6.8) | 91.3 (\pm 57.2) | 2.0 (\pm 1.0) |

In Table 5, the area under the curve (AUC) of the change in systolic blood pressure is shown for different treatments.

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Table 5 Mean (\pm SD) Under the Curve of Systolic Blood Pressure Change (mm Hg) and Ratio

| Treatment | Period 1 Placebo | Period 2 Study Drug | Period 2/Period 1 Ratio |
|------------------|---------------------|------------------------|----------------------------|
| Placebo | 86.3 \pm 6.7 | 87.5 \pm 9.7 | 1.0 \pm 0.1 |
| 1 mg TVP-1012 | 85.3 \pm 9.6 | 84.2 \pm 5.7 | 1.0 \pm 0.1 |
| 2 mg TVP-1012 | 94.0 \pm 8.4 | 85.6 \pm 11.1 | 0.9 \pm 0.1 |
| 10 mg selegiline | 88.0 \pm 2.1 | 96.7 \pm 14.7 | 1.2 \pm 0.2 |

Endpoint Calculation : Two approaches of endpoint calculation were performed:

1. Endpoint Calculation based on Strictly Protocol Criteria

This endpoint was calculated according to an increase of ≥ 30 mmHg in systolic blood pressure.

2. Endpoint Calculation based on Clinical Criteria

This endpoint was to be calculated according to an increase of ≥ 30 mmHg in systolic blood pressure **and/or** the following clinical criteria :

(These clinical criteria were included in the Statistical Analysis Plan (SAP) but were never in the protocol nor in the protocol amendments.)

- a) The dose of tyramine which induced an increase in systolic blood pressure by 30 mmHg or more and for subjects having reached the endpoint as defined in the protocol twice during the same study period but at different tyramine doses and if the first event is a simple episode without adverse cardiovascular experience, then the second event (higher dose of tyramine) was regarded as the true endpoint
- b) The dose of tyramine which induced an increase in systolic blood pressure by 30 mmHg or more and if the first event is not a simple episode or adverse cardiovascular experience was reported on this tyramine dose level, then the first event (lower dose of tyramine) was regarded as the true endpoint.
- c) The dose of tyramine which induced an increase in systolic blood pressure by 30 mmHg or more and for subjects having not reached the endpoint as defined in the protocol but having adverse cardiovascular experience, and if no higher doses of tyramine were foreseen in the protocol, then the highest dose of tyramine was regarded as the true endpoint.
- d) The dose of tyramine which induced an increase in systolic blood pressure by 30 mmHg or more and for subjects having not reached the endpoint as defined in the protocol but no cardiovascular experiences occurred, and if no higher doses of tyramine were foreseen in the protocol, the endpoint for the respective period could not be defined.

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The effect of tyramine administration on systolic blood pressure is expressed as TYR 30, a dose of tyramine required to cause a blood pressure elevation of at least 30 mmHg at a single time point. TYR 30 ratio (TYR 30 period 1/TYR 30 period 2) was calculated for each subject to compare the dose of tyramine required to cause the blood pressure elevation alone (period 1) or concomitantly with the study drug (period 2). The ratio is the average value of the treatment group. Table 6 shows tyramine threshold doses for individual based upon protocol criterion or "clinical criteria." Table 7 shows individual Tyramine Pressor Ratios (i.e. TSFs) based upon either criteria. Table 8 shows the mean effect of treatment on Tyramine Pressor Ratios.

Table 6 Individual Tyramine Threshold Doses for Protocol Criterion (≥ 30 mm Hg Systolic Blood Pressure Increment Above Pre-Tyramine Value) and for "Clinical Criteria"

Data listing of Patients reached Endpoint - Per Protocol

| | | period | |
|--------------------|-------------|--------------------|--------------------|
| | | 1 | 2 |
| | | Tyramine Dose (mg) | Tyramine Dose (mg) |
| Experimental Group | Patient No. | | |
| DEPRENYL 10mg | 619 | 850 | 400 |
| | 620 | 850 | 800 |
| | 623 | 850 | 400 |
| | 625 | 400 | 400 |
| | 626 | 400 | 50 |
| | 1622 | 800 | 200 |
| PLACEBO | 604 | 800 | 800 |
| | 608 | 800 | 800 |
| | 609 | 850 | 850 |
| | 611 | 850 | . |
| | 614 | 450 | 800 |
| | 616 | 100 | . |
| | 621 | 400 | 800 |
| | 624 | 400 | 850 |
| | 627 | 400 | 400 |
| | 1611 | 100 | 50 |
| 1616 | 850 | 400 | |
| TVP-1012 1mg | 601 | 800 | 850 |
| | 602 | 400 | 400 |
| | 603 | 400 | 450 |
| | 605 | 800 | 800 |
| | 606 | 400 | 400 |
| 607 | 800 | 400 | |
| TVP-1012 2mg | 610 | 800 | 200 |
| | 612 | 800 | 400 |
| | 613 | 800 | 400 |
| | 615 | 800 | 400 |
| | 617 | 800 | 200 |
| | 618 | 850 | 400 |

Data listing TYR30 - Clinical Criteria

| | | period | |
|--------------------|-------------|--------------------|--------------------|
| | | 1 | 2 |
| | | Tyramine Dose (mg) | Tyramine Dose (mg) |
| Experimental Group | Patient No. | | |
| DEPRENYL 10mg | 619 | 850 | 400 |
| | 620 | 850 | 800 |
| | 623 | 850 | 400 |
| | 625 | 400 | 400 |
| | 626 | 400 | 400 |
| | 1622 | 800 | 200 |
| PLACEBO | 604 | 800 | 800 |
| | 608 | 800 | 800 |
| | 609 | 850 | 850 |
| | 611 | 850 | . |
| | 614 | 450 | 800 |
| | 616 | 100 | . |
| | 621 | 400 | 800 |
| | 624 | 400 | 850 |
| | 627 | 400 | 400 |
| | 1611 | 800 | 850 |
| 1616 | 850 | 400 | |
| TVP-1012 1mg | 601 | 800 | 850 |
| | 602 | 400 | 400 |
| | 603 | 400 | 450 |
| | 605 | 800 | 800 |
| | 606 | 400 | 400 |
| 607 | 800 | 800 | |
| TVP-1012 2mg | 610 | 800 | 200 |
| | 612 | 800 | 400 |
| | 613 | 800 | 400 |
| | 615 | 800 | 400 |
| | 617 | 800 | 200 |
| | 618 | 850 | 400 |

Tyramine doses given ranged between 50 mg to 800 mg

850 mg = protocol specified criterion not met at highest dose given (i.e. 800 mg)

450 mg = protocol specified criterion not met at highest dose given (i.e. 400 mg)

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Table 7 Individual Subject Tyramine Pressor Ratio (TYR30) According to Protocol Criterion or "Clinical Criteria"

Data Listings TYR30 Ratio

| Protocol P94159 | | TYR30 Ratio (Per Protocol) | TYR30 Ratio (Clinical) |
|--------------------|--------------|----------------------------|------------------------|
| Experimental Group | Patient No. | | |
| DEPRENYL 10mg | 619 | 2.1 | 2.1 |
| | 620 | 1.1 | 1.1 |
| | 622 | . | . |
| | 623 | 2.1 | 2.1 |
| | 625 | 1.0 | 1.0 |
| | 626 | 8.0 | 1.0 |
| | 1622 | 4.0 | 4.0 |
| PLACEBO | 604 | 1.0 | 1.0 |
| | 608 | 1.0 | 1.0 |
| | 609 | 1.0 | 1.0 |
| | 611 | . | . |
| | 614 | 0.6 | 0.6 |
| | 616 | . | . |
| | 621 | 0.5 | 0.5 |
| | 624 | 0.5 | 0.5 |
| | 627 | 1.0 | 1.0 |
| | 1611 | 2.0 | 0.9 |
| | 1616 | 2.1 | 2.1 |
| | TVP-1012 1mg | 601 | 0.9 |
| 602 | | 1.0 | 1.0 |
| 603 | | 0.9 | 0.9 |
| 605 | | 1.0 | 1.0 |
| 606 | | 1.0 | 1.0 |
| 607 | | 2.0 | 1.0 |
| TVP-1012 2mg | 610 | 4.0 | 4.0 |
| | 612 | 2.0 | 2.0 |
| | 613 | 2.0 | 2.0 |
| | 615 | 2.0 | 2.0 |
| | 617 | 4.0 | 4.0 |
| | 618 | 2.1 | 2.1 |

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Table 8 Mean Tyramine Pressor Ratio (TYR30) for Different Treatments According to Protocol Criterion or “Clinical Criteria”

Descriptive Statistics of TYR30 Ratio

| Protocol P94159 | | TYR30 Ratio (Per Protocol) | TYR30 Ratio (Clinical) |
|--------------------|------|----------------------------|------------------------|
| Experimental Group | | | |
| DEPRENYL 10mg | Mean | 3.1 | 1.9 |
| | Std | 2.7 | 1.2 |
| | N | 6 | 6 |
| | Min | 1.0 | 1.0 |
| | Max | 8.0 | 4.0 |
| PLACEBO | Mean | 1.1 | 1.0 |
| | Std | 0.6 | 0.5 |
| | N | 9 | 9 |
| | Min | 0.5 | 0.5 |
| | Max | 2.1 | 2.1 |
| TVP-1012 1mg | Mean | 1.1 | 1.0 |
| | Std | 0.4 | 0.0 |
| | N | 6 | 6 |
| | Min | 0.9 | 0.9 |
| | Max | 2.0 | 1.0 |
| TVP-1012 2mg | Mean | 2.7 | 2.7 |
| | Std | 1.0 | 1.0 |
| | N | 6 | 6 |
| | Min | 2.0 | 2.0 |
| | Max | 4.0 | 4.0 |

Table 8 shows that 1.0 mg TVP-1012 does not increase the sensitivity of the healthy subjects to tyramine as evidenced by the TYR 30 ratio of ~ 1. An increase in sensitivity is observed at the 2.0 mg dose of TVP-1012 (TYR 30 ratio of 2.7). Due to the high variability of the parameter, it is assumed that this effect is comparable to the effect of 10 mg selegiline (TYR 30 ratio of 3.1 for protocol criterion or 1.9 for “clinical criteria”). The differences between the TYR 30 ratios are not statistically significant.

I requested that the sponsor provide additional tables showing actual tyramine thresholds based upon data in which the individual met the protocol specified criterion by showing a ≥ 30 mm Hg increase in systolic blood pressure after tyramine. Table 9 shows a listing of individual data and Table 10 shows the mean data of these subjects. The sponsor had not commented on results in these tables.

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Table 9 Data Listing of TYR30 and TSF (TYR Ratio) Results Based Upon Actually Meeting Protocol Specified Criterion (≥ 30 mm Hg SBP Increment)

| Protocol P94159 | | Tyramine Dose (mg) - Period 1 | Tyramine Dose (mg) - Period 2 | Tyramine Sensitivity Factor (Period1/Period2) |
|----------------------------|-------------|-------------------------------|-------------------------------|---|
| Treatment Group | Subject No. | | | |
| DEPRENYL (Selegiline) 10mg | 619 | * | 400 | * |
| | 620 | * | 800 | * |
| | 623 | * | 400 | * |
| | 625 | 400 | 400 | 1.0 |
| | 626 | 400 | 50 | 8.0 |
| | 1622 | 800 | 200 | 4.0 |
| PLACEBO | 604 | 800 | 800 | 1.0 |
| | 608 | 800 | 800 | 1.0 |
| | 609 | * | * | * |
| | 611 | * | - | - |
| | 614 | * | 800 | * |
| | 616 | 100 | - | - |
| | 621 | 400 | 800 | 0.5 |
| | 624 | 400 | * | * |
| | 627 | 400 | 400 | 1.0 |
| | 1611 | 100 | 50 | 2.0 |
| | 1616 | * | 400 | * |
| TVP-1012 1mg | 601 | 800 | * | * |
| | 602 | 400 | 400 | 1.0 |
| | 603 | 400 | * | * |
| | 605 | 800 | 800 | 1.0 |
| | 606 | 400 | 400 | 1.0 |
| | 607 | 800 | 400 | 2.0 |
| TVP-1012 2mg | 610 | 800 | 200 | 4.0 |
| | 612 | 800 | 400 | 2.0 |
| | 613 | 800 | 400 | 2.0 |
| | 615 | 800 | 400 | 2.0 |
| | 617 | 800 | 200 | 4.0 |
| | 618 | * | 400 | * |

* Subject did not reach the TYR30 endpoint.

- Subjects 611 and 616 did not have measurements in period 2.

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Table 10 Mean TSF Ratio Based Upon Actually Meeting Protocol Specified Criterion (≥ 30 mm Hg SBP Increment)

| Protocol P94159 | Tyramine Sensitivity Factor (Period1/Period2) (Per Protocol) | | | | |
|-------------------------------|--|------|---|------|------|
| | Mean | Std | N | Min | Max |
| Treatment Group | | | | | |
| DEPRENYL (Selegiline) 10mg | 4.33 | 3.51 | 3 | 1.00 | 8.00 |
| PLACEBO | 1.10 | 0.55 | 5 | 0.50 | 2.00 |
| TVP-1012 1mg | 1.25 | 0.50 | 4 | 1.00 | 2.00 |
| TVP-1012 2mg | 2.80 | 1.10 | 5 | 2.00 | 4.00 |

ECG Parameters

Descriptive statistics of ECG parameters, such as heart rate (HR), PR-interval, QRS-duration, QT- and QTc-duration, are presented in Appendix 14.2, Electrocardiographic safety; pages 243-632. Generally all ECG recordings gave normal results. Few subjects, however, showed minor deviations from normal ranges being of no clinical relevance that are listed below:

- Subject No 602 showed at Day 9 of Period 1, 30 minutes after administration of placebo (T0.5) a first degree atrio-ventricular block, the same finding was observed at Day 9 of Period 1 at T3, T6.5, at Day 10 of Period 1 at T0, T0.5. These events were not of clinical significance.
- Subject No 602 showed at Day 1 of Period 2 before administration of 1.0 mg TVP-1012 (T0) a first degree atrio-ventricular block, the same finding was observed at Day 1 of Period 2 at T12, at Day 8 of Period 2 at T0, T0.5, T3, T6, at Day 9 of Period 2 at T0, T3, T6, at Day 10 of Period 2 at T0.5, T6, T6.5. These events were not of clinical significance.
- Subject No 604 showed at Day 7 of Period 1 twelve hours after administration of placebo a shortened PR-interval (116 ms instead of 120 ms).
- Subject No 609 showed at Day 8 of Period 2 three hours after administration of placebo (T3) a first degree atrio-ventricular block, the same finding was observed at Day 8 of Period 2 at T3.5, T6. These events were not of clinical significance.

Plasma Tyramine Determinations

Plasma concentrations of tyramine measured after the different tyramine administrations in Period 1 and Period 2 of the study are given in the following tables. Table 11 and Table 12 show the mean \pm SD values of tyramine after the different doses and their ratios assessed at 1 hour after tyramine administrations at Day 8, Day 9 and Day 10. The 800 mg tyramine data are not

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tabulated due to the different number of subjects per period who have received this dose due to the fact, that the study objectives have been reached earlier.

Table 11 Mean \pm SD values of the Plasma Concentrations of Tyramine and their Period 2/Period 1 ratios Assessed 1 hour after 50 mg and 100 mg Tyramine During Multiple Oral Administration of TVP-1012

| Group | 50 mg tyramine | | | 100 mg tyramine | | |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | P 1 | P 2 | Ratio | P 1 | P 2 | Ratio |
| Placebo (n = 9) | 1.48 \pm 2.95 | 0.54 \pm 0.13 | 0.98 \pm 0.44 | 1.04 \pm 0.71 | 1.38 \pm 1.43 | 1.61 \pm 1.43 |
| 1 mg TVP-1012 (n = 6) | 0.50 \pm 0.00 | 0.50 \pm 0.00 | 1.00 \pm 0.00 | 0.61 \pm 0.26 | 5.07 \pm 6.25 | 9.66 \pm 12.8 |
| 2 mg TVP-1012 (n = 6) | 0.50 \pm 0.00 | 1.78 \pm 1.63 | 3.56 \pm 3.26 | 0.51 \pm 0.02 | 12.9 \pm 6.36 | 25.4 \pm 12.5 |
| 10 mg selegiline (n = 6) | 0.50 \pm 0.00 | 4.86 \pm 2.72 | 9.71 \pm 5.43 | 0.71 \pm 0.32 | 17.2 \pm 10.2 | 24.4 \pm 13.3 |

P 1 = Study Period 1; P 2 = Study Period 2; Ratio = P 2/P 1 - ratio

Table 12 Mean \pm SD values of the Plasma Concentrations of Tyramine and their Period 2/Period 1 Ratios Assessed 1 hour after 200 mg and 400 mg Tyramine during Multiple Oral Administration of TVP-1012

| Group | 200 mg tyramine | | | 400 mg tyramine | | |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|------------------|------------------|
| | P 1 | P 2 | Ratio | P 1 | P 2 | Ratio |
| Placebo (n = 9) | 3.35 \pm 4.07 | 2.34 \pm 1.23 | 1.68 \pm 1.46 | 19.9 \pm 34.8 | 22.8 \pm 23.2 | 2.80 \pm 2.89 |
| 1 mg TVP-1012 (n = 6) | 6.04 \pm 3.71 | 10.1 \pm 6.49 | 2.87 \pm 2.89 | 7.97 \pm 3.50 | 81.3 \pm 51.2 | 11.4 \pm 7.17 |
| 2 mg TVP-1012 (n = 6) | 5.48 \pm 3.33 | 34.1 \pm 17.7 | 11.4 \pm 11.2 | 23.1 \pm 11.1 | 93.4 \pm 79.7* | 3.55 \pm 2.57* |
| 10 mg selegiline (n = 6) | 5.60 \pm 3.81 | 44.6 \pm 28.4 | 15.0 \pm 17.8 | 18.4 \pm 14.7 | 100 \pm 49.2* | 7.02 \pm 5.86* |

P 1 = Study Period 1; P 2 = Study Period 2; Ratio = P 2/P 1 - ratio; * n = 4

The data shown indicate that there is a high inter- and probably also intra-individual variability in the tyramine plasma concentrations in each treatment group and also at each tyramine dose level. Whereas during placebo administration the tyramine plasma concentrations remain nearly unchanged during Period 1 and Period 2, they always increased in period 2 under both TVP-1012 administrations and under the selegiline administration. It appears from the data, that the effect on tyramine plasma concentrations is dose dependant in the two TVP-1012 groups and comparable between the 2 mg TVP-1012 dose and the 10 mg selegiline dose. Tyramine plasma concentrations increased in the presence of selegiline and also dose- dependently in the presence of TVP-1012. The effects seem to be similar at 2.0 mg TVP-1012 and 10 mg selegiline.

Plasma DHPG Levels

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Table 13 presents the DHPG plasma concentrations under the different treatments and their Period 2 / Period 1 - ratio.

Table 13 Mean (\pm SD) of DHPG plasma levels (pg/ml) and ratio

| Treatment | Period 1 Placebo | Period 2 Study Drug | Period 2/Period 1 Ratio |
|------------------|---------------------|------------------------|----------------------------|
| Placebo | 897 \pm 205 | 931 \pm 157 | 1.07 \pm 0.27 |
| 1 mg TVP-1012 | 869 \pm 143 | 949 \pm 278 | 1.09 \pm 0.26 |
| 2 mg TVP-1012 | 974 \pm 323 | 945 \pm 253 | 1.01 \pm 0.31 |
| 10 mg selegiline | 1039 \pm 292 | 849 \pm 195 | 0.86 \pm 0.27 |

The data show that only after administration of 10 mg selegiline, a small drop in DHPG plasma concentration was observed, indicating a slight MAO-A inhibitory effect. No change in DHPG plasma concentration was observed following both TVP-1012 administrations.

Inhibition of Platelet MAO-B

The sponsor noted that samples (human platelets of subjects) collected to provide an index of inhibition of MAO-B by rasagiline were not presented because samples collected and to be assayed by another institution were lost.

Pharmacokinetic (PK) Evaluation

Table 14 summarizes the descriptive statistics (mean \pm SD) of t_{max} , C_{max} , and AUC of plasma rasagiline (PAI) at steady state at Day 10 in the 1 mg and 2 mg TVP-1012 groups. The data show that for both dose levels maximum plasma concentrations of rasagiline of about 5.8 ng/ml and 10.9 ng/ml, respectively, were reached in about 40 minutes. Although the increase in C_{max} was slightly less than dose-proportional, the AUC increased by a factor of about 4.2 from the 1 mg to the 2 mg dose level.

Table 14 Mean \pm SD values of main Pharmacokinetic Parameters of Plasma Rasagiline (PAI) after Multiple Oral Administration of TVP-1012 at Day 10 (Steady State) of Study

| Parameter | 1 mg TVP-1012 | 2 mg TVP-1012 |
|-------------------|-----------------|------------------|
| t_{max} (h) | 0.58 \pm 0.20 | 0.67 \pm 0.26 |
| C_{max} (ng/ml) | 5.82 \pm 2.47 | 10.92 \pm 3.75 |
| AUC (ng/ml•h) | 5.51 \pm 1.83 | 23.01 \pm 3.40 |

Table 15 summarizes the descriptive statistics (mean \pm SD) of t_{max} , C_{max} , and AUC of plasma AI at steady state at Day 10 in the 1 mg and 2 mg TVP-1012 groups. The data show that for both dose levels maximum plasma concentrations of plasma AI of about 2.4 ng/ml and 5.3 ng/ml, respectively, were reached much later than that of the parent compound. Whereas the increase in C_{max} was nearly dose-proportional, the AUC increased by a factor of about 2.6 from the 1 mg to

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the 2 mg dose level.

Table 15 Mean \pm SD values of Main Pharmacokinetic Parameters of Plasma AI after Multiple Oral Administration of TVP-1012 at Day 10 (Steady State) of Study

| Parameter | 1 mg TVP-1012 | 2 mg TVP-1012 |
|-------------------|------------------|------------------|
| t_{max} (h) | 2.08 \pm 1.56 | 2.58 \pm 1.63 |
| C_{max} (ng/ml) | 2.37 \pm 0.54 | 5.32 \pm 0.51 |
| AUC (ng/ml·h) | 14.21 \pm 4.13 | 36.91 \pm 3.96 |

No formal statistical analysis was done on pharmacokinetic data. Due to the small number of subjects under TVP-1012 (n = 6 per dose group) and under the different tyramine doses only descriptive statistics were performed and no hypothesis testing was done.

Safety Evaluations (Adverse Events, Physical Examinations, ECGs, Blood Tests, Vital Signs)

An analysis of the adverse events (AEs) clearly showed that the main AEs were from cardiovascular system origin and within this system palpitation was the most frequently reported AE. It appears that there were no differences in this AE between the different treatment groups (Placebo, TVP-1012 or selegiline), but that the AEs are more related to the dose of tyramine. The other AEs were rare and occurred in few subjects only. A relationship of the AEs to the study drug was difficult to establish, however, in the opinion of the investigator a relationship between AEs and administration of the study medications could not be excluded in most of the events. The intensity of the AEs was generally mild or moderate and never severe.

There was one serious AE (SAE) in subject 616. On day 9 of period 1 this subject developed a paranoid reaction. The subject was hospitalized in psychiatric unit for 3 weeks. This subject has only received placebo and a dose of 50 mg tyramine. This subject did not have any related medical history. There were no deaths, or other clinically relevant events observed during this study.

Physical examinations, performed at screening, during the study and at the end-of-study examination revealed no clinically relevant abnormalities.

Generally all ECG recordings gave normal results. Few subjects, however, showed minor deviations from normal ranges being of no clinical relevance and these minor deviations were presented in a listing.

Generally, analyses of hematological and biochemical/clinical chemistry parameters gave normal results. Few subjects, however, showed minor deviations from normality and were not considered by the sponsor to be of clinical relevance.

All subjects presented normal urinalysis examination results. The tests for screening for drugs of abuse gave also negative results in all subjects.

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Descriptive statistics of hemodynamic parameters, such as supine pulse rate (PR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in the supine and standing positions at screening, at study completion and after the different drug administrations. There were no differences in vital signs between the screening and the end-of-study examination in all subjects. Also when the days 1 to 7 of the different study periods and treatment schedules were compared, there were no clinically relevant differences between study groups or periods. Vital signs assessed in the supine and standing positions showed normal diurnal fluctuations.

8.2.3. Sponsor's Discussion and Conclusions of Study Results

Pharmacodynamics

Co-administration of tyramine increased similarly the systolic blood pressure in all four study groups. **Whereas the endpoint was reached at similar tyramine doses for the placebo and 1.0 mg TVP-1012 (rasagiline) groups, it was reached at lower tyramine doses for the 2.0 mg TVP-1012 and the 10 mg selegiline groups.**

The potentiation of tyramine plasma levels is comparable with 2 mg TVP-1012 and 10 mg selegiline, probably due to some peripheral blocking of its degradation.

Considering the comparability of the effects of 2.0 mg TVP-1012 and 10 mg selegiline, it can be concluded that a daily dose of 2.0 mg TVP-1012 can be administered in further clinical trials without tyramine restrictions.

Pharmacokinetics

Definite conclusions on the dose-dependency of the pharmacokinetics of TVP-1012 and its metabolite are difficult to draw due to the small subject number and the administration of only two dose levels (1.0 mg and 2.0 mg TVP-1012). In addition, when the pharmacokinetics were assessed, TVP-1012 was always given together with tyramine. However, it appears that the pharmacokinetics of the parent drug TVP-1012, are dose-dependent with a less than dose-proportional increase in C_{max} and a more than dose-proportional increase in AUC. For the metabolite A1, AUC values also increased more than dose-proportionally. Based on previous PK studies it is known that the t_{max} of rasagiline (PAI) could be 20 minutes. As in this study, the first blood samples were taken as soon as 30 minutes after drug administration, this could explain the lower C_{max} as compared to other PK studies.

Safety

The tolerability of 1.0 mg and 2.0 mg TVP-1012 was good in the present study. No adverse events clearly attributable to the study medication were observed. The tolerability was comparable to that of placebo or 10 mg selegiline. Minor increases in transaminases (aminotransferases) were of no clinical relevance and resolved spontaneously. There were no particular effects on vital signs, ECG parameters or other laboratory parameters. The most frequent AE observed was palpitation which is frequent with blood pressure enhancing drugs and, therefore, most probably due to tyramine.

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The overall tolerability of TVP-1012 during this study was good and comparable to that of placebo or selegiline. There were no indications to suggest that TVP-1012 causes any clinically significant modification of hemodynamic, electrocardiographic, hematological, biochemical, or clinical parameters.

The majority of the AEs were experienced after the administration of the higher doses of tyramine and are well-known AEs for systolic blood pressure increasing agents (palpitations). Nearly all other AEs are frequently found in subjects taking part in clinical trials. In addition, none of the AEs was severe or serious in nature.

There were some slightly out of range values for transaminases activities during the study. However, none of the laboratory tests showed any clinically relevant out of range values at any time-point throughout the study and they normalized spontaneously even under treatment.

8.2.4. Reviewer's Comments

I have several problems/concerns with the design, conduct, and/or analysis of this study and will provide my comments on these various concerns.

- The achievement of the protocol specified endpoint (i.e. ≥ 30 mm Hg systolic blood pressure increment) was based upon a single systolic blood pressure reading collected after the pre-treatment value before tyramine was administered. This is a precarious endpoint because subjects could mount a single increment at that threshold due to an acute stress response. Requiring that the increment occur over a more sustained period such as 3 consecutive increments at or above the specified threshold is a way of trying to decrease the chances of the increment of being a false positive and increasing the chances of the response of being a true positive. This criterion has been used previously by other investigators and is an approach that I strongly endorse.

The final study report and analyses contained were complicated by mentioning that "clinical criteria" were also applied. However, the second approach for establishing the main study endpoint specifically noted that the protocol specific blood pressure increment was applied AND / OR clinical criteria (4 of which were described in the results section). This description did not say that clinical criteria described were systemically applied but gave the option of using the protocol specified blood pressure increment OR clinical criteria. **After much initial confusion and discussion about the application and use of the "clinical criteria," I have confirmed that clinical criteria were never systemically applied to determining endpoints for all subjects during the conduct of the study (that was completed before the criteria were formally mentioned) nor in the analyses.** It appears that the investigator of this study deviated from the protocol in a few instances and gave subjects higher doses of tyramine because he thought the initial 30 mm Hg systolic blood pressure increment was not a true positive response to tyramine. It seemed to me that the sponsor then devised the clinical criteria to try to account for the protocol violations/deviations of the investigator.

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Of interest, the first clinical criterion did not seem logical. This criterion provided that if a subject met the protocol specified systolic blood pressure increment without an “adverse cardiovascular experience” (that was not defined), then the subject should receive a higher dose of tyramine and if the protocol specified blood pressure increment was achieved again, that higher tyramine dose would be recorded as the threshold dose. If this occurred, then I would have expected that the higher tyramine dose would have demonstrated that the initial increment observed was a true positive and thus the lower tyramine dose should have been recorded as the true threshold dose. My view is that attention should be paid only to the strict protocol specified blood pressure increment criterion and that no significant attention should be given to the “clinical criteria.”

It is also of interest to note that the tyramine threshold data and TSF ratios for individual subjects were not included in the final study report for this study but were contained in a summary document (Appendix 18.2 of the Integrated Summary of Safety - ISS). Furthermore, when these data were presented, the results were noted to be “clinical criteria.” A data listing showing tyramine threshold data and TSF ratios for individual subjects based upon the protocol specified systolic blood pressure increment was only provided by the sponsor following request from DNDP!

- The sponsor had included calculations of mean TSF when subjects did not experience a protocol specified blood pressure increments and arbitrarily assigned tyramine doses as threshold doses. I do not think that this is advisable and thus have focused on evaluating TSF only when protocol specified blood pressure responses were achieved. Although 27 subjects underwent tyramine testing in both periods, 10 did not achieve a protocol specified blood pressure increment in at least 1 period. The results of the tyramine challenges as reflected by mean TSF (based upon actual protocol specified TYR30 systolic blood pressure increments) show that the 1 mg rasagiline (N = 4) had a similar mean TSF – 1.3 as placebo – 1.1 (N = 5) and did not suggest tyramine potentiation. In contrast, mean TSF for rasagiline was 2.7 (N = 5) and for selegiline was 4.3 (N = 3) and these elevated ratios did suggest some tyramine potentiation. However, the number of subjects per treatment group is extremely limited and does not provide a good representation of what results might be if a much larger sample size had been studied and provided TYR30 threshold doses. This limited result suggests that there is an increase in tyramine sensitivity with the 2 mg rasagiline dose.
- I think that it is pertinent to point out that these results were derived from the study of a small number of young males (19-32 years, with average age of 23 – 27 for all groups). It would be highly desirable to assess the effect of rasagiline on a different demographic population consisting of both males and female and also older subjects, particularly considering that most patients using rasagiline are likely to be over 40. I base this comment on both pharmacokinetic and pharmacodynamic considerations. There are minimal data in which pharmacokinetic parameters of rasagiline were studied in formal PK studies comparing males and females during multidosing and these data showed that rasagiline exposure (i.e. AUC_{last}) was nearly 70 % higher in females. Population PK data also suggest that rasagiline exposure increases by ~ 1 % per year of age. There were

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no formal PK studies of rasagiline to assess the effect of age on PK parameters. Thus, these data suggest that females and older individuals may experience somewhat higher rasagiline exposure. Considering the preliminary findings of this tyramine study that subjects exposed to a higher dose of rasagiline seemed to develop an increase in tyramine sensitivity, it is possible and I would expect that mean TSF for both doses would be higher if larger numbers of subjects were studied and these subjects included females and older individuals up to 70 year. It is also possible that there could be a greater sensitivity to tyramine in elderly/older subjects. I am not aware of any data that have been collected or analyzed that address this issue. Given all these observations, it would be important to study tyramine sensitivity after rasagiline treatment in older (e.g. 40-70 years) males and females.

- It is relevant to note that the selegiline that was used as a comparator was administered as a single 10 mg dose rather than as 5 mg BID (at morning and lunchtime) according to the U.S. label. I am not aware of data that have shown whether this makes a difference in extent of tyramine potentiation (i.e. TSF). Although 10 mg selegiline (an irreversible selective MAO-B inhibitor) is not generally considered to exhibit any significant MAO-A inhibition, surprisingly there are no published studies that have characterized the TSF when selegiline is dosed BID. Various publications, that are extremely heterogeneous in many study design issues, have shown that swallowed selegiline (10 mg QD - Eldepryl) is associated with a TSF ranging between 2 – 4 in response to oral tyramine administered under fasting conditions. In addition, 2 fasting tyramine studies in NDA 21479 (Zydis selegiline) found a mean TSF of 2.7 and 3.6 for a single dose of 10 mg selegiline. An unpublished tyramine challenge study (while fasting) conducted by the sponsor (Somerset Pharmaceuticals) of selegiline (i.e. Eldepryl) in which selegiline was administered as 5 mg BID showed a TSF of ~ 2. This result, however, contrasts with that of another sponsor (Elan Pharmaceuticals, NDA 21479 for Zydis selegiline) that found that swallowed selegiline (i.e. Eldepryl) administered as 5 mg BID showed a 6.8 mean TSF and this result was similar to the mean TSF result (6.7) for the lowest dose (1.25 mg/day) of Zydis selegiline. Although it is not clear why there might be a somewhat different TSF result for when 10 mg of selegiline is administered as a single dose instead of 2 divided doses, I consider this question to be yet unresolved.

The mean TSF (based upon tyramine threshold doses associated with actual protocol specified systolic blood pressure increments) was similar for 1 mg/day rasagiline (1.3; N = 4) and for placebo (1.1; N = 5) in the study under review. In contrast, the mean TSF for 2 mg/day rasagiline (2.7; N = 5) and for selegiline (4.3; N = 30) was elevated. These results suggest that there is some tyramine potentiation with the higher dose of rasagiline likely related to some inhibition of MAO-A. The results of only 3-5 subjects per treatment group do not permit an opportunity to observe a variable range of responses. Thus, the extremely small number of subjects in each treatment group do not allow one to draw firm conclusions about the potential for rasagiline to increase the sensitivity to tyramine and the magnitude of the increase for each dose. I consider these results as only very preliminary in suggesting that 1 mg/day rasagiline does not increase tyramine sensitivity and 2 mg/day does increase tyramine sensitivity.

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- In response to my request, the sponsor provided additional analyses of individual subjects for the ratio (Period 2 / Period 1) of their maximal systolic blood pressure responses to all doses of tyramine administered to each treatment group. Mean ratios of each treatment group are shown in Table 16. Mean ratio for 800 mg tyramine was not shown because minimal data were available for these calculations. Whereas the mean ratio of the 1 mg rasagiline group only exceeded all placebo mean ratios at the highest dose of tyramine (400 mg), the mean ratios for 100, 200, and 400 mg tyramine doses in subjects treated with 2 mg rasagiline and 10 mg selegiline were greater than all placebo mean ratios. These result in selegiline and high dose rasagiline groups suggested an effect of treatment consistent with some inhibition of MAO-A. Included in the mean calculations of individual subject ratios were rare, isolated ratios that exceeded 10 in all treatment groups except 1 mg rasagiline. This increased ratio did not seem to be consistently exhibited by the same subject with the exception of subject #617 (2 mg rasagiline group) who showed an increased ratio > 10 for the 100 and 200 mg tyramine challenges (subject # 617 did not have ratios for higher tyramine doses).

Table 16 Mean of Individual Subject Ratio (Period 2 / Period 1) of Maximal Systolic Blood Pressure After Various Doses of Tyramine

| Treatment | Period 2 / Period 1 Ratio for Systolic Blood Pressure Maximal Change After Tyramine | | | |
|-------------------------------|---|----------|----------|----------|
| | 50 mg | 100 mg | 200 mg | 400 mg |
| Selegiline 10 mg Q Day | | | | |
| Mean All (N) | 4.20 (5) | 1.76 (5) | 3.69 (6) | 2.78 (5) |
| Placebo | | | | |
| Mean All (N) | 0.59 (9) | 0.99 (9) | 1.28 (9) | 1.24 (9) |
| Rasagiline 1 mg Q Day | | | | |
| Mean All (N) | 1.38 (6) | 1.17 (5) | 1.02 (5) | 1.86 (6) |
| Rasagiline 2 mg Q Day | | | | |
| Mean All (N) | - 1.03 (6) | 4.13 (6) | 3.97 (6) | 2.53 (4) |

- There is a question in my mind as to whether there may have been a problem with the biological potency of the sponsor's tyramine. It is of great interest and in my experience, highly unusual that 18 of 29 subjects either did not meet the protocol specified pressor response (i.e. ≥ 30 mm Hg systolic blood pressure increment) during period 1 or showed a tyramine threshold dose of 800 mg. Seven of these subjects did not show a tyramine threshold response in period 1 with sequential dosing up to 800 mg. **In NDA 21479, pre-treatment/baseline tyramine testing was conducted in 63 subjects in 4 treatment groups and none of these subjects required a tyramine dose > 700 mg to achieve a pressor response of ≥ 30 mm Hg systolic blood pressure increment. In another sponsor's NDAs (21336 and 21708), none of 21 subjects administered 2 pre-treatment/baseline tyramine tests each showed a tyramine threshold dose of ≥ 800 mg to achieve a pressor response of ≥ 30 mm Hg systolic blood pressure increment.**

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The mean pre-treatment tyramine dose ranged from ~ 400-600 mg in all these groups in these other NDAs. In addition, it is relatively uncommon in the published literature for subjects to require a dose of ≥ 800 mg tyramine to increase systolic blood pressure ≥ 30 mm Hg when tyramine is administered in the fasting state. **Thus, it is difficult for me to escape the conclusion that there may have been a problem with the biological potency of tyramine administered in this study for inducing a pressor response.** I was told that the supplier of tyramine HCl in this study and all of the sponsor's studies was

The sponsor also adopted a convention of arbitrarily assigning a tyramine threshold dose of 50 mg above the highest dose administered (e.g. 450 mg or 850 mg for 400 mg and 800 mg doses, respectively) in a period when the subject did not exhibit a protocol specified blood pressure increment. This convention has the potential of underestimating the increased tyramine sensitivity that might exist. For example, if the baseline/pre-treatment tyramine threshold is assigned as 450 mg and the post-treatment threshold is 100 mg, this subject would have a TSF of 4.5. However, if the subject's pre-treatment threshold is actually 1000 mg, then the TSF would really be 10, a TSF more than 2 fold higher than calculated based upon the sponsor's arbitrary convention. It is desirable that the TSF assigned be based upon actual data rather than arbitrarily assigned data. My experience with reviewing TSFs in NDAs and a considerable number of publications describing tyramine test results after drug treatment suggests that it is quite unusual not to have characterized a TSF ratio based upon actual data derived from achieving the specific change in vital sign (most commonly a systolic blood pressure increment of ≥ 30 mm Hg).

- The design of the present study administered increasing doses of tyramine on the same day at 3 hour intervals. Ideally, it would be better to administer tyramine challenges on separate days because of the possibility that responses might be less if exposure to tyramine challenge is repeated at relatively short intervals. In addition, this study used increasing tyramine doses that were doubling. Thus, after 200 mg the next doses were 400 and 800 mg. Other tyramine studies usually use 100 mg increments after 100 mg. This approach of using 100 mg increments would allow one to characterize a change in sensitivity more precisely than the more crude approach of this study.

It is also important to note that the sponsor started tyramine testing with 50 mg of tyramine. Often this testing after drug treatment begins with a lowest dose of ≤ 25 mg. Thus, by not giving subjects the chance of showing a tyramine threshold dose at such a low dose, this design of starting post-treatment tyramine challenge with 50 mg has the potential of underestimating the increased sensitivity to tyramine. Two subjects did show a tyramine threshold dose of 50 mg based upon a protocol specified increment in blood pressure.

- It is noteworthy that this study was not a typical, randomized trial in which all subjects were randomized to one of several treatments. This study was conducted serially by studying 3 groups of subjects (N = 9/group). The first group of subjects was to receive "low" dose rasagiline (1 mg/day) or placebo in a 2:1 randomization scheme (2 "active"

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drug : 1 placebo). The second group was to receive “high” dose rasagiline (2 mg/day) or placebo and the third group was to receive selegiline or placebo. A selegiline group was added as a protocol amendment. Thus, there was a potential bias of suspecting that 2/3 of subjects in each group were receiving “active” drug and the medical personnel would know what was the “active” treatment for each group. This design would seem to compromise to some extent the lack of bias associated with a randomized trial in which medical personnel do not have any idea what is the randomized treatment. The first period was also conducted under single blind conditions because the medical personnel knew that this was to collect baseline/pre-treatment tyramine data.

- The sponsor had provided graphs of systolic blood pressure response for each tyramine dose in each period. There were no individual blood pressure responses of any subject in any group that stood out as very unusual examples of hypertensive responses to the tyramine administered in the challenge with the exception of one subject (# 612) who exhibited an approximate 80 mm Hg rise in systolic blood pressure at 1 hour after 400 mg tyramine. This subject had been treated with 2 mg daily rasagiline.
- I also requested that the sponsor provide data analyses of responses based upon tyramine threshold dose (protocol) or highest tyramine dose administered. These analyses showed generally similar results as those presented by the sponsor in the final study report based upon “clinical criteria.” This is not too surprising considering that results in the “clinical criteria” analyses differed from those according to the protocol specified threshold criteria because of 3 subjects out of a total of 27 included in the analyses.
- The 4 mg/day rasagiline, the highest dose that was to be studied initially when the protocol was written, was never studied. Neither was 3 mg/day rasagiline studied. This dose was added as another group to be studied in 9/96 in a protocol amendment. The amendment explained the rationale for this dose as : “A mild interaction was observed between the tyramine and TVP-1012 at dose of 2 mg.” I have been told that the blood pressure data in response to tyramine had been examined according to groups (1, 2, or 3) and that group 2 appeared to include some different responses (despite the fact that data had not been unblinded as to specific treatment such as “active” drug or placebo).

In addition, protocol amendment 3 provided for adding exercise tolerance test at pre-treatment and protocol amendment 4 provided for adding cardiac echography test at pre-treatment and both had to be normal to be included in the trial. Despite these amendments, no additional subjects were studied. It had also been noted that the review of ECGs parameters under “blinded” conditions of groups suggested the possibility that rasagiline (during period 2) may have caused a dose-related exacerbation of an ‘ischemic’ response to tyramine observed in period 1. There was concern that this apparent effect may not have been linear with an increasing dose of rasagiline and the sponsor concluded that it would be inadvisable to advance to the 3 mg/day rasagiline dose. Thus, the sponsor completed a statistical analysis plan (that was not submitted) on November 13, 1996, locked the database and unblinded the data for analyses without ever studying higher daily doses (3 or 4 mg) of rasagiline.

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- The sponsor presented data on plasma tyramine levels in patients at 1 hour (recall mean T_{max} is 0.5 hrs and ranges from 0.33-1 hour) after oral administration. In general, these data (Table 11, Table 12) showed that the ratio of plasma tyramine in Period 2/Period 1 was typically higher after treatment with each active drug (rasagiline 1 and 2 mg and selegiline 10 mg). This plasma tyramine ratio appeared to be dose-dependently increased. In contrast, this ratio was not substantially elevated (1.0, 1.6, 1.7, 2.8 for increasing doses of tyramine). These data (i.e. measuring plasma tyramine levels during tyramine challenge testing of pressor responses) is relatively unique and potentially provides additional insight into the question about MAO-A inhibition. It is recognized that these data are based upon a relatively small number of subjects that showed significant intra- and inter-individual variability and mean plasma tyramine levels show not exhibit good linearity with dosing. Nevertheless, it appears that even the 1 mg rasagiline dose is usually associated with an increased plasma tyramine ratio compared to placebo and this observation suggests some inhibition of MAO-A, an observation not suggested based upon the small number of tyramine pressure results. In all instances, the increased plasma tyramine ratio for the 2 mg rasagiline dose is similar to that for selegiline of somewhat lower. It is of interest that the sponsor has interpreted the plasma tyramine data as suggesting some degree of MAO-A inhibition for both rasagiline doses and more for the higher dose but that the results for the 2 mg rasagiline are similar to those for 10 mg selegiline.
- It is interesting to note that C_{max} and AUC were considerably lower in this study for subjects treated with 1 mg rasagiline than results of another PK study of males. In contrast, the C_{max} and AUC associated with 2 mg rasagiline in this study were more similar to those obtained in another PK study of males. Thus, the possibility exists that the rasagiline-related tyramine sensitivity results observed with the small number of subjects treated with 1 mg in this study may not be accurately representative of results expected from 1 mg rasagiline.
- I do not have any other noteworthy or substantive comments to make about the PK results of the plasma measurements of rasagiline or its major metabolite, aminoindan.
- PK measurement of plasma DOPEG/DHPG, a metabolite derived from MAO-A acting on the precursor of plasma DOPEG/DHPG (i.e. DOPGAL) that is also a metabolite of norepinephrine, did not show significant decrements in the ratio of Period 2/Period 1 DOPEG for any of the treatments. There was a minimal decrease of this ratio (e.g. 0.9) associated with selegiline treatment. A decrease in the ratio of plasma DOPEG/DHPG would suggest MAO-A inhibition. However, my impression is that measurement of PK parameters in plasma and urine is a relatively crude index of MAO-A inhibition and PK samples are not as sensitive as the pharmacodynamic measure, sensitivity of pressor response to tyramine. I am not aware of data indicating that PK parameters are as or more sensitive than the sensitivity to tyramine challenge.
- I constructed Table 17 showing the frequency of cardiovascular adverse events (AEs) associated with the various treatments in both periods. There is no clear suggestion of an

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increase in the frequency of cardiovascular AEs in period 2 for any active treatment including rasagiline or selegiline.

Table 17 Frequency of Cardiovascular AEs Relative to Tyramine and Treatment Received

| Treatment | Tyramine Dose Administered | Tyramine 100 mg | | Tyramine 200 mg | | Tyramine 400 mg | | Tyramine 800 mg | |
|----------------------------------|----------------------------|-----------------|-----|-----------------|-----|-----------------|-----|-----------------|-----|
| | | Period 1 or 2 | P1 | P2 | P1 | P2 | P1 | P2 | P1 |
| Placebo N = 11 | Cardiovascular | | | | 1/1 | 3/3 | 1/1 | 4/3 | 7/4 |
| | Hypertension | | | | | | | | |
| | Palpitation | | | | 1/1 | 3/3 | 1/1 | 3/3 | 6/4 |
| | Vasodilatation | | | | | | | 1/1 | 1/1 |
| | Vasospasm | | | | | | | | |
| Rasagiline 1 mg/day N = 6 | Cardiovascular | | | | | 4/3 | 4/4 | 4/3 | 2/2 |
| | Hypertension | | | | | | | | |
| | Palpitation | | | | | 3/3 | 4/4 | 3/3 | 2/2 |
| | Vasodilatation | | | | | | | 1/1 | |
| | Vasospasm | | | | | 1/1 | | | |
| Rasagiline 2 mg/day N = 6 | Cardiovascular | | 1/1 | 1/1 | 1/1 | 1/1 | 5/3 | 5/3 | |
| | Hypertension | | | | | | 1/1 | | |
| | Palpitation | | | | | | 4/3 | 5/3 | |
| | Vasodilatation | | 1/1 | 1/1 | 1/1 | 1/1 | | | |
| | Vasospasm | | | | | | | | |
| Selegiline 10 mg/day N = 6 | Cardiovascular | | | | | 2/2 | 4/3 | | 1/1 |
| | Hypertension | | | | | | | | |
| | Palpitation | | | | | 2/2 | 4/3 | | 1/1 |
| | Vasodilatation | | | | | | | | |
| | Vasospasm | | | | | | | | |

Frequency of events/Number of subjects with respective event
Abstracted from sponsor's Tables 17-20 in final study report

- My overall impression based upon results of this study is that there are data that suggest some degree of MAO-A inhibition with rasagiline. The TSF ratios and plasma tyramine data suggest dose-dependent MAO-A for 2 mg rasagiline and the plasma tyramine data suggest some MAO-A inhibition with 1 mg rasagiline. Although the sponsor is presently only seeking approval for 1 mg rasagiline, there is a definite need for better quantitative characterization of the extent MAO-A inhibition. Such characterization is not only relevant but necessary for the 1 mg rasagiline dose primarily because of major, significant limitations in the scope of the data generated. A larger, more comprehensive randomized, double-blinded, placebo-controlled trial should be conducted prior to approval.

It is also potentially relevant to note that a report of the TEMPO monotherapy trial including the randomized, double-blinded, placebo-controlled phase and double-blinded,

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active extension phase has recently been published. This publication suggests that 2 mg daily of rasagiline therapy may delay disease progression in patients with early Parkinson's Disease. **Thus, it seems likely that 2 mg daily rasagiline would be used off-label to delay disease progression if rasagiline was approved for monotherapy and adjunctive therapy of Parkinson's Disease with highest recommended daily dose of 1 mg. This observation further supports the need for fully and accurately characterizing rasagiline's effect on tyramine sensitivity prior to approval so that the risk of a hypertensive "cheese" reaction from rasagiline treatment can be more reasonably assessed.**

In addition, the inspection of this study site by the Division of Scientific Investigations (DSI) (see section on : FDA Bioresearch Monitoring Program Inspections for detailed summary) did not add any reassurance as to the quality of the data collected at this site. The inspection concluded that:

1. The site lacked documentation of the actual foods consumed by the subjects during study participation. Although the site claimed that protocol requirements regarding fasting conditions were met, there was no written assurance that fasting or dietary restrictions were met based upon data recorded in the CRFs.
2. There was no assurance that blood pressures were taken at the times defined by the protocol in that the site failed to document the actual times of manual measurements, and did not verify that automated measurements conformed to the protocol defined times.

8.2.5. Reviewer's Conclusions

- The increased tyramine sensitivity (i.e. TSF) and plasma tyramine level results of this study during rasagiline treatment suggest some inhibition of MAO-A during treatment with rasagiline.
- An increased mean TSF associated with 2 mg daily rasagiline treatment and a greater increased ratio of plasma tyramine with 2 mg daily rasagiline (vs 1 mg daily) shows the dose-dependent nature of this MAO-A inhibition.
- Numerous limitations in the conduct and design of this study provide only a preliminary characterization of MAO-A inhibition and the risk for a hypertensive "cheese" reaction (related to increased tyramine sensitivity from MAO-A inhibition) associated with rasagiline treatment.
- Additional, more precise, quantitative characterization of the increase in tyramine sensitivity associated with rasagiline treatment needs to be conducted prior to approval of rasagiline. Ideally, this characterization should be derived from conducting a randomized, double-blinded, placebo-controlled trial of a larger number of older males and females challenged initially with a lower dose of tyramine dose (e.g. 25 mg) under fasting conditions.

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8.3. Study TVP-1012/132

8.3.1. Description of Protocol TVP-1012/132

Title of Study : Pharmacodynamic Interaction Between Oral Rasagiline Mesylate (TVP- 1012) and Oral Tyramine in Parkinsonian Patients using Levodopa/ Carbidopa

Study initiation date : 3/16/98
Study completion date : 4/14/00

Objectives

Primary Objective :

The primary objective of this clinical pharmacology study was to evaluate the safety and tolerability of 1 and 2 mg/day rasagiline mesylate (TVP-1012) when given with oral tyramine mixed with food to Parkinsonian patients on chronic LD/carbidopa therapy.

Safety evaluations were to be based on:

1) Adverse Experiences 2) Clinical Laboratory Parameters 3) Intensive Blood Pressure and ECG Monitoring

Secondary Objectives :

The secondary objectives of this study were to evaluate:

- 1) Pharmacokinetics of TVP-1012 (PAI) and its major metabolite (AI) during a 70 day treatment period at a daily dose of 1 or 2 mg in patients on chronic levodopa/carbidopa
- 2) Pharmacodynamics of TVP-1012 as measured by platelet MAO-B inhibition.
- 3) Pharmacokinetics of levodopa in TVP-1012 treated patients in comparison to the Pharmacokinetics before initiation of TVP-1012 therapy
- 4) The changes in Unified Parkinson Disease Rating Scale (UPDRS), Quality of Life Scale and On/Off Fluctuation Diary

Study Design

This double-blind, placebo-controlled, randomized study was designed to examine the safety, tolerability and efficacy of rasagiline in Parkinsonian patients on chronic levodopa (LD)/carbidopa therapy. Eighteen patients were to be enrolled. One group of 9 patients were to be randomly assigned to receive 1 mg rasagiline or placebo per day. Following satisfactory completion of the in-patient period of the 1 mg/day group (see below), another group of 9 patients were to be randomly assigned to receive 2 mg rasagiline or placebo per day. In each

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group of 9 patients, 6 were to be randomly assigned to active drug and 3 to placebo. They were to continue to receive their normal LD/carbidopa dose. Drop-outs prior to the completion of Visit 6 (Day 24) were to be replaced. All patients were to receive study drug or placebo for a period of 10 weeks (70 days) with daily blood pressure assessment. During the first 3 weeks of the study, patients were to be out-patients on a restricted tyramine diet. On the morning of Visit 4 (Day 22+ 3 days), the subjects were to enter the clinical pharmacology unit of Pennsylvania Hospital where they were to reside as in-patients for a period of 3 days. During this period, patients were to be on a very low tyramine diet. A controlled dose of tyramine was to be added to a standardized morning meal according to the following schedule: Visit 4: 25 mg; Visits 5: 50 mg and Visit 6: 75 mg. Prior to receiving tyramine, subjects will receive their normal dose of LD/carbidopa and their assigned dose of rasagiline or placebo. Intensive cardiovascular and pharmacokinetic/ pharmacodynamic evaluations were to be performed. Patients were to be released from the clinical pharmacology unit at the completion of the Visit 6 evaluations. Figure 2 outlines key features of the study design.

Subjects were to continue on their study medication and were to be followed as out-patients while on an unrestricted tyramine diet for the following 46 days. Evaluations were to be performed on Days 42, 56 and 70 (each + 3 days). Study medication were to be discontinued after Day 70 (Visit 9). Safety and pharmacodynamic activity were to be evaluated at post-drug follow-up visits on Days 84 and 98 (each + 3 days). No new Parkinsonian therapy could be started until completion of the final (Day 98) follow-up Visit 11.

Figure 4 Study Design

| Visit | Screening | Screening | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|-----------|-----------|---|---|----|-------|-------|-------|----|----|-------|----|----|
| Day | - 2 weeks | -7 | 1 | 7 | 21 | 22 | 23 | 24 | 42 | 56 | 70 | 84 | 98 |
| Tyramine | | 75 mg | | | | 25 mg | 50 mg | 75 mg | | | 75 mg | | |
| Tyramine restricted diet for 24 days | | | | | | | | | | | | | |
| Rasagiline (1 or 2 mg/day) or placebo were administered for 70 days | | | | | | | | | | | | | |

Assessments

1. Pharmacokinetic/Pharmacodynamic Sampling

LD Pharmacokinetics:

Day -7: Prior to taking morning dose of LD and 0.5, 1, 2 and 4 hours after

Day 1: Prior to taking morning dose of LD and 0.5, 1, 2, and 4 hours after

Day 23: Prior to taking morning dose of LD and 0.5, 1, 2, 4, 8, 12 and 24 hours after

Day 70: Prior to taking morning dose of LD and 0.5, 1, 2, and 4 hours after

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TVP-1012 (PAI and AI) Pharmacokinetics: Day 1: Prior to taking study drug and 0.5, 1, 2, and 4 hours after Day 23: Prior to taking study drug and 0.5, 1, 2, 4, 8, 12 and 24 hours after Day 70: Prior to taking study drug and 0.5, 1, 2 and 4 hours after

MAO-B Inhibition: Day 1: One sample drawn before study drug is taken Day 22: One sample drawn before study drug is taken Day 70: One sample drawn before study drug is taken Day 84: One sample taken during visit Day 98: One sample taken during visit at Day 1 is also taken.

Serum Potassium Levels: Day -7: Prior to ingesting tyramine. No further samples taken unless tyramine interaction occurs. In the event of this interaction, potassium samples were to be taken at 0.5, 1, 2 and 4 hrs after taking tyramine Day 22: Same Day 23: Same Day 24: Same Day 70: Same

2. Other Assessments :

- Laboratory tests
- Telemetry: 3-lead ECG, BP and HR
- Chest X-ray
- Physical Exam
- Vital Signs: Supine, sitting and standing BP and HR
- 12 Lead ECG
- BP Diaries
- UPDRS
- Hoehn 8 Yahr
- Schwab 8 England ADL
- Quality of Life
- "On"/"Off " Diaries

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Figure 5 Schedule of Events / Assessments

| Study Schedule | Washout | | Out-Patient Period 1 | | | In-Patient Period 2 | | | Out-Patient Period 3 | | | Washout Period 4 | |
|----------------------------------|---|----------------|----------------------|----------|-----------|---------------------|----------------|----------------|----------------------|-----------|-------------------|------------------|------------|
| | Screening V0 | Day -7 V-1 | Baseline Day 1 V1 | Day 7 V2 | Day 21 V3 | Day 22 V4 | Day 23 V5 | Day 24 V6 | Day 42 V7 | Day 56 V8 | Day 70 of Term V9 | Day 84 V10 | Day 98 V11 |
| | Informed Consent Demography/Eligibility | X | | X | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | |
| TYP-1012 | | | X | X | X | X | X | X | X | X | X | | |
| Neurological Exam | X | | | | | X | X | X | X | X | X | | |
| Quality of Life | | | X | | X | | | | | | X | | X |
| UPDRS, H&Y, S&E | X | | X | | | | | | X | | X | | X |
| On/Off Diaries | | X | X | X | X | | | | X | X | X | X | |
| Previous Concomitant Meds | X | | | | | | | | | | | | |
| Tyramine In morning meal | | X ¹ | | | | X ² | X ³ | X ⁴ | | | X ⁵ | | |
| Low Tyramine Diet | | | X | X | X | | | | | | | | |
| Unrestricted Tyramine Diet | | | | | | | | | X | X | X | X | X |
| Blood Pressure Diary | | X | X | X | X | | | | X | X | X | X | X |
| Vital Signs | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical Exam | X | | | | | X | X | X | X | X | X | X | X |
| ECG | X | X | X | X | | X | X | X | X | X | X | X | X |
| Telemetry | | | | | | X | X | X | | | X | | |
| X-Ray | X | | | | | | | | | | | | |
| Lab Tests | X | | X | | | X | | | | | X | | |
| Serum Potassium | | X ⁶ | | | | X ⁶ | X ⁶ | X ⁶ | | | X ⁶ | | |
| MAO-B Activity | | | X | | | X | | | | | X | X | X |
| PAI & AI Pharmacokinetics | | | X | | | | X ¹ | | | | X | | |
| Levodopa Pharmacokinetics | | X ¹ | X | | | | X ¹ | | | | X ¹ | | |
| Adverse Events | | | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant Meds | | | X | X | X | X | X | X | X | X | X | X | X |
| Compliance & Drug Accountability | | | | X | X | X | X | X | X | X | X | | |

X¹ - Samples taken prior to L/C and 0.5, 1, 2 & 4 hr after.

X² - 25 mg tyramine

X³ - 50 mg tyramine

X⁴ - 75 mg tyramine

X⁵ - Samples taken prior to L/C & study drug and 0.5, 1, 2, 4, 8, 12 and 24 hr after

X⁶ - Baseline potassium taken. Samples to be taken at 0.5, 1, 2 and 4 hr only in the event of a tyramine interaction

Shaded areas represent procedures performed at Pennsylvania Hospital In-Patient Unit

Study Sites : 1

All out-patient visits (Screening, and Days 1, 7, 21, 42, 56, 70, 84, and 98) were to be performed at the office of:

Matthew Stern, MD Parkinson's Disease and Movement Disorder Center at Pennsylvania Hospital 700 Spruce Street, Suite 305 Philadelphia, PA 19106

The Day -7 and Day 70 outpatient visits and all in-patient visits (Days 22, 23 and 24) were to be performed at the clinical pharmacology unit at:

Pennsylvania Hospital 800 Spruce Street Philadelphia, PA 19106

Patient Selection

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Prior to or at the Screening Visit, all patients were to sign an Institutional Review Board (IRB) approved Informed Consent Form. At the Screening Visit a complete medical history was to be recorded, physical and neurological examinations were to be performed and laboratory tests and other required procedures were to be performed to ensure that the patient meets the following enrollment criteria.

Inclusion Criteria :

1. Medical Status: Patients must have diagnosed idiopathic PD and be on chronic levodopa/carbidopa therapy (minimum dosage of carbidopa is 75 mg per day) for at least three months and on a stable dose for at least 60 days prior to randomization. The severity of the disease must be of stage 1 - 4 according to Hoehn and Yahr staging (see Appendix II). Patients may experience daily clinical motor response fluctuations to levodopa/carbidopa therapy requiring up to 6 levodopa/carbidopa administrations daily.
2. Sex: Patients may be male or female. Women must be post-menopausal or surgically sterilized or use an adequate method of contraception. Women of childbearing potential must have a negative pregnancy test (beta-HCG) prior to entry into the study.
3. Age: 35-80.
4. Patients must be willing and able to give signed written informed consent.
5. Patients who, before randomization, have had:
 - a 60 day washout period from selegiline or other MAO-B inhibitors
 - a six-week washout period from:
tricyclic antidepressants fluoxetine or other selective serotonin reuptake inhibitors
 - a two-week washout period from
pethidine and dextromethorphan
sympathomimetic drugs (including nose and eye drops) gentamycin

Patients must be clinically stable and be on stable anti-Parkinsonian medications (i.e., stable dose of levodopa/carbidopa, dopamine agonist, anti-cholinergics or amantidine) for at least 60 days prior to randomization.

Exclusion Criteria :

Any of the following was to exclude the patient from participation in the study:

1. Patients who do not tolerate selegiline.

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2. Clinically significant unstable cardiovascular/vascular diseases such as:

- Uncontrolled hypertension with the following blood pressure: Systolic blood pressure > 150 mm Hg and/or Diastolic blood pressure > 90 mm Hg
- Orthostatic hypotension (asymptomatic 30 mm Hg systolic difference or symptomatic 20 mm Hg systolic difference)
- Known secondary malignant hypertension
- Clinically significant arrhythmia
- Ischemic Heart Disease (including angina pectoris) or recent myocardial infarction (within last 12 months)
- Cardiomyopathy
- NYHA Class II or greater heart failure (see Appendix XII).
- Unexplained syncope within the past 6 months
- Coagulation disorders (i.e., bleeding disorders, thrombotic disorders)
- Symptomatic valvular heart disease

3. History of cerebrovascular accident

4. Clinically significant pulmonary, gastrointestinal, hepatic or endocrine disorder.

5. Any evidence of clinically significant abnormal renal function.

6. Life-threatening malignancy and terminally ill patients.

7. Psychiatric illness which compromises ability to give informed consent or to complete study.

8. Patients exhibiting psychoses (as defined by the DSM IV) and/or hallucinations.

9. Patients exhibiting dementia.

Patients exhibiting depression potentially requiring therapeutic intervention during the trial.

Participation in another clinical trial during the previous 3 months.

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12. Patients who are unable or unwilling to comply with the protocol requirements or are considered by the investigator to be unfit for the study.
13. Patients who use any substances of abuse.
14. Patients who have donated blood within 60 days prior to Screening.
15. Patients who have had neurosurgery relevant to Parkinson's disease (e.g., pallidotomy).

Dosage Regimen

Rasagiline (or placebo) was to be taken orally each morning, at least 30 minutes before breakfast, with 8 oz. of water, except the day of visit to the study center. The subject was to take the first dose of study medication at the baseline (Day 1) Visit 1. Thereafter, medication dispensed the day of the visit was to be started one day after the visit. On in-patient Visits 4, 5 and 6, rasagiline or placebo was also to be taken 30 minutes prior to breakfast.

1 mg rasagiline dose was to be administered as one 1 mg rasagiline tablet. 2 mg rasagiline dose was to be administered as one 2 mg rasagiline tablet. Placebo was to be administered as tablets identical to the rasagiline tablets.

At Visits -1 and 9 and in-patient Visits 4, 5 and 6, tyramine was to be administered to the subject by opening the unsealed tyramine capsule, emptying the entire contents of the capsule(s) into appropriate very low tyramine breakfast food (e.g., applesauce, 4 oz) and mixing well. Note that on Visit 5 (Day 23), two 25 mg capsules were to be used to deliver a total dosage of 50 mg tyramine. One tyramine capsule was to be used at Visit -1 (75 mg), Visit 4 (25 mg), Visit 6 (75 mg) and Visit 9 (75 mg). Patients were supposed to consume the entire portion of tyramine-containing food.

During the study, the subject was to use his or her own supply of LD/carbidopa, at the usual dose and time of day, except for days of visits to the study center. On those visit days, the subject was to refrain from taking LD/carbidopa until arrival at the study center, and was to take the LD/carbidopa at the same time that the rasagiline was administered. Likewise, on in-patient Visits 4, 5 and 6, the subject's LD/carbidopa was to be administered at the same time that the rasagiline was taken.

Specific Conduct of Study

Visit 4 - Day 22 (Day 19 - Day 25) - Pennsylvania Hospital

Early on the morning of Day 22 (+ 3 days) the patient were to refrain from taking the study medication and levodopa/carbidopa and were to report to the study center in the fasting state for Visit 4. The following procedures were to be performed.

- Vital signs (supine, sitting and standing)

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- Recording of concomitant medications
- Recording of adverse events

The patient was to be made comfortable in bed in a supine position (the head of the bed may be elevated up to 45 degrees); however, it was important that the same degree of elevation was to be maintained for all cardiovascular evaluations on this day and Visits 5 and 6. Leads for telemetric monitoring of BP, HR and ECG will be applied. A baseline 12-lead ECG was to be performed.

Blood samples for routine clinical lab tests and MAO-B activity will be drawn.

The subject was to take his/her assigned study medication and levodopa/carbidopa dose at this time. One half hour later, a baseline serum potassium was to be drawn and the patient was to be served a standardized morning meal in which 25 mg of tyramine has been mixed in one of the low tyramine foods (e.g., applesauce). Additional serum potassium samples were to be drawn in the event of an interaction.

The following cardiovascular evaluations were to be performed:

- **Telemetry: ECG, BP and HR were to be recorded every five minutes for the first two hours after tyramine ingestion, then every 15 minutes for the following two hours.**
- 12-lead ECGs: performed at 0.5, 1, 2 and 4 hours after tyramine ingestion. An ECG will be done at 6 hrs in the event that changes on prior ECGs are observed, and at the onset and conclusion of any cardiovascular reaction.
- Supine, sitting and standing BP and HR: recorded at 2, 4, 6, 8 and 12 hours after tyramine ingestion.

On in-patient Visits 4, 5 and 6, patients will be served meals and snacks with low tyramine content.

The same specific procedures were to be followed on days 23, 24, and 70 (or termination visit) with the exception that 50 mg tyramine was to be given on day 23 and 75 mg tyramine was to be given on days 24 and 70 (or termination visit). In addition, multiple PK blood samples were obtained for rasagiline and LD at various times up to 24 hours.

At day 70/visit 9 or termination visit, the patient was to be discharged with instructions to report immediately to the neurologist's office for the remainder of the scheduled Visit 9 assessments. In the event that the patient experiences a tyramine interaction or other adverse event, or if it is not possible for the patient to see the neurologist immediately after the above visit to Pennsylvania Hospital, patient will be discharged to home and will continue to take study medication. Patient must return within 3 days to the neurologist's office.

At the day -7 visit a digital blood pressure monitor was to be given to the subject for home self readings of blood pressure and pulse. Patient was to be instructed in the use of the home blood

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pressure monitor and the correct completion of the BP diaries. Sufficient diaries were to be dispensed for completion. Patient were to begin recording BP and HR this evening. **Twice a day during the study the subject was to measure his blood pressure: once in the morning about one hour after taking study medication and LD/carbidopa and once in the evening after dinner.** The subject should have measured his blood pressure after he/she had been sitting for five minutes; recording was to be made on the same arm throughout the study. Patients will record the times and BP and HR readings in a diary, which was to be brought to the study site at each visit to be reviewed by the investigator. In addition, the patient was to be instructed to measure his/her BP and notify the site immediately in the event of persistent, severe headache, difficulty breathing or chest pain, lightheadedness, abrupt visual disturbances (such as blurring of vision, double vision or loss of visual field). Should the patient record duplicate blood pressures of > 150/90, he or she should have contacted the investigator. If the patient recorded a high BP (i.e., systolic > 170 mm Hg and/or diastolic > 110 mm HG for duplicate readings) the patient was to be evaluated by the investigator immediately. (If an MAO-B inhibitor-tyramine interaction was suspected, the patient could be treated with a rescue protocol). Study medication could be stopped until the patient was examined by the investigator.

Discontinuation of Study Therapy

Completed Patients

A completed study patient was defined as a patient who had met the inclusion criteria of the study, and had successfully completed 10 weeks of active drug treatment under this protocol.

Treatment Discontinuations

If a patient potentially meets any study termination criteria, the Sponsor was to be informed and a decision was to be made whether to discontinue participation in the study.

Study termination criteria were as follows:

- a. Subject with any clinically significant or intolerable adverse event. This included but was not limited to: sustained (\approx 24 hours) hypertension (>160/100 mm Hg); sustained bradycardia (<50 beats/minute); development of new, clinically significant ECG abnormality; occurrence of a tyramine/MAO inhibitor reaction requiring pharmacological intervention
- b. Subject refusal to continue for whatever reason
- c. Investigator's judgment that continued treatment was not in the best interest of the patient.
- d. Pregnancy
- e. Poor compliance with study drug administration or study visits

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A full explanation for discontinuation of therapy was to be documented in the CRF. All efforts should have been made to evaluate a subject at the time of premature termination from the study. Patients who were terminated prior to Day 25 were to be replaced.

Any subject who manifested a severe degree of intolerance to the drug should have remained under medical observation as long as deemed appropriate by the study neurologist.

When therapy was permanently discontinued for any reason, the day when treatment ceased was to be considered the "day off study". All examinations, laboratory tests, etc. required at this time were delineated under Day 70 Visit 9.

Laboratory tests demonstrating significant deleterious changes were to be repeated and followed up until they return to normal or baseline levels. If an AE is present at the last follow-up visit, it was to be followed until the medical condition returns to baseline or was considered stable or chronic.

Temporary Discontinuation of Study Medication

If a subject developed an adverse event which was perceived by the investigator to be potentially related to the study material or if the subject was temporarily unable to take study medication (intercurrent illness, need for surgery, etc.), study medication could be temporarily discontinued. If the investigator deemed it inappropriate to restart study medication, or the subject was unwilling to resume the study the subject was to be considered permanently terminated from the study, and was to follow procedures outlined. Subjects requiring surgery with general anesthesia should have discontinued study medication 10 days before surgery if possible and restarted study medication according to their investigator's and physician's advice.

Dose Reduction

There was no provision in this study for reduction of study drug dosage for any reason. Patients who could not tolerate the assigned study drug dosage should have been terminated from the study. If evidence of LD-associated adverse events occur during the 10 week active drug portion of the trial, the dose of LD/carbidopa could be reduced for the remainder of the study. After dosing termination, the dose of LD/carbidopa could be increased during the follow-up portion of the trial at the investigator's discretion.

Concomitant Medications

Other anti-Parkinsonian medications were allowed at stable doses. Subjects were to receive all customary therapy for concomitant medical conditions during the course of the trial except: selegiline or other MAO inhibitors. Other prohibited medications included :

- tricyclic antidepressants, fluoxetine or other serotonin reuptake inhibitors
- gentamycin, pethidine (hesperidins) or dextromethorphan

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- sympathomimetics (including over-the-counter cold remedies, oral or nasal). Symptoms of upper respiratory tract infections could be treated with either anti-histamines or intranasal steroids

Adverse Experiences

Adverse Experience Reporting

The investigator was to report all adverse experiences (AEs) that occur through the duration of the study according to the appropriate, standard procedures. Any untoward medical occurrence (sign, symptom or laboratory finding), regardless of severity and whether or not attributed to the study medication, was to be recorded in the AE section of the CRF.

Hypertensive reaction could occur as a result of too high a dose of rasagiline. Special attention was to be paid to severe headache, which may be a presenting symptom of hypertension.

Of special concern was the possibility of a tyramine reaction that required intervention. Symptoms of this could be: sustained (> 8 hrs) hypertension (> 160/100 mm HG), sustained bradycardia (< 40 beats per minute) or development of a new, clinically significant ECG abnormality. Should a clinically significant tyramine/rasagiline reaction occur, a rescue protocol was available.

Statistical Methodology and Randomization

A total of eighteen patients were to be recruited into this double-blind, placebo- controlled, randomized study to examine the pharmacodynamic interaction between TVP-1012 (rasagiline) and oral Tyramine in Parkinsonian patients using LD/Carbidopa. The first phase of this trial was to employ a randomization of 9 patients, 6 randomized to receive Rasagiline 1 mg/day and 3 to receive matching placebo. Following the satisfactory completion of this phase, another set of 9 patients were to be randomized, 6 randomized to receive Rasagiline 2 mg/day and 3 to receive matching placebo. Drop-outs prior to the end of the second Tyramine challenge (day 24) were to be replaced and were to receive duplicate drug or placebo as the patients who terminated.

After a patient met all inclusion criteria, and the screening ECG has been reviewed and approved by Dr. ——— cardiovascular consultant, an appointment was to be made for the Day -7 visit (Visit -1) and the patient was to be assigned a patient number.

Significance Level

Due to the low number of patients, normal statistical testing was not planned for this trial, as it might be difficult to interpret results due to the potential confounding effect of dose changes/response. However, statistical testing at 5% two-tailed significance level could have been performed in an effort to characterize the presence of trends.

SAS software was to be used for statistical analysis and data presentation of the information collected in this study.

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Definitions of Data Cohorts and Handling of Missing Data Two data cohorts were to be evaluated:

Intent-to-treat Cohort (ITT): Consists of all patients who have been randomized. According to the ITT principle, all patients randomized will be kept in their originally assigned treatment group. Safety analyses (see Section 10.5) and preliminary efficacy assessment (see Section 10.8) will refer only to this data cohort.

Completers Cohort (CO): Consists of all patients who completed the first 24 days of the treatment. Pharmacokinetics, pharmacodynamics, Rasagiline/Tyramine interaction assessment, preliminary efficacy assessment and LD/Carbidopa consumption will refer to this data cohort.

The Last Observation Carried Forward (LOCF) approach was to be applied to account for early withdrawal and any interim missing data.

Safety Assessment :

Safety assessment will only be performed for the ITT cohort. The following analyses are planned to assess the safety and tolerability of Rasagiline:

Adverse Experiences

The incidence and the frequency of adverse experiences were to be presented by body system and preferred terminology according to the Costart dictionary. Data were to be tabulated by dose assigned, gender, maximal severity, maximal outcome, maximal action taken and maximal relationship to the tested drug. Serious Adverse Experiences and hospitalizations were to be listed and discussed on a case by case basis.

Laboratory Data and Vital Signs

Frequency counts of abnormal laboratory measurements were to be presented at each scheduled visit by treatment group. Descriptive statistics of laboratory measurements, as well as their changes from baseline were to also be presented by study group at each visit. Shift analysis from baseline to the last observed value and grade change analysis were also to be provided. Listings of measurements of potential clinical significance were also to be presented by study group. Scatterplots of each continuous-type laboratory test were to be provided illustrating the relationship between the baseline and the last observed values obtained for each patient, by treatment group.

Pharmacokinetics and Pharmacodynamics

Pharmacokinetics and pharmacodynamics assessment were only to be performed for the completers cohort. Descriptive statistics including mean, standard deviation, minimum and maximum values will be used to summarize the data which will be presented by the assigned treatment. The following analyses are planned for this trial:

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PAI (rasagiline) and AI (aminoindan) Pharmacokinetics: Blood samples for PAI and AI will be taken at days 1, 23, and 70. Cmax, Tmax, and AUC were to be calculated for each of the patients at each of these days.

Levodopa Pharmacokinetics: Blood samples for levodopa will be taken at days -7, 1, 23 and 70. Cmax, Tmax, and AUC were to be calculated for each of the patients at each of these days. The ratio between these PK parameters calculated for days 23 and 70, to those measured at day 1 were to be calculated (on a patient basis) to reflect possible regimen modification and/or treatment effect.

MAO-B Activity: Blood samples for MAO-B activity will be taken at days 1, 22, 70, 84 and 98. The inhibition of the MAO-B activity were to be calculated at days 22, 70, 84 and 98 as the percent reduction from the actual measurement taken at day 1 prior to the initiation of rasagiline (or its matching placebo).

Potassium Levels: Blood samples for potassium were to be taken on days -7, 22, 23, 24 and 70 prior to ingesting tyramine, and in the event that a tyramine interaction occurs. Descriptive statistics of the potassium levels for measurements prior to ingesting tyramine were to be done.

Rasagiline/Tyramine Interaction Assessment (Vital Signs)

The rasagiline/tyramine interaction assessment based on intensive vital signs data collection were only to be performed for the completers cohort. Intensive vital signs monitoring was to be performed on day -7 (every 15 minutes) following the consumption of 75 mg of tyramine, on days 22, 23, 24 and 70 (every 5 minutes) following the consumption of 25 mg, 50 mg, 75 mg and 75 mg, accordingly, of tyramine. On each of these days and for each patient, the maximal increase of supine systolic blood pressure from the measurement taken prior to tyramine administration at the same day (Δp) and the time to that increase (Δt) were to be calculated. The ratio $\Delta p/\Delta t$ were also to be calculated reflecting the systolic blood pressure increase per time unit. The change in Δp , Δt and $\Delta p/\Delta t$ ratio of day 23, 24 and 70 to that of day -7 and 22 were also to be calculated. The area under the curve presenting the individual systolic blood pressure levels were also to be calculated. Descriptive statistics of these indices, summarizing data by the assigned treatment and the dose of tyramine administered were to include mean, standard deviation, minimum and maximum values.

Preliminary Efficacy Assessment

Assessment was to be performed for the ITT cohort. Descriptive statistics including mean, standard deviation, minimum and maximum values were to be used to summarize the data which were to be presented by assigned treatment. The following analyses were planned for this trial:

- UPDRS ("Total" : Mentation. ADL. Motor. and Complications) when patient is ON and Off.
- Hoehn and Yahr Scale and Schwab and England Scale:
- Quality of Life Assessment (QOL)
- On/Off Diaries
- LD/Carbidopa Consumption

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Significant Protocol Amendments

Protocol amendments incorporated (until 1/15/98) were made prior to initiating first enrollee.

Table 18 Summary Of Significant Protocol Amendments

| General Study Amendments | | |
|------------------------------------|--|------------------|
| Amendment No. | Rationale | Amendment Date |
| I | Changes dose of oral tyramine on Day 23 from 75 to 50 mg to provide a safer escalation of tyramine dosage. | November 7, 1997 |
| II | Clarifies use of anti-Parkinsonian drugs prior to and during the study. States that the subjects may be included in the study if taking stable doses of LD/CD, dopamine agonists, amantadine or anti-cholinergics. Concomitant use of these anti-Parkinsonian drugs at stable doses was permitted. All study-related procedures originally scheduled to be performed at _____ were now to be performed at Pennsylvania Hospital. | January 15, 1998 |
| III | Adds bupropion hydrochloride antidepressant to list of "a two-week washout period from". | April 8, 1998 |
| IV | The subject is not on β -Blockers (e.g. Beta Adrenergic Blocking Agents, β -Adrenergic blocking agents with diuretics) and α/β -adrenergic blockers. Administrative change to allow for the same day Pennsylvania Hospital Visit 9 and neurologist's Office Visit 9 to permit the last ECG completed at Pennsylvania Hospital to be recorded in the Neurologist's Office Visit. Adds supine, sitting and standing BP and HR: recorded at 2, 4, 6, 8 and 12 hours after taking drug and LD/CD. | May 29, 1998 |
| VI | Affects Amendment IV. Deletes Supine, sitting and standing BP & HR: at 6,8,12 hours after taking study drug and LD/CD | June 2, 1999 |
| Subject Specific Amendments | | |
| V | To gain additional information on the variability of subject #206's vital signs via a subject specific protocol. The following information was obtained during a monthly dosing with rasagiline 1mg and 2 mg/day: vital signs, AEs, ECG, 24-hour ambulatory BP measurements, pharmacokinetics (PAI, AI and LD) and catecholamine hormones secretion. | May 27, 1999 |
| VII | To further evaluate subject #209's response to tyramine 25, 50 and 75 mg in the absence of rasagiline for at least one month. Additional tyramine challenges were performed via a subject specific protocol. Further assessments of this subject included 3 tyramine challenges. The subject repeated the tyramine challenges following a 5-month rasagiline wash out period. Challenges were performed on December 13, 14 and 15 1999. | August 11, 1999 |
| VIII | To evaluate subject # 206 for PK parameters of rasagiline (PAI) and its major metabolite (AI) during the treatment period at a daily dose of 1 and 2 mg | January 24, 2000 |

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8.3.2. Sponsor's Presentation of Results of TVP-1012/132

Patient Disposition

Twenty (20) idiopathic PD subjects on chronic LD/ CD therapy (out of 29 screened) were randomly allocated to placebo or active treatment. Assignment to active treatment occurred sequentially, first to 1mg rasagiline and then to 2 mg rasagiline, creating three treatment groups: Placebo 6 subjects (6 completed) 1 mg rasagiline 7 subjects (6 completed) 2 mg rasagiline 7 subjects (6 completed) Eighteen (18) subjects completed the trial.

Two subjects discontinued the trial prematurely for the following reasons: . Subject # 105 (1 mg rasagiline) - elevated BP and tachycardia; Subject # 206 (2 mg rasagiline) - elevated BP probably due to a suspected rasagiline/ tyramine response. Detailed narratives are provided.

Subject #105, a 73 year-old female, was diagnosed with PD in 1996, had no fluctuations and had been treated with LD for two years at study initiation. Her general medical history included varicose veins (1997), mild dementia (1997) and edema (1998). She underwent washout from amantadine 200mg bid in February 1998 and from selegiline 5mg qd in August 1997. She enrolled in the study on March 31, 1998 and was assigned to treatment with 1mg rasagiline. Screening diagnostic assessments and vital signs included SBP/DBP/pulse: Supine 150/90/68, sitting 120/70/66, standing 100/70/64. ECG and chest x-ray recordings were normal. Ongoing medication during study: carbidopa/LD 62.5/250 mg tid, Ginkgo Biloba 120 mg qd. Study Conduct – On Day –7 (March 24, 1998, before initiation of study drug) the subject exhibited fluctuations of SBP up to 170 mm Hg, prior to challenge with 75 mg tyramine. No BP increase following administration of tyramine was observed. On the day of randomization, prior to exposure to the study drug, the subject's supine BP was 170/110, though BP measured at home was within normal range and there was no known history of chronic hypertension. On Day 22 (April 21, 1998), baseline vital signs were taken before challenge with tyramine. The subject's BP was 156/82 mmHg, with tachycardia up to 126 beats per minute. Because of these vital sign findings tyramine challenge was not performed and the subject discontinued her participation in the study. The last dosing day was Day 22, on April 21, 1998. Early discontinuation was attributed to AE (elevated BP and tachycardia), which were assessed as not related to administration of rasagiline.

Subject #206 discontinued study drug (2 mg rasagiline) after 33 days of therapy. This was a 51 year-old Caucasian female, diagnosed with PD in January 1998. She was treated with LD/CD with no fluctuations. Her general medical history included appendectomy (1954); hysterectomy (1986); hypothyroidism (1997); lumpectomy with benign findings (1994); migraine (1956), not active; Herpes (1988); mild diarrhea, insomnia, decreased appetite (1998). PD was diagnosed in 1998 presenting with difficulty in handwriting and slowness of movements mainly on the right side.

Screening diagnostic assessments and vital signs:

Physical examination was normal.

Vital signs (systolic/diastolic/pulse): Supine 110/80/58, sitting 100/70/56, standing 100/70/60.

Chest x-ray was unremarkable and screening ECG was normal.

Ongoing medications during study: LD/CD 75/300 tid (1/98), pergolide 6 mg po tid (8/98), acyclovir 200mg qd ('88), lorazepam 2 mg prn (1/98), thyroxine 50 mcg qd (9/97), conjugated

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estrogens 0.625mg qd (9/97). (Patient underwent washout from nefazodone hydrochloride 100mg bid on 9/10/98)

Screening date: 10 September 1998. Enrollment Date: 15 October 1998

Study Conduct – During the baseline challenge with 75 mg tyramine on day –7 no signs of tyramine reaction were observed. She started 2mg rasagiline on 15 October 1998 and during the following 3 weeks no unusual findings were observed in blood pressure. She took acetaminophen PM (diphenhydramine and paracetamol) for sleeping from October 26 to November 9. On day 22 (first tyramine dose), baseline blood pressure was 156/99, and 20 minutes after administration of 25 mg of tyramine, the blood pressure became elevated with peak levels of 181/102-188/96 sustained for 15 minutes. Blood pressure returned to normal, patient remained asymptomatic, no ECG changes were found and no intervention was needed. The next day, second tyramine dosing day, the patient exhibited slightly elevated blood pressure prior to taking her regular dose of carbidopa/LD, therefore the 50 mg tyramine was withheld for 30 minutes. Her blood pressure was 141/86 prior to tyramine administration. Ten to fifteen minutes after the tyramine dosage, the blood pressure became elevated up to peak levels of 192/103 and was sustained for around 40 minutes. Pulse remained unchanged. Patient remained asymptomatic, blood pressure returned to normal without any intervention. In view of these events the patient was given placebo dose on the third day (instead of tyramine 75mg).

Following this administration and throughout the day the patient remained at around baseline levels with blood pressure of 110-130/60-75. The patient was discharged from the clinic and was instructed to keep a low tyramine diet. She reported on episodes of hypotension as well as hypertension, as measured at home.

These episodes were sometimes symptomatic and sometimes asymptomatic. Study drug was discontinued on 16 November 1998 after 33 days of treatment. The patient was instructed to monitor her blood pressure at 30, 60, 90 and 120 minutes following LD/CD ingestion during a month. Blood pressure variability was reported. A thyroid function test was performed and found to be normal. Blood levels of rasagiline and LD were obtained during the study as defined in the protocol. Both were very high in this patient in comparison to the study population. On day 23, the rasagiline C_{max} was 27.7 ng/ml in this patient in comparison to 10.45 + 8.6 ng/ml in the 2 mg rasagiline group. On day 23, the LD C_{max} was 14600 ng/ml in this patient in comparison to 3868.9 + 5357.6 ng/ml in the 2 mg rasagiline group. Blood levels of catecholamines were analyzed from the samples prepared for LD levels. There were no clinically significant results.

Protocol Violations, Deviations, and Prohibited Concomitant Medications

Misinterpretation of the protocol led to a consistent deviation from its instruction to provide tyramine with the morning meal. Instead, tyramine (in 4 oz of applesauce) was uniformly administered to subjects in a fasting state, prior to their consumption of the morning meal. The morning meal (typically muffin or cereal) was given 5-10 minutes after the patient began consuming tyramine in the applesauce.

The incidence of additional protocol violations is shown in Table 7, which demonstrates a low incidence of protocol violation.

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Due to possible rasagiline/ tyramine interaction, subject # 206 (2 mg group) did not receive the tyramine dose on visit 6 and was given applesauce only. The coordinator and the nurse were blind to this change.

Table 19 Incidence of Protocol Violations

| TVP-1012/132 | Treatment Group | | | | | | | |
|---|-----------------|------|------------|------|---------------|------|------------|------|
| | 1 MG (N=7) | | 2 MG (N=7) | | PLACEBO (N=6) | | All (N=20) | |
| | N | % | N | % | N | % | N | % |
| CD Dose <75 mg/day at Baseline | 1 | 14.3 | 0 | 0.0 | 0 | 0.0 | 1 | 5.0 |
| Baseline SBP>150 mm Hg | 2 | 28.6 | 0 | 0.0 | 1 | 16.7 | 3 | 15.0 |
| Baseline DBP>90 mm Hg | 2 | 28.6 | 1 | 14.3 | 1 | 16.7 | 4 | 20.0 |
| Compliance to Rasagiline <70% during Whole Study | 0 | 0.0 | 1 | 14.3 | 0 | 0.0 | 1 | 5.0 |
| Compliance to Rasagiline <100% on day 22, 23, 24 and 70 | 1 | 14.3 | 1 | 14.3 | 0 | 0.0 | 2 | 10.0 |
| Early Discontinuation | 1 | 14.3 | 1 | 14.3 | 0 | 0.0 | 2 | 10.0 |
| All | 3 | 42.9 | 2 | 28.6 | 1 | 16.7 | 6 | 30.0 |

Demographic Characterizations

Summary statistics of baseline demographic characteristics (sex, age, height and weight) are presented in Table 8 and Table 9. Although sex distribution was not equal between treatment groups the difference was not statistically significant due to the small number of subjects. The mean age was ~ 61 years (range 47- 78). No significant differences between treatment groups were observed in height or weight.

Table 20 Distribution of Subjects by Gender

| TVP1012/132 | 1mg | | 2mg | | Placebo | |
|--------------------------|-----|-------|-----|-------|---------|-------|
| | N | % | N | % | N | % |
| TOTAL NUMBER OF SUBJECTS | 7 | 100.0 | 7 | 100.0 | 6 | 100.0 |
| FEMALE | 3 | 42.9 | 2 | 28.6 | 4 | 66.7 |
| MALE | 4 | 57.1 | 5 | 71.4 | 2 | 33.3 |

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Table 21 Descriptive Statistics of Demographic Characteristics

| TVPI012/132 | | 1mg | 2mg | Placebo |
|-------------|------|-------|-------|---------|
| AGE (years) | N | 7 | 7 | 6 |
| | MEAN | 63.4 | 59.1 | 59.8 |
| | STD | 10.5 | 9.0 | 10.3 |
| | MIN | 47.0 | 47.0 | 49.0 |
| | MAX | 76.0 | 68.0 | 78.0 |
| WEIGHT (kg) | N | 7 | 7 | 6 |
| | MEAN | 77.0 | 70.1 | 78.7 |
| | STD | 26.0 | 13.1 | 21.2 |
| | MIN | 46.0 | 53.0 | 54.0 |
| | MAX | 114.0 | 84.0 | 106.0 |
| HEIGHT (cm) | N | 7 | 7 | 6 |
| | MEAN | 174.1 | 176.3 | 167.5 |
| | STD | 13.0 | 7.9 | 11.4 |
| | MIN | 157.0 | 168.0 | 156.0 |
| | MAX | 192.0 | 191.0 | 185.0 |

Baseline Disease Characteristics

Parkinson's Disease Diagnosis

Most subjects in all treatment groups had defined symptoms and signs of the disease such as tremor, rigidity and bradykinesia. Most subjects exhibited tremor at the time of diagnosis. Bradykinesia was more prevalent in the 2 mg group than the two other groups; however, differences were not statistically significant. The characteristics of tremor, rigidity, bradykinesia and postural disturbances were compatible with those reported for PD subjects, thus representing the general Parkinsonian population.

Duration of Parkinson's Disease

Mean disease duration at trial entry was similar across treatment groups: 4.3 years for the placebo, 5.6 years for the 1 mg and 5.3 years for the 2 mg rasagiline group (range 0- 16 years). Subjects had been treated with LD for more than 80% of the time since diagnosis. In all treatment groups, subjects received about three to four daily doses of LD as their standard therapy. The duration of response for fluctuations is 0- 6 years and dyskinesia ranged from 0- 5 years.

LD Therapy Symptoms

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Associated with long term, chronic exposure to LD, 45% of the subjects within all treatment groups experienced response fluctuations prior to trial entry. Dyskinesias were reported in 20% of the subjects: two in the placebo group and one in each of the rasagiline treated groups.

All subjects were treated concomitantly with standard LD therapy both prior to and during study participation. The next most frequently used medications were analgesics and anti-inflammatory agents.

Treatment Compliance

The mean compliance with treatment varied between 97.8% for the placebo group and up to 99.5% for the 2 mg group.

Safety Results

Safety results from this study were included in the Safety Review conducted by Dr. Lisa Jones.

Pharmacodynamic Results

Table 22 clearly demonstrates that MAO-B activity was totally inhibited in the two rasagiline treated groups on Days 22 and 70 compared to MAO-B levels on Day 1 and also compared to the placebo group. The level of inhibition was similar in the 1 mg and in the 2 mg rasagiline treated groups. MAO B activity was recovered during the washout period in both groups.

Home BP Diaries

At baseline, no differences were detected between treatment groups in any of the blood pressure parameters measured. No significant differences were found between subjects' hospital and at-home manometer readings. Data gathered from daily home BP diaries suggests no pattern associated with rasagiline treatment. Throughout the study period (including the period during which tyramine restriction was not required), only three subjects had SBP values exceeding 180 mm Hg. These were two placebo subjects (# 106 and # 108) and subject # 206.

ECG Measurements

The distribution of 12- lead ECG recording interpretation by visit shows that the vast majority of subjects exhibited normal ECG recordings (Table 28). Four subjects had abnormal ECG recordings, each on a single occasion. These include: one subject at screening; one on randomization day; one on Day 7 (subject # 105 treated with 1 mg rasagiline, most likely a result of poor lead placement as per CRF comment) and one subject in the placebo group had an abnormal ECG recording on Day 98 (subject # 108, see narrative below). The cardiovascular consultant considered none of these recordings as clinically significant.

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Table 22 Descriptive Statistics of Percent (%) of MAO-B Inhibition

| Protocol TVP-1012/132 | | 1mg | 2mg | Placebo |
|-----------------------|---------|--------|--------|---------|
| Day 22 (Visit 4) | N | 6 | 6 | 6 |
| | Mean | 97.30 | 100.00 | -17.31 |
| | Std | 6.62 | 0.00 | 31.12 |
| | Minimum | 83.78 | 100.00 | -48.91 |
| | Maximum | 100.00 | 100.00 | 16.50 |
| Day 70 (Termination) | N | 6 | 6 | 6 |
| | Mean | 100.00 | 96.96 | -28.80 |
| | Std | 0.00 | 7.45 | 31.03 |
| | Minimum | 100.00 | 81.74 | -66.67 |
| | Maximum | 100.00 | 100.00 | 11.83 |
| Day 84 (Washout) | N | 6 | 6 | 6 |
| | Mean | 16.72 | 0.13 | -16.38 |
| | Std | 5.64 | 21.84 | 36.64 |
| | Minimum | 9.91 | -23.68 | -57.61 |
| | Maximum | 27.03 | 31.45 | 41.56 |
| Day 98 (Washout) | N | 6 | 6 | 6 |
| | Mean | -25.17 | 6.35 | -43.37 |
| | Std | 30.51 | 24.14 | 37.84 |
| | Minimum | -54.37 | -21.05 | -99.17 |
| | Maximum | 33.78 | 41.61 | -5.19 |

Cross-reference Appendix 15.4.20

Orthostatic Blood Pressure Measurements

Overall, no significant differences were detected in mean supine- standing, supine-sitting or sitting- standing systolic blood pressure (SBP) measurements during the study at any treatment dose (Table 23).

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Table 23 Mean Systolic Blood Pressure Differences : Supine – Sitting, Sitting – Standing, Supine – Standing, by Visit and Treatment Group

| PROTOCOL TVP1012/132 | TREATMENT GROUP | | | | | | | | |
|--------------------------|-----------------|------------------|-----------------|----------------|------------------|-----------------|----------------|------------------|-----------------|
| | 1mg | | | 2mg | | | Placebo | | |
| | SUPINE-SITTING | SITTING-STANDING | SUPINE-STANDING | SUPINE-SITTING | SITTING-STANDING | SUPINE-STANDING | SUPINE-SITTING | SITTING-STANDING | SUPINE-STANDING |
| VISIT | | | | | | | | | |
| SCREENING | 10.0 | 6.9 | 16.9 | 4.3 | 3.4 | 7.7 | 6.3 | 0.7 | 7.0 |
| RANDOMIZATION DAY: DAY 1 | 10.6 | -3.7 | 6.9 | -0.3 | 5.4 | 5.1 | 3.7 | 3.7 | 7.3 |
| DAY 7 | 4.0 | 5.4 | 9.4 | 7.1 | 2.6 | 9.7 | 4.0 | -1.7 | 2.3 |
| DAY 21 | 6.0 | 4.9 | 10.9 | 4.0 | 3.4 | 7.4 | -1.3 | -1.3 | -2.7 |
| DAY 42 | 9.0 | -1.7 | 7.3 | 6.0 | 4.0 | 10.0 | -4.0 | 6.0 | 2.0 |
| DAY 56 | 9.7 | -1.0 | 8.7 | -1.0 | 5.7 | 4.7 | 4.0 | 1.3 | 5.3 |
| TERMINATION: DAY 70 | -1.5 | 3.3 | 1.8 | 10.4 | 3.3 | 13.7 | -9.0 | 2.7 | -6.3 |
| DAY 84 - WASHOUT | -2.7 | 2.3 | -0.3 | 7.7 | -2.7 | 5.0 | 1.0 | 3.7 | 4.7 |
| DAY 98 - WASHOUT | 4.0 | 1.0 | 5.0 | 2.0 | 2.3 | 4.3 | 1.7 | 3.0 | 4.7 |

Assessment of Rasagiline / Tyramine Interaction

Clinically Significant Vital Signs

During the course of the tyramine challenge a total of 62 vital sign measurements were considered potentially clinically significant (PCS) (Table 29). Orthostatic vital signs (blood pressure and pulse - supine, sitting, standing) had been assessed at time 0, 2, 4, 6, 8, 10, and 12 hours post-tyramine. Time 0 was determined when the patient began consuming tyramine in the applesauce. 6 vital sign measurements were considered PCS in the placebo group. Forty-six (46) vital sign measurements were initially considered PCS in the active treatment groups. However, 12 of these events occurred as single random incidents with no clinical significance and no association with tyramine administration was detected. The other 34 PCS vital signs events in the active groups occurred in four subjects. One subject (#104) belonged to the 1 mg rasagiline treatment group and the other three subjects belonged to the 2 mg rasagiline treatment group (subjects # 206, 208 and 209). Subjects #206 and #209 developed possible tyramine reactions and are discussed in details in Section 8.5.4. The other two cases (Subjects #104 and #208) exhibited PCS abnormal vital signs related to hypotension. These patients are not presented because the focus of my review is oriented toward hypertensive risks of treatment.

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Table 24 Frequency of Potentially Clinically Significant (PCS) Vital Sign Events During Tyramine Challenge (Days 22, 23, 24, and 70)

| PROTOCOL TVP1012/132 | TREATMENT GROUP | | |
|---|-----------------|-----|---------|
| | 1mg | 2mg | Placebo |
| SITTING - STANDING SBP <-30 mmHg | | 2 | |
| SITTING - STANDING SBP >30 mmHg | 2 | 2 | 1 |
| SITTING DBP CHANGE FROM PRE-TYRAMINE <-30 mmHg | 1 | 2 | 1 |
| SITTING DBP CHANGE FROM PRE-TYRAMINE > 30 mmHg | | 3 | |
| STANDING DBP CHANGE FROM PRE-TYRAMINE <-30 mmHg | 2 | 2 | 3 |
| STANDING DBP CHANGE FROM PRE-TYRAMINE > 30 mmHg | 1 | 4 | |
| STANDING SBP CHANGE FROM PRE-TYRAMINE <-60 mmHg | | 5 | 1 |
| SUPINE - SITTING SBP <-30 mmHg | | 1 | 2 |
| SUPINE - SITTING SBP >30 mmHg | 1 | 4 | 1 |
| SUPINE - STANDING SBP <-30 mmHg | | 2 | 3 |
| SUPINE - STANDING SBP >30 mmHg | 3 | 4 | 1 |
| SUPINE DBP CHANGE FROM PRE-TYRAMINE <-30 mmHg | 1 | 2 | 2 |
| SUPINE DBP CHANGE FROM PRE-TYRAMINE > 30 mmHg | | 2 | |
| SUPINE SBP CHANGE FROM PRE-TYRAMINE <-60 mmHg | | | 1 |
| ALL | 11 | 35 | 16 |

Telemetry

On Days 22, 23, 24 and 70 vital signs were taken as described previously. However, between time 0 and 2 hours measurements were taken every 5 minutes. Between 2 hours and 4 hours, measurements were taken every 15 minutes. The results obtained for each treatment day were compared to the baseline measurements (Day-7). The maximal increase in systolic BP and the time interval to that increase were assessed as well as the ratio between them. Table 25 shows a summary of results at day - 7 (baseline/pre-treatment) and Table 26 - Table 28 show results of 25, 50, and 75 mg tyramine.

Appears This Way
On Original

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Table 25 Baseline Vital Signs / Tyramine Assessment at Day - 7

| PROTOCOL TVP1012/132 | 1mg | | | | | 2mg | | | | | Placebo | | | | |
|---|-------|------|---|-----|-----|-------|-------|---|-----|-----|---------|------|---|-----|-----|
| | MEAN | STD | N | MIN | MAX | MEAN | STD | N | MIN | MAX | MEAN | STD | N | MIN | MAX |
| SBP: PRE-TYRAMINE CHALLENGE (TIME 0) | 142.2 | 20.6 | 6 | 121 | 170 | 122.2 | 19.8 | 6 | 99 | 142 | 144.5 | 21.6 | 6 | 106 | 170 |
| MAXIMAL SBP | 154.3 | 14.3 | 6 | 135 | 170 | 139.2 | 19.4 | 6 | 121 | 174 | 156.0 | 19.3 | 6 | 130 | 182 |
| MAXIMAL SBP DIF FROM PRE-TYRAMINE | 12.2 | 10.5 | 6 | 0 | 30 | 17.0 | 13.4 | 6 | 0 | 36 | 11.5 | 13.0 | 6 | 0 | 31 |
| TIME (min.) TO MAXIMAL SBP (Tmax) | 27.5 | 32.1 | 6 | 0 | 90 | 87.5 | 100.1 | 6 | 0 | 240 | 32.5 | 39.6 | 6 | 0 | 105 |
| MAX SBP DIF FROM PRE-TYR: DAY -7 CHANGE | | | 0 | | | | | 0 | | | | | 0 | | |
| SLOPE: MAX SBP CHANGE/Tmax (mmHg/hour) | 30.3 | 25.2 | 6 | 0 | 60 | 28.9 | 34.4 | 6 | 0 | 88 | 16.8 | 17.8 | 6 | 0 | 41 |
| SLOPE: DAY -7 CHANGE | | | 0 | | | | | 0 | | | | | 0 | | |
| POSITIVE AUC (mmHg*hr Corrected/hour) | 2.6 | 2.8 | 6 | 0 | 8 | 5.4 | 4.8 | 6 | 0 | 13 | 3.8 | 5.4 | 6 | 0 | 12 |
| POSITIVE AUC: DAY -7 CHANGE | | | 0 | | | | | 0 | | | | | 0 | | |
| AUC (mmHg*hr Corrected/hour) | 130.4 | 12.3 | 6 | 115 | 149 | 120.7 | 15.3 | 6 | 103 | 145 | 132.2 | 17.3 | 6 | 115 | 161 |
| AUC: DAY -7 CHANGE | | | 0 | | | | | 0 | | | | | 0 | | |

*75 mg tyramine were consumed, no rasagiline consumed

Table 26 Rasagiline / Tyramine* (25 mg) Interaction Assessment at Day 22

| PROTOCOL TVP1012/132 | 1mg | | | | | 2mg | | | | | Placebo | | | | |
|---|-------|-------|---|-----|-----|-------|------|---|-----|-----|---------|-------|---|-----|-----|
| | MEAN | STD | N | MIN | MAX | MEAN | STD | N | MIN | MAX | MEAN | STD | N | MIN | MAX |
| SBP: PRE-TYRAMINE CHALLENGE (TIME 0) | 137.8 | 16.1 | 6 | 115 | 156 | 130.7 | 24.4 | 6 | 97 | 166 | 136.8 | 20.3 | 6 | 113 | 163 |
| MAXIMAL SBP | 147.7 | 16.1 | 6 | 125 | 171 | 143.5 | 14.3 | 6 | 123 | 166 | 155.5 | 20.5 | 6 | 132 | 185 |
| MAXIMAL SBP DIF FROM PRE-TYRAMINE | 9.8 | 4.4 | 6 | 3 | 15 | 12.8 | 10.6 | 6 | 0 | 26 | 18.7 | 24.3 | 6 | 0 | 54 |
| TIME (min.) TO MAXIMAL SBP (Tmax) | 138.3 | 102.8 | 6 | 5 | 240 | 30.8 | 58.8 | 6 | 0 | 150 | 47.5 | 71.5 | 6 | 0 | 180 |
| MAX SBP DIF FROM PRE-TYR: DAY -7 CHANGE | -2.3 | 10.1 | 6 | -16 | 11 | -4.2 | 17.8 | 6 | -36 | 17 | 7.2 | 18.7 | 6 | -14 | 36 |
| SLOPE: MAX SBP CHANGE/Tmax (mmHg/hour) | 21.7 | 42.3 | 6 | 2 | 108 | 61.9 | 76.7 | 6 | 0 | 192 | 59.8 | 129.6 | 6 | 0 | 324 |
| SLOPE: DAY -7 CHANGE | -8.7 | 56.8 | 6 | -53 | 98 | 33.0 | 64.7 | 6 | -41 | 104 | 42.9 | 118.0 | 6 | -21 | 283 |
| POSITIVE AUC (mmHg*hr Corrected/hour) | 0.8 | 0.5 | 6 | 0 | 1 | 2.6 | 2.8 | 6 | 0 | 7 | 7.3 | 11.1 | 6 | 0 | 22 |
| POSITIVE AUC: DAY -7 CHANGE | -1.8 | 2.7 | 6 | -7 | 1 | -2.9 | 5.8 | 6 | -13 | 3 | 3.4 | 10.4 | 6 | -10 | 20 |
| AUC (mmHg*hr Corrected/hour) | 124.9 | 13.9 | 6 | 107 | 147 | 119.8 | 16.8 | 6 | 103 | 150 | 127.0 | 15.6 | 6 | 110 | 152 |
| AUC: DAY -7 CHANGE | -5.5 | 7.2 | 6 | -18 | 1 | -0.9 | 5.4 | 6 | -8 | 5 | -5.2 | 8.3 | 6 | -17 | 5 |

*25 mg tyramine

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Table 27 Rasagiline / Tyramine* (50 mg) Interaction Assessment at Day 23

| PROTOCOL TVP1012/132 | 1mg | | | | | 2mg | | | | | Placebo | | | | |
|---|-------|------|---|-----|-----|-------|------|---|-----|-----|---------|-------|---|-----|-----|
| | MEAN | STD | N | MIN | MAX | MEAN | STD | N | MIN | MAX | MEAN | STD | N | MIN | MAX |
| SBP: PRE-TYRAMINE CHALLENGE (TIME 0) | 138.5 | 16.4 | 6 | 112 | 153 | 121.3 | 15.9 | 6 | 98 | 139 | 131.8 | 16.0 | 6 | 101 | 143 |
| MAXIMAL SBP | 146.5 | 16.1 | 6 | 121 | 165 | 140.0 | 19.5 | 6 | 116 | 172 | 158.7 | 22.2 | 6 | 138 | 191 |
| MAXIMAL SBP DIF FROM PRE-TYRAMINE | 8.0 | 5.2 | 6 | 0 | 16 | 18.7 | 11.6 | 6 | 6 | 36 | 26.8 | 17.5 | 6 | 8 | 51 |
| TIME (min.) TO MAXIMAL SBP (Tmax) | 60.8 | 75.8 | 6 | 0 | 195 | 117.5 | 92.5 | 6 | 20 | 240 | 71.7 | 86.2 | 6 | 5 | 225 |
| MAX SBP DIF FROM PRE-TYR: DAY -7 CHANGE | -4.2 | 9.8 | 6 | -22 | 6 | 1.7 | 15.5 | 6 | -16 | 29 | 15.3 | 13.0 | 6 | 3 | 38 |
| SLOPE: MAX SBP CHANGE/Tmax (mmHg/hour) | 52.2 | 80.3 | 6 | 0 | 192 | 14.4 | 10.3 | 6 | 3 | 31 | 117.2 | 170.1 | 6 | 3 | 456 |
| SLOPE: DAY -7 CHANGE | 21.9 | 84.6 | 6 | -54 | 152 | -14.5 | 32.7 | 6 | -70 | 18 | 100.4 | 181.2 | 6 | -33 | 456 |
| POSITIVE AUC (mmHg*hr Corrected/hour) | 0.5 | 0.5 | 6 | 0 | 1 | 5.2 | 5.4 | 6 | 0 | 13 | 3.7 | 4.5 | 6 | 0 | 12 |
| POSITIVE AUC: DAY -7 CHANGE | -2.1 | 2.4 | 6 | -6 | 0 | -0.2 | 5.0 | 6 | -7 | 8 | -0.1 | 2.6 | 6 | -5 | 2 |
| AUC (mmHg*hr Corrected/hour) | 122.5 | 13.2 | 6 | 110 | 145 | 118.4 | 15.3 | 6 | 105 | 148 | 123.0 | 14.6 | 6 | 105 | 148 |
| AUC: DAY -7 CHANGE | -7.9 | 6.0 | 6 | -16 | -2 | -2.3 | 6.8 | 6 | -12 | 6 | -9.2 | 10.4 | 6 | -27 | 3 |

*50 mg Tyramine

Table 28 Rasagiline / Tyramine* (75 mg) Interaction Assessment at Day 24

| PROTOCOL TVP1012/132 | 1mg | | | | | 2mg | | | | | Placebo | | | | |
|---|-------|------|---|-----|-----|-------|------|---|-----|-----|---------|------|---|-----|-----|
| | MEAN | STD | N | MIN | MAX | MEAN | STD | N | MIN | MAX | MEAN | STD | N | MIN | MAX |
| SBP: PRE-TYRAMINE CHALLENGE (TIME 0) | 131.7 | 19.5 | 6 | 107 | 151 | 125.0 | 20.4 | 7 | 100 | 155 | 130.5 | 21.2 | 6 | 102 | 155 |
| MAXIMAL SBP | 143.8 | 9.6 | 6 | 134 | 158 | 150.6 | 19.3 | 7 | 131 | 184 | 148.7 | 15.6 | 6 | 126 | 170 |
| MAXIMAL SBP DIF FROM PRE-TYRAMINE | 12.2 | 12.2 | 6 | 0 | 29 | 25.6 | 8.1 | 7 | 11 | 31 | 18.2 | 13.3 | 6 | 0 | 34 |
| TIME (min.) TO MAXIMAL SBP (Tmax) | 80.8 | 81.2 | 6 | 0 | 195 | 148.6 | 95.1 | 7 | 20 | 240 | 75.8 | 87.5 | 6 | 0 | 195 |
| MAX SBP DIF FROM PRE-TYR: DAY -7 CHANGE | 0.0 | 14.6 | 6 | -24 | 14 | 8.6 | 14.0 | 7 | -7 | 29 | 6.7 | 12.4 | 6 | -9 | 26 |
| SLOPE: MAX SBP CHANGE/Tmax (mmHg/hour) | 21.4 | 33.7 | 6 | 0 | 87 | 27.1 | 33.4 | 7 | 3 | 87 | 29.4 | 40.3 | 6 | 0 | 104 |
| SLOPE: DAY -7 CHANGE | -8.9 | 52.0 | 6 | -57 | 77 | 1.8 | 57.2 | 7 | -80 | 87 | 12.6 | 51.6 | 6 | -36 | 104 |
| POSITIVE AUC (mmHg*hr Corrected/hour) | 3.4 | 5.6 | 6 | 0 | 14 | 4.8 | 5.2 | 7 | 1 | 16 | 3.5 | 4.0 | 6 | 0 | 11 |
| POSITIVE AUC: DAY -7 CHANGE | 0.8 | 5.4 | 6 | -3 | 12 | -0.6 | 6.2 | 7 | -10 | 8 | -0.3 | 4.0 | 6 | -7 | 5 |
| AUC (mmHg*hr Corrected/hour) | 119.7 | 11.3 | 6 | 104 | 136 | 119.3 | 15.5 | 7 | 97 | 149 | 122.4 | 13.9 | 6 | 102 | 140 |
| AUC: DAY -7 CHANGE | -10.7 | 6.6 | 6 | -21 | -0 | -2.4 | 7.8 | 7 | -14 | 10 | -9.8 | 11.2 | 6 | -23 | 3 |

*75 mg Tyramine

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Table 29 Rasagiline / Tyramine* (75 mg) Interaction Assessment at Day 70

| PROTOCOL TVP1012/132 | 1mg | | | | | 2mg | | | | | Placebo | | | | |
|---|-------|------|---|-----|-----|-------|-------|---|-----|-----|---------|------|---|-----|-----|
| | MEAN | STD | N | MIN | MAX | MEAN | STD | N | MIN | MAX | MEAN | STD | N | MIN | MAX |
| SBP: PRE-TYRAMINE CHALLENGE (TIME 0) | 128.5 | 9.6 | 6 | 118 | 141 | 132.5 | 20.8 | 6 | 100 | 160 | 135.5 | 21.5 | 6 | 107 | 161 |
| MAXIMAL SBP | 152.3 | 8.3 | 6 | 139 | 162 | 155.0 | 24.0 | 6 | 122 | 191 | 160.3 | 13.6 | 6 | 149 | 187 |
| MAXIMAL SBP DIF FROM PRE-TYRAMINE | 23.8 | 6.5 | 6 | 16 | 34 | 22.5 | 12.2 | 6 | 11 | 45 | 24.8 | 17.9 | 6 | 3 | 53 |
| TIME (min.) TO MAXIMAL SBP (Tmax) | 74.2 | 76.7 | 6 | 10 | 210 | 96.7 | 102.8 | 6 | 15 | 240 | 147.5 | 99.0 | 6 | 10 | 240 |
| MAX SBP DIF FROM PRE-TYR: DAY -7 CHANGE | 11.7 | 7.7 | 6 | 1 | 21 | 5.5 | 22.2 | 6 | -24 | 39 | 13.3 | 15.4 | 6 | -5 | 31 |
| SLOPE: MAX SBP CHANGE/Tmax (mmHg/hour) | 43.2 | 34.1 | 6 | 6 | 96 | 52.7 | 66.9 | 6 | 3 | 180 | 17.5 | 18.4 | 6 | 2 | 53 |
| SLOPE: DAY -7 CHANGE | 12.9 | 42.7 | 6 | -43 | 86 | 23.8 | 77.1 | 6 | -25 | 178 | 0.7 | 30.8 | 6 | -33 | 53 |
| POSITIVE AUC (mmHg*hr Corrected/hour) | 4.9 | 2.8 | 6 | 1 | 8 | 3.4 | 3.1 | 6 | 1 | 8 | 5.8 | 5.4 | 6 | 0 | 14 |
| POSITIVE AUC: DAY -7 CHANGE | 2.3 | 4.8 | 6 | -5 | 8 | -2.0 | 6.1 | 6 | -11 | 6 | 1.9 | 5.5 | 6 | -7 | 8 |
| AUC (mmHg*hr Corrected/hour) | 128.1 | 12.6 | 6 | 111 | 146 | 121.2 | 16.3 | 6 | 105 | 149 | 132.1 | 14.6 | 6 | 120 | 161 |
| AUC: DAY -7 CHANGE | -2.3 | 2.1 | 6 | -5 | 1 | 0.4 | 5.8 | 6 | -11 | 5 | -0.1 | 8.5 | 6 | -15 | 10 |

*75 mg Tyramine

Abnormal ECG Measurements

Subject #209, a 68-year old male was assigned to receive 2 mg rasagiline on May 5, 1999. During Termination Visit (Day 70), 16-30 minutes post 75 mg tyramine consumption, the subject experienced a probable tyramine reaction including hypertension and ECG-documented sinus bradycardia. The subject had a pertinent medical history of venous insufficiency. Pertinent concomitant medications included furosemide. No other ECG changes were recorded on tyramine-challenge days at 0.5, 1, 2 and 4 hours post-tyramine consumption.

Summary of Two Cases of Rasagiline/Tyramine Interaction

Subjects #206 and #209 exhibited probable rasagiline/tyramine interactions. Individual protocols were then issued for each of these subjects. Their narratives, including the special protocol results, are summarized below.

Subject #206

This was a 51 year-old Caucasian female, diagnosed with PD in January 1998. She was treated with LD/CD with no fluctuations. Her general medical history included appendectomy (1954); hysterectomy (1986); hypothyroidism (1997); lumpectomy with benign findings (1994); migraine (1956), not active; Herpes (1988); mild diarrhea, insomnia, decreased appetite (1998). PD was diagnosed in 1998 presenting with difficulty in handwriting and slowness of movements mainly on the right side.

Results Obtained during the Per Protocol Study

Physical examination at Screening was normal. Vital signs by position were: supine 110/80/58, sitting 100/70/56, standing 100/70/60. Chest X-ray was unremarkable and screening ECG was normal.

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Ongoing medications during the study included: LD/CD 300/75 tid (Jan 98), pergolide 6mg po tid (Aug 98), acyclovir 200mg qd ('88), lorazepam 2mg prn (Jan 98), thyroxine sodium 50mcg qd (Sept 97), conjugated estrogens 0.625mg qd (Sept 97). (Subject underwent washout from nefazodone hydrochloride 100mg bid on 10 Sept 1998).

During the baseline challenge with 75 mg tyramine on Day -7 no signs of tyramine reaction were observed (Figure 6). The subject initiated treatment with 2 mg rasagiline on October 15, 1998 and during the following 3 weeks no unusual findings were observed in BP. She took Acetaminophen PM (diphenhydramine and paracetamol) as a sleep aid from October 26 to November 9. On November 5, 1998, Day 22 (first tyramine dose), baseline BP was 156/99, and 20 minutes after administration of 25 mg of tyramine, the BP became elevated with peak levels of 181/102-188/96 sustained for 15 minutes. BP returned to normal without intervention, no ECG changes were observed and subject remained asymptomatic. The next day, on the second tyramine dosing day, the subject exhibited slightly elevated BP prior to taking her regular dose of LD/CD, therefore, the 50 mg tyramine was withheld for 30 minutes. Her BP was 141/86 prior to tyramine administration. Ten to fifteen minutes after the tyramine dosage, the BP became elevated up to peak levels of 192/103 and was sustained for approximately 40 minutes. Pulse remained unchanged. The subject remained asymptomatic and BP returned to normal without any intervention. In view of these events the subject was given placebo dose (instead of tyramine 75mg) on the third day. **The reader should note that Figure 6 (right lower panel) notes that 75 mg tyramine was given, but this did not occur because the patient was intentionally treated with placebo.** There was no significant increase in systolic blood pressure after placebo.

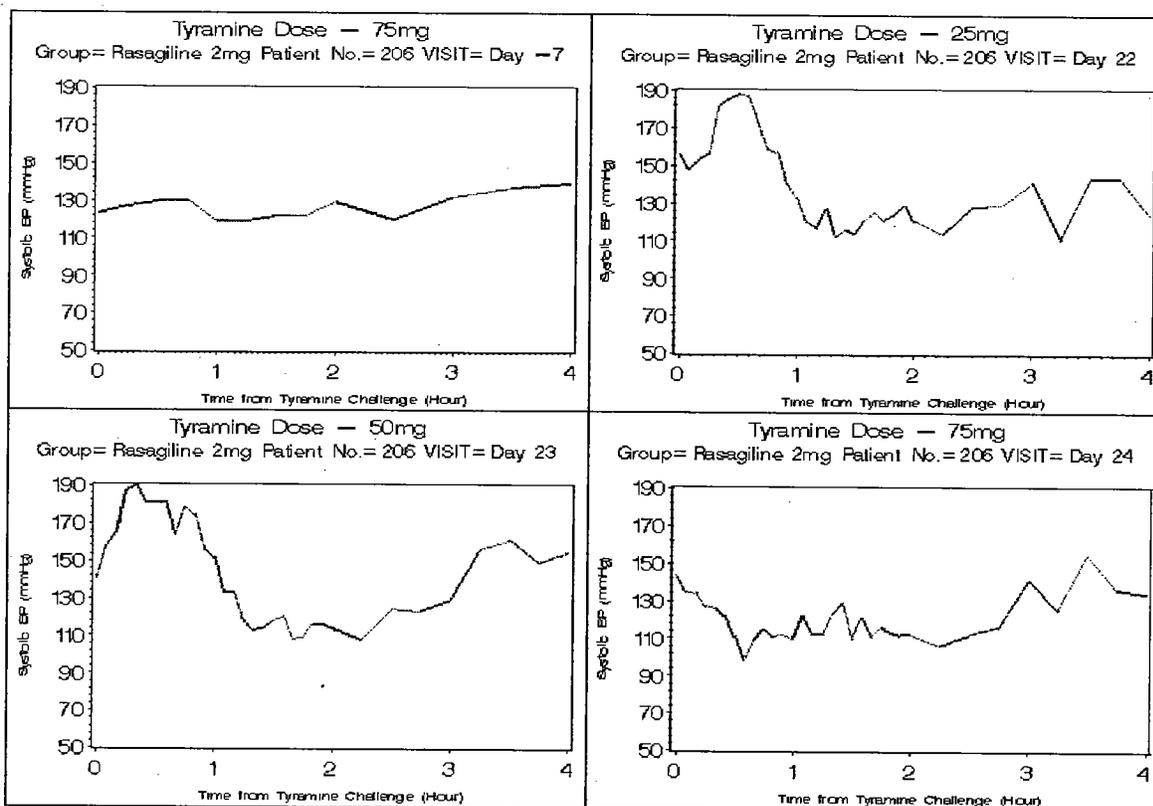
Following placebo administration and throughout the day the subject remained at around baseline levels with BP of 110-130/60-75. The subject was discharged from the clinic and was instructed to maintain a low tyramine diet. The subject reported episodes of hypotension as well as hypertension, as measured at home. These episodes were sometimes symptomatic and sometimes asymptomatic. Study drug was discontinued on November 16, 1998, after 33 days of treatment. The subject was instructed to monitor her BP at 30, 60, 90 and 120 minutes following LD/CD ingestion for one month. BP variability was reported. A thyroid function test was performed and found to be normal.

Blood levels of rasagiline and LD were obtained during the study as defined in the protocol. Both were very high in this subject compared to the study population. On Day 23, the rasagiline C_{max} was 27.7 ng/ml in this compared to 10.45 ± 8.6 ng/ml in the 2 mg rasagiline group. On Day 23, the LD C_{max} was 14,600 ng/ml in this subject compare to $3,869 \pm 5,358$ ng/ml in the 2 mg rasagiline group.

Blood levels of catecholamines were analyzed from the samples prepared for LD levels. There were no clinically significant results.

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Figure 6 Plot of Systolic Blood Pressure Over Time in Patient # 206 After Various Doses of Tyramine



Results Obtained during the Subject's Specific Evaluation (Amendment V of the Study Protocol)

It was decided to further evaluate the subject to gain additional information on the variability of her vital signs. The details of this evaluation are documented in Amendment V, a subject specific protocol. The following information was obtained after re-challenge with rasagiline 1mg/day and 2 mg/day: Vital signs, AEs, ECG, 24-hour ambulatory BP Measurements, pharmacokinetics (PAI, AI and LD) and catecholamine hormones secretion.

- Further assessments included 4 periods performed from January to April 2000:
- Period 1: 3-5 days off anti-Parkinson medications (LD and dopamine agonist)
 - Period 2: More than 7 days on anti-Parkinson medications
 - Period 3: 34 days on concomitant rasagiline 1 mg
 - Period 4: 34 days on concomitant rasagiline 2 mg

Supine and standing BP were measured at hospital visits, which were performed at the end of each period. BP was within normal range with tendency towards orthostatic hypotension, unrelated to rasagiline treatment.

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24-hour ambulatory BP monitoring was performed at the end of each period. High variability in BP and heart rate was found during all periods.

AE reports included several episodes of lightheadedness before and during rasagiline treatment. One of these episodes led to a one-day discontinuation of rasagiline 2 mg (after 33 days, one day before termination). During this last event of lightheadedness, BP showed marked orthostatic hypotension. The subject also reported one event of "hot and sweating" while treated for 30 days with rasagiline 2 mg.

ECG recordings were done at each visit. No clinically significant changes were detected.

Rasagiline concentration two hours post- administration was 2.93 ng/ml after 1 mg rasagiline and 9.01 ng/ml after 2 mg rasagiline. By contrast, on day 23 of the main study, two hours after 2 mg rasagiline administration, rasagiline concentration in this subject was 6.93 ng/ml, while the concentration at 2 hour of the 2 mg group was 2.70 ± 1.28 ng/ml.

LD concentrations, two hours post dosing were around normal values (543.1-819.1 ng/ml).

Plasma and urine catecholamine results did not show clinically significant results.

Subject #209

This was a 68 year-old Caucasian male. PD was diagnosed in 1983 characterized by tremor, rigidity and bradykinesia. He had been treated with LD since 1984 and suffered from fluctuations during the year prior to study participation. His general medical history included a herniated disc (1996); atonic bladder and cystostomy (1998); venous insufficiency (1992); hernia (1988); pancreatitis and cholecystectomy (1968); enlarged prostate (1998); degenerative arthritis (1996).

Results Obtained during the Per Protocol Study

Baseline diagnostic assessments included normal findings on physical examination. Vital signs (systolic/diastolic/pulse) were supine 120/84/52, sitting 118/86/56, standing 118/80/60.

Chest x-ray was normal ECG was normal. Screening was performed on March 24 1999 and the subject was enrolled on May 5 1999.

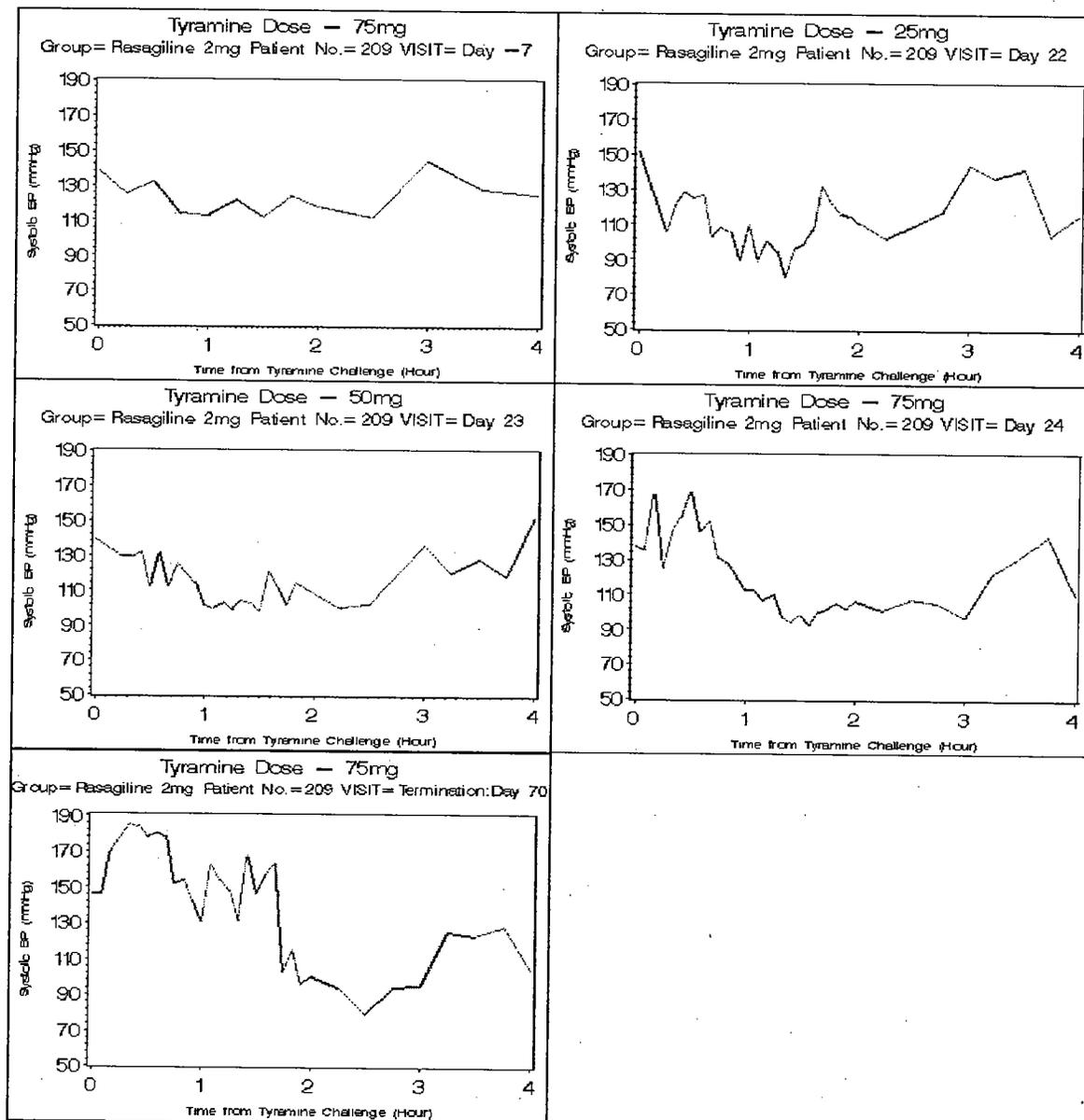
Ongoing medications included LD/CD 600/150 qid, LD/CD CR 600/150 qid, pergolide 4.5mg tid, tolcapone 300 mg tid, amantadine 200 mg bid, etodolac 200mg prn, furosemide 40 mg prn.

On the baseline challenge (Day -7) with 75 mg tyramine, the subject showed no reaction or sensitivity (Figure 7). The subject started rasagiline treatment on May 5 1999. The subject had an episode of diarrhea five days after the study start. He took analgesics and antibiotics for dental surgery from The subject reported lightheadedness for 10 days starting 45 days after study initiation.

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On Days 22 and 23, no reaction was observed to the 25 and 50 mg tyramine challenges. On Day 24, following 75mg tyramine dose, BP increased in one of the measurements to 168/85, 30 minutes post tyramine ingestion (baseline was 137/89). Pulse increased from 59 bpm at baseline to 79 bpm. The subject was asymptomatic. There was no need for any intervention and further increase in BP was not reported.

Figure 7 Plot of Systolic Blood Pressure Over Time in Patient # 206 After Various Doses of Tyramine



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On Day 70, after the 75 mg tyramine challenge, the subject's BP rose to a maximum of 191/108 at 15 minutes post dose. This elevation persisted for an additional 25 minutes with BP sustained around 180 mmHg systolic and several diastolic elevations over 100 mmHg (pre-tyramine was 146/81). Sinus bradycardia and transient ECG changes (AV-block) were also observed in the 3-lead ECG performed during the tyramine challenge. No intervention was needed nor taken. The subject remained asymptomatic throughout. ECG returned to normal as the BP decreased 20 minutes after the maximal elevation. Sinus bradycardia was observed several times during the study. The subject was discharged from the clinic and continued BP monitoring at home. The subject completed study treatment per protocol on July 15 1999.

Blood samples were taken during the study according to protocol to determine blood rasagiline and LD levels. Maximal LD levels were found to be high in this subject compared to the study population. On Day 70, the LD Cmax was 5122.5 ng/ml in this subject compared to 2244 ± 1435 ng/ml in the 2 mg rasagiline group. Blood rasagiline levels were within the upper normal range. On day 70, rasagiline Cmax was 6.18 ng/ml in this subject compared to 8.63 ± 4.5 ng/ml in the 2 mg rasagiline group. No samples taken at 0.5 hour due to tyramine reaction.

Results Obtained during the Subject's Specific Evaluation (Amendment VII of the Study Protocol)

To further evaluate his response to tyramine 25, 50 and 75 mg in the absence of rasagiline for at least one month, additional tyramine challenges were performed. The details of this evaluation are documented in Amendment VII, a subject specific protocol. Further assessments of this subject included three tyramine challenges. The subject repeated the tyramine challenges (25, 50, 75 mg) following a 5-month rasagiline washout period. Challenges were performed on December 13, 14 and 15 1999.

The subject completed the evaluation as planned. No tyramine reaction was observed at any of the tyramine doses administered. BP and heart rate remained around baseline values. ECG was normal during all three challenges days.

Pharmacokinetic (PK)Results

Table 30 depicts the mean calculated rasagiline PK parameters as were calculated from the measurements of Days 23 and 70. Indeed, calculation of the Tmax shows that regardless of the dose, the mean time to reach maximal rasagiline concentration in the plasma was less than one hour. As expected, the Cmax showed a clear dose dependency. As a result of these two parameters, the AUC0- 4h appears to be positively related to the dose increase.

In summary, levels of both rasagiline and its metabolite aminoindan (AI) were positively associated with the administered dose of rasagiline. Taken together, the pharmacokinetic profiles of rasagiline and AI observed in this study are comparable to levels previously observed in PD subjects or in healthy volunteers in other studies.

To assess a possible interaction between rasagiline and LD in subjects on chronic LD/ CD treatment the LD levels were strictly monitored. No significant differences in LD maximal

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plasma level (C_{max}) were detected between Day 1 when the subjects were treated with rasagiline and LD/ CD and Day 23 and Day 70, when rasagiline and tyramine were administered together with LD/ CD, in all treatment groups. Moreover, no significant differences were observed in plasma LD levels between Day - 7 (tyramine and LD/ CD only) and Day 23, indicating rasagiline- LD interaction.

Table 30 Descriptive Statistics of Rasagiline PK Parameters

| Protocol TVP-1012/132 | | Day 1 | | | Day 23 | | | Day 70 | | |
|--------------------------------|---------|-------|------|---------|--------|-------|---------|--------|-------|---------|
| | | 1mg | 2mg | Placebo | 1mg | 2mg | Placebo | 1mg | 2mg | Placebo |
| C _{max} (ng/mL) | N | 7 | 7 | 6 | 6 | 7 | 6 | 6 | 6 | 6 |
| | Mean | 3.14 | 6.47 | 0.00 | 5.66 | 10.45 | 0.00 | 4.95 | 8.63 | 0.00 |
| | Std. | 1.7 | 5.1 | 0.0 | 2.1 | 8.6 | 0.0 | 3.1 | 4.5 | 0.0 |
| | Minimum | 1.5 | 1.3 | 0.0 | 3.2 | 0.0 | 0.0 | 0.3 | 2.4 | 0.0 |
| | Maximum | 6.4 | 16.7 | 0.0 | 8.7 | 27.7 | 0.0 | 9.4 | 13.5 | 0.0 |
| T _{max} (Hr.) | N | 7 | 7 | 0 | 6 | 6 | 0 | 6 | 6 | 0 |
| | Mean | 0.88 | 0.69 | - | 0.94 | 0.87 | - | 0.70 | 0.86 | - |
| | Std. | 0.6 | 0.2 | - | 0.3 | 0.3 | - | 0.4 | 0.3 | - |
| | Minimum | 0.5 | 0.5 | - | 0.6 | 0.5 | - | 0.0 | 0.7 | - |
| | Maximum | 2.3 | 1.1 | - | 1.3 | 1.2 | - | 1.2 | 1.3 | - |
| AUC(0-4 hr.) (Hours*ng/mL) | N | 7 | 7 | 0 | 6 | 6 | 0 | 6 | 6 | 0 |
| | Mean | 2.36 | 5.34 | - | 9.49 | 19.78 | - | 6.95 | 14.00 | - |
| | Std. | 1.7 | 4.3 | - | 4.6 | 12.4 | - | 4.8 | 4.1 | - |
| | Minimum | 0.6 | 1.7 | - | 4.6 | 10.1 | - | 0.6 | 6.3 | - |
| | Maximum | 5.8 | 14.7 | - | 18.2 | 43.3 | - | 14.9 | 17.7 | - |
| AUC(0-24 hr.) (Hours*ng/mL) | N | 0 | 0 | 0 | 6 | 6 | 0 | 0 | 0 | 0 |
| | Mean | - | - | - | 10.44 | 25.87 | - | - | - | - |
| | Std. | - | - | - | 6.8 | 19.3 | - | - | - | - |
| | Minimum | - | - | - | 4.6 | 13.2 | - | - | - | - |
| | Maximum | - | - | - | 23.8 | 63.8 | - | - | - | - |

8.3.3. Sponsor's Discussion of Study Results

This double blind, placebo-controlled, randomized, single center, clinical pharmacology study enrolled 20 PD subjects on chronic LD/CD therapy. Participants were randomly allocated to one of three treatment groups (1 mg or 2 mg rasagiline or placebo).

The study was designed to evaluate the safety and tolerability of 1 and 2 mg rasagiline concomitantly administered with chronic LD/CD, and challenged with moderate to high doses of oral tyramine (up to 75 mg). For safety considerations, the 2 mg group commenced treatment only after the completion of the tyramine challenge of the 1 mg group. The tyramine capsule was to have been taken in applesauce following the morning meal to approximate reality, in which the only source of tyramine is food. However, the tyramine capsules were given with applesauce

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before the morning meal, under fasting conditions, allowing for rapid absorption and increased bioavailability.

Study participants were aged from 47-78 years with mean disease duration of approximately 5 years in all treatment groups. All subjects were treated with LD/CD for more than 80% of the time elapsed since PD diagnosis. All subjects (except one) appeared to have normal baseline ECG recordings, normal chest X-rays. Approximately 30 subject-months of exposure to rasagiline were accumulated and participants consumed more than 1.3 grams of rasagiline during the study. Of the 19 subjects who reported AEs, eight were recovered at the time of study completion. Eleven (11) subjects (four subjects in each the 1 mg group and in the placebo group and three subjects in the 2 mg group) had not recovered at the time of study completion and were maintained under treatment observation. Thirty-one (31) events out of the 62 reported AEs were under observation upon completion of the study.

All AEs were considered mild to moderate. No serious AEs were reported. Two subjects exhibited suspected tyramine/rasagiline interactions manifested by systolic but not diastolic BP changes. Both were in the 2 mg rasagiline group. Subjects #206 and #209 experienced reactions at the 50 mg and 75 mg tyramine dose, respectively. Their reactions were characterized by transient, short-term elevations in the BP. In both cases, reactions were asymptomatic and unaccompanied by significant changes in heart rate, physical examination or ECG abnormalities. No intervention was required in either subject and the reactions resolved entirely within 1-2 hours. One subject (#206) was discontinued from the study. The other (#209) experienced the reaction at the termination challenge, on the last dosing day. Both subjects were concomitantly treated with several additional medications including pergolide. Subsequent evaluations by the principal investigator, a local clinical cardiology consultant and a cardiovascular safety consultant independently concluded that these BP elevations probably represented a tyramine/rasagiline interaction. None of the subjects receiving 1 mg rasagiline showed any suspected tyramine-rasagiline interaction or elevation in BP.

It is evident from all vital sign measurements during the study as well as from telemetry performed during tyramine challenge that the results obtained for subjects in the 1 mg group are not different from those observed in placebo-treated subjects. In addition, review of all measurements derived from daily BP diaries, which were completed by the subjects twice daily, showed unremarkable findings. Throughout the period from after the tyramine challenge to study completion, subjects were not compelled to maintain a tyramine-restricted diet. Therefore, these measurements reflect the "true" behavior of concomitantly consumed rasagiline and tyramine. Two subjects withdrew from the trial due to AEs. These were subject #105 from the 1 mg rasagiline group and subject #206 from the 2 mg rasagiline group (see above). Overall, rasagiline treatment without tyramine challenge did not affect vital signs.

No PCS vital signs were attributed to treatment with rasagiline. Laboratory (blood chemistry, urinalysis and hematology) evaluations revealed no PCS results attributable to rasagiline treatment or to the tyramine/rasagiline interaction.

No drug effect on the total UPDRS score was detected. However, a drug-associated improvement in QOL as measured with the QOL questionnaires was reported by the subjects in all the assessed parameters (total, mobility, ADL, emotional well being, stigma, social support,

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cognition, communication and bodily discomfort). Apart from two subjects (one in 1 mg group and one in the 2 mg group), no changes were detected in the total daily dose of LD throughout the study period. No accumulation of rasagiline occurred. Moreover, similar values were found within each treatment group throughout the study. Blood rasagiline levels measured 30 minutes post drug intake in the active treatment groups indicated a dose dependant relationship. No traces of rasagiline or its metabolite were found at follow-up. The T_{max} was between 30-60 minutes, regardless of the dose administered. The C_{max} was dose dependent and was proportional to dose increment. The AUC_{0-4h} was positively related to dose increase.

Due to the longer t_{1/2} of aminoindan (AI), low levels were found in plasma prior to drug intake. However, no accumulation of the metabolite occurred, as evidenced by constant levels throughout the study. The levels measured 30 minutes after rasagiline administration in the different treatment groups indicate a dose dependent relationship. The T_{max} was between 2.2-3.3 hours, regardless of the dose administered. The C_{max} was dose proportional and the AUC_{0-4h} was positively correlated to the dose.

LD and CD plasma levels did not differ between the two-rasagiline treatment groups and the placebo group. Levels were similar before and after treatment with rasagiline and/or tyramine. Thus, the rasagiline treatment and the combined administration of rasagiline and tyramine did not affect the LD/CD plasma levels. MAO-B activity was totally inhibited in both active treatment groups compared to MAO-B activity detected on Day 1. During the washout period, MAO-B activity returned to baseline in the two-rasagiline treatment groups.

8.3.4. Sponsor's Conclusions

It can be concluded from the present study that some of the subjects who were treated with rasagiline 2 mg/day adjunctive to chronic LD/CD were probably sensitive to extremely high tyramine doses consumed under fasting condition. However, subjects treated with rasagiline 1 mg/day while maintaining chronic LD/CD therapy and exposed to the same extremely high level of tyramine seemed to be unaffected by the combined treatment. These subjects responded to tyramine challenge similarly to the placebo treated group.

No tyramine reactions were observed while the subjects did not maintain dietary tyramine restriction during the last 7 weeks of the study. In addition, rasagiline treatment significantly improved the subjects' subjective condition in all the assessed QOL parameters.

8.3.5. Reviewer's Comments

- The sponsor's approach in this study and in 2 other tyramine challenge substudies was to administer a significant amount (e.g. 25 - 75 mg) of exogenous tyramine that would approximate the amount of tyramine that an individual could potentially be exposed to in a "high" tyramine containing food or drink (e.g. 40-50 mg). In following this approach, the sponsor assessed blood pressure responses to exogenous tyramine (added to applesauce or yogurt or ice cream) given just before or after other food and compared response among various treatment groups (placebo vs 1 and 2 mg rasagiline or placebo vs 0.5 and 1 mg rasagiline). **However, I caution that this type of approach must be validated before one**

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could make any interpretations about changes in tyramine sensitivity (and MAO-A inhibition) related to the presence or absence of blood pressure responses to tyramine in these studies.

One way of validating this approach would be to study also a positive control group (e.g. subjects who have a significantly increased sensitivity to tyramine because of a drug treatment inhibiting MAO-A) and show the sensitivity of these subject to tyramine administered with food and also just before and after other food. Such data would show the magnitude of the increased sensitivity to tyramine. Another means for validating this approach of assessing and comparing blood pressure response by treatment group to a fixed dose of tyramine given with food and just before and after a meal would be to show that the plasma tyramine pharmacokinetics (including shape of the curve) is not substantially altered.

In one publication (Bieck et al., *J Neural Transm*, Suppl 28: 21-31, 1989), various amounts of tyramine contained in English cheddar cheese was supposed to have been administered to 10 subjects and compared with pressor responses after administration of an equivalent amount of tyramine in capsules (and 100 mg water). This comparison was conducted during treatment with an MAO inhibitor, brofaromine (150 mg/d). Figure 8 depicts results of this experiment and shows that pressor responses were less for tyramine administered with food than with tyramine given in capsules. **Although this study did not specify that subjects were fasting, I suspect that this was the case and that no other food was given around the time of the study.** To interpret the results of this study one would have to assume that the content of tyramine supposedly given in the cheese was accurate. Considering this assumption, I would expect that the plasma tyramine profile would have been different in subjects given the cheese containing tyramine. The authors interpret these results as suggesting that digestion of the cheese results such low plasma tyramine concentrations as to be relatively ineffective for producing a significant pressor response. However, despite these findings, the authors also acknowledge 2 other reports (Korn et al., *Psychopharmacol*, 88 : 153-157, 1986; Schulz et al., *Psychopharmacol*, 91: 515-516, 1987) that demonstrated that cheese containing tyramine produced pressor responses in subjects treated with tranlycypromine, a potent inhibitor of MAO-A. It seems also possible that rate and extent of absorption of tyramine in food could possibly vary but the tyramine contained in liquid such as wine might be rapid or immediate and complete. At this time, my impression would be that the issue remains unresolved as to the comparability (relative to pressor responses) of administering a known amount of tyramine in a capsule with the administering an equivalent amount of tyramine in a food.

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Figure 8 **Pressor Effects of Tyramine Administered in Capsules and in Cheese in Subjects Treated with Brofaromine (MAO Inhibitor)**

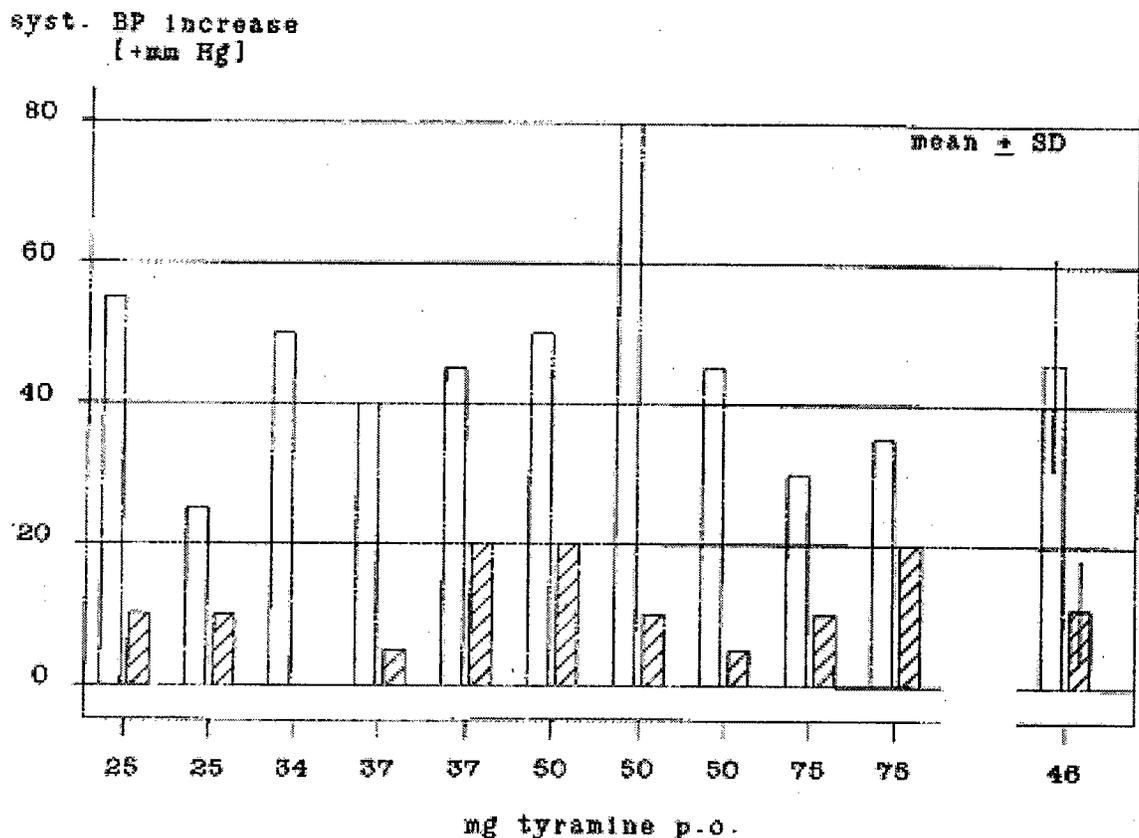


Fig. 3. Pressor effect of oral TYR in capsules □ or cheese ▨ in 10 subjects during treatment with brofaromine (150 mg/d, 14 d). Abscissa: individual PD₃₀ values of oral TYR in mg. Ordinate: increase of systolic BP

The sponsor has not validated in any way its unconventional approach for characterizing tyramine sensitivity by administered tyramine with food and before and after other food. Although I am aware that there are a limited number of publications that show results of blood pressure responses to oral tyramine administered with a meal after various drug treatments, I think that it is a stretch to say that this is an approach that it used to characterize a drug's effect on altering tyramine sensitivity. **I strongly consider the results of these studies involving tyramine administration with food and either just before or just after a meal to be of indeterminate significance in the absence of any validation for the sponsor's approach to confirm or suggest that the lack of a blood pressure response is a true negative.**

The sponsor seems to think that tyramine absorption and plasma tyramine PK are not altered by tyramine administration with applesauce or yogurt or ice cream but this is based upon the sponsor's speculation (and I think wishful thinking), not data. The sponsor does not have any

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data to support its impression about the lack of effect of these foods on tyramine PK and its ability to evoke a pressor response when given with these foods.

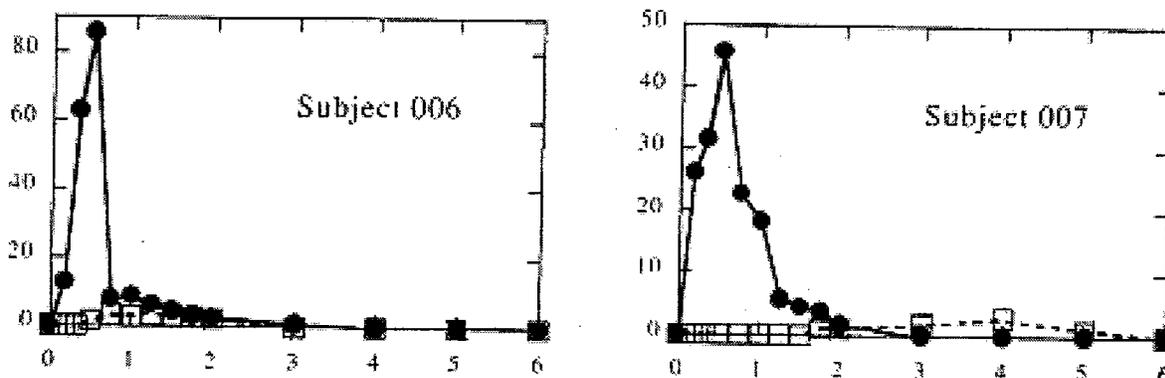
It is also relevant to note that the sponsor's plans to address the tyramine sensitivity and tyramine issues had been discussed with DNDP in at least 2 meetings (6/18/97, 8/23/00). The DNDP thought that data should be collected without tyramine dietary restrictions and that a provocative stimulus could be given by administering tyramine with a meal. This was thought to represent a more "real-world situation." The concept had been recognized that eating decreases the bioavailability of tyramine. **However, I am not aware nor do I think that information from other studies were specifically raised or discussed about how eating food with tyramine and shortly before and after a meal could alter the plasma tyramine profile and thus diminish or virtually abolish pressor responses. I am not aware that the sponsor was asked to validate its methods. My impression is there was not an appreciation among the participants about how administering tyramine with food could potentially confound the interpretation of "negative" results (e.g. no significant pressor reactions in patients given 50-75 mg tyramine with food and just before or after a meal).**

- The publication by Berlin et al. (*Clin Pharmacol Ther*, 46 : 344 – 351, 1989) clearly shows that subjects who have experienced MAO-A inhibition from moclobemide (200 mg TID) and reflect this inhibition with a moderately increased TSF (e.g. ~ 5) are not very sensitive to tyramine administered with food. The mean tyramine threshold of these subjects was 306 mg and ranged from 150 to 500 mg. Furthermore, subjects with extremely severe MAO-A inhibition from tranlycypromine (10 mg BID) and this inhibition with a markedly increased TSF (e.g. ~ 38) are very sensitive to tyramine administered with food. The mean tyramine threshold of these subjects was 35 mg and ranged from 20 to 50 mg. The results of this study suggests that even if rasagiline was associated with moderate MAO-A inhibition, it is unlikely that patients challenged with tryamine ranging from 25 to 75 mg administered with some food and immediately before or after a meal would exhibition a significant blood pressure pressor response. The most likely explanation would seem to be that the bioavailability of tyramine was diminished (i.e. the subject experienced a lower amount of tyramine) and possibly even that the intensity of the stimulus as reflected by the shape of the plasma tyramine curve may have also been diminished.

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Figure 9 Examples of Plasma Tyramine Pattern for Tyramine (250 mg tyramine HCl) Administered Under Fasting Conditions (closed circles and straight lines) and With a Meal (open squares and dashed lines)



- Given that the shape of the plasma tyramine curve (Figure 9) changes quite dramatically from a spike pattern to that of a gradual increase and decrease when tyramine is given with a meal, it would not be surprising to think that the pharmacodynamic action of tyramine might be significantly altered and not necessarily proportional to the overall exposure (i.e. AUC). For example, even if the AUC was unchanged but the shape of the curve was altered as it is, conceivably the ability of tyramine to provoke a hypertensive/pressor response could be significantly attenuated or even abolished.

A study by Korn et al. (*J Cardiovasc. Pharmacol*, 11: 17, 1988) provides insight into my concern about how altering the shape of the PK curve for plasma tyramine can alter the pressor responses. Table 31 shows how a meal markedly decreased plasma tyramine C_{max} and AUC and also markedly diminished blood pressure responses. Figure 10 shows the effect of administration of tyramine with meal on the shape of the plasma tyramine profile and the corresponding systolic blood pressure response. Figure 10 clearly shows that the meal diminished plasma tyramine exposure and dramatically altered the shape of the tyramine curve and markedly decreased the systolic blood pressure increment. The upper panels show the effect (on blood pressure and plasma tyramine) of the mean tyramine threshold dose of 3 subjects before (left panel, closed circles) and after 100 mg TID moclobemide (right panel, open circles) when tyramine was administered under fasting conditions. The lower panels show analogous data resulting from administration of tyramine capsules with a tyramine-free meal (i.e. 2 bread rolls, some jam, and weak herbal tea - 100 mls instead of water) The dose of tyramine corresponded to the each subject's tyramine threshold dose determined from study when tyramine was administered under fasting conditions before and after moclobemide treatment. Blood pressure measurements are depicted by the more frequent datapoints and plasma tyramine measurements are depicted by the less frequent datapoints.

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Table 31 Effect of a Meal on Peak Plasma Tyramine Concentration and Peak Systolic Blood Pressure (SBP) Changes Following Oral Tyramine Doses Before and After Moclobemide (MAO inhibitor)

| Subjects | Oral pressure tyramine dose (mg) | Phase 1 | | | | Oral pressure tyramine dose (mg) | Phase 2 | | | |
|----------|----------------------------------|-----------|-----------|-----------|-----------|----------------------------------|-----------|-----------|-----------|-----------|
| | | A | | B | | | A | | B | |
| | | C (ng/ml) | Δ (mm Hg) | C (ng/ml) | Δ (mm Hg) | | C (ng/ml) | Δ (mm Hg) | C (ng/ml) | Δ (mm Hg) |
| 1 | 600 | 108.1 | 65 | 48.1 | 15 | 100 | 94.9 | 65 | 19.9 | 20 |
| 2 | 400 | 109.1 | 50 | 13.4 | 15 | 150 | 84.1 | 75 | 35.1 | 25 |
| 3 | 400 | 182.8 | 50 | 17.9 | 5 | 150 | 108.0 | 70 | 16.7 | 10 |

Phase 1, before; Phase 2, after moclobemide; A, tyramine given with tap water; B, tyramine given with a meal.

Figure 10 Effect of Administering Tyramine Without and With a Meal on Plasma Tyramine and Systolic Blood Pressure Increment Before and After Moclobemide (MAO inhibitor)

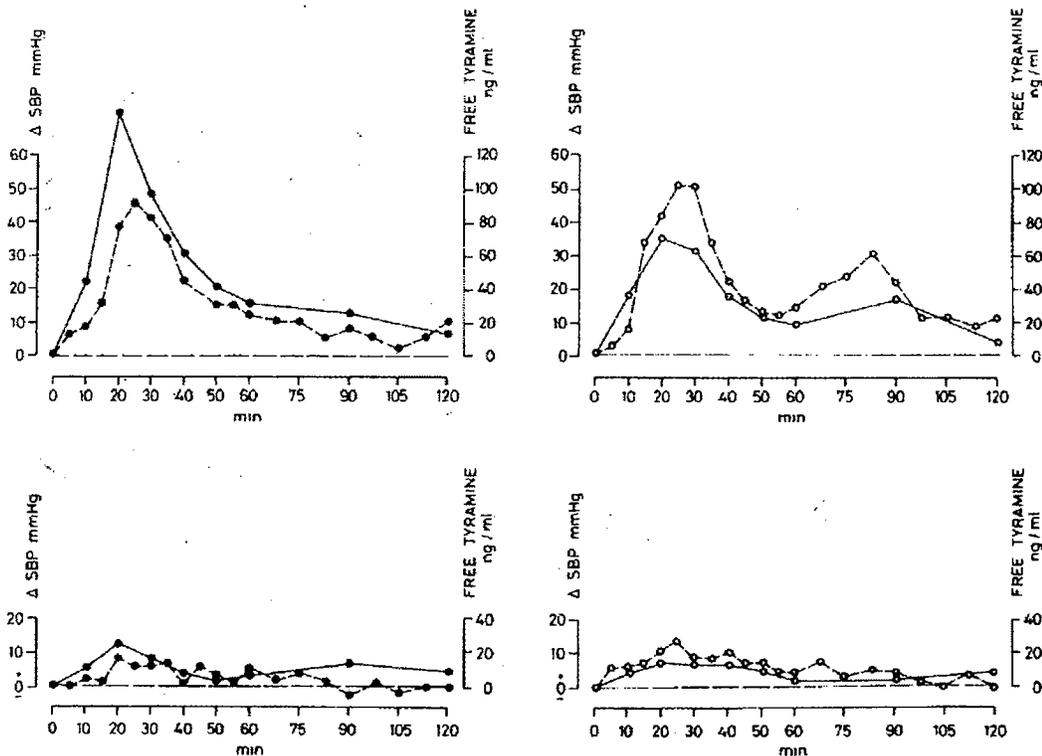


FIG. 5. Concentration of the free tyramine in plasma before (●—●) and after (○—○) moclobemide treatment and ΔSBP before (●—●) and after (○—○) moclobemide treatment following individual effective doses of tyramine. **Upper panel,** tyramine given with tap water; **lower panel,** tyramine given with a meal. Values are means ± SEM, n = 3.

This publication by Korn et al also noted how a drug (e.g. moclobemide) increased T_{max} for plasma tyramine in a subject and the corresponding pressor response that appeared to closely

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follow and parallel the increase in tyramine. Figure 10 that shows the mean results of 3 subjects do not clearly suggest this effect of moclobemide on T_{max}. This report also commented that moclobemide increased plasma tyramine concentration on the average 2.6 fold. Thus, it may seem prudent also to consider how a test drug itself might also affect tyramine sensitivity not only by inhibiting MAO-A but also by possibly altering the plasma profile of tyramine via a drug-tyramine interaction if tyramine is administered close to the time of administration of a drug. In the study (#132) under review, study medication (placebo or rasagiline) and LD/CD were administered 30 minutes prior to tyramine in applesauce. However, there is no information available as to whether either rasagiline or LD/CD alters the absorption and PK of tyramine.

Another publication by Audebert et al. (*Eur J Clin Pharmacol*, 43; 507-512, 1992) showed the effect of administering tyramine with different types of meals on pressor responses.

I also note that my concern about the sponsor's approach of administering tyramine just before (as in this study) or after a meal potentially confounds blood pressure responses because absorption of tyramine is not rapid and immediate. I believe that the shape of the plasma tyramine curve could be significantly altered even if tyramine was administered as a capsule and not sprinkled on food. Based upon my review (of the publication by Berlin et al. - cited previously) of the shape of pattern of the plasma tyramine curves on "average," most tyramine absorption appears to occur over approximately 1.5 hours when administered in the fasting state and this period of absorption increases to approximately 3 hours when tyramine is administered with a meal. Thus, it would be best that no food be given without several hours before or after tyramine to exclude the possibility that plasma tyramine PK was altered and correspondingly a pressor response to that amount of tyramine.

Table 32 describes the tyramine threshold dose (i.e. dose required to increase systolic blood pressure by ≥ 30 mm Hg) in 8 healthy subjects in the fasting state and after a tyramine was given with a standard meal **AND** after moclobemide treatment. Lower tyramine threshold doses were observed and the time to this pressor response was markedly prolonged from a mean of 42 minutes to a mean of 175 minutes (range 150 -230). However, it was not possible to assess the effect of moclobemide treatment alone on responses under the same fasting or fed state. Subjects were studied pre-treatment under fasting conditions and after treatment under conditions in which tyramine was administered via a capsule with a certain type of meal as shown. **The observation of how the meal prolongs the time to the peak pressor response bears relevance to the Study 132 under review because the frequency for measuring blood pressure was decreased during the last 2 hours of monitoring to 15 minute intervals (from 5 minute intervals for the first 2 hours). The study design used in Study 132 could decrease the opportunity for observing peak pressor response that always occurred after 2 hours (120 minutes) when tyramine was given with a standard meal to subjects whose data are shown in Table 32.**

I also note that my concern about the sponsor's approach of administering tyramine just before (as in this study) or after a meal potentially confounds blood pressure responses because absorption of tyramine is not rapid and immediate. I believe that the shape of the plasma tyramine curve could be significantly altered even if tyramine was administered as a capsule and not sprinkled on food. Based upon my review (of the publication by Berlin et al.

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- cited previously) of the shape of pattern of the plasma tyramine curves on "average," most tyramine absorption appears to occur over approximately 1.5 hours when administered in the fasting state and this period of absorption increases to approximately 3 hours when tyramine is administered with a meal. Thus, it would be best that no food be given without several hours before or after tyramine to exclude the possibility that plasma tyramine PK was altered and correspondingly a pressor response to that amount of tyramine.

Table 32 Effect of Tyramine Administered With Different Meals and Moclobemide (MAO Inhibitor) on Pressor Responses

Table 2. Tyramine threshold dose (expressed in milligrams). Systolic Blood Pressure increase (Δ PS, expressed in mm Hg) during an exercise test, tyramine test in the fasting condition and during the moclobemide-tyramine interaction with a standardized meal, and lipid-rich and protein-rich meals and the response time between administration and peak blood pressure (Δ T, in minutes)

| Subjects | Sex | Exercise test | Tyramine test (fasting) | | | Moclobemide-tyramine interaction | | | | | | | |
|----------|-----|---------------|-------------------------|------|-------------|----------------------------------|---------------|-------------|------------|-----------------|------------|-------------------|------------|
| | | | Δ PS | Dose | Δ PS | Δ T | Standard meal | | | Lipid-rich meal | | Protein-rich meal | |
| | | | | | | | Dose | Δ PS | Δ T | Δ PS | Δ T | Δ PS | Δ T |
| 1 | M | 50 | 400 | 45 | 20 | 350 | 43 | 230 | 36 | 210 | 40 | 150 | |
| 2 | M | 45 | 400 | 33 | 35 | 250 | 36 | 120 | 37 | 70 | 12 | 95 | |
| 3 | M | 30 | 400 | 36 | 30 | 400 | 25 | 170 | 7 | 240 | 20 | 190 | |
| 4 | F | 55 | 600 | 32 | 35 | 300 | 44 | 195 | 10 | 210 | 0 | | |
| 5 | M | 55 | 600 | 54 | 50 | 200 | 37 | 160 | 16 | 115 | 11 | 180 | |
| 6 | F | 45 | 400 | 30 | 40 | 150 | 37 | 195 | 17 | 190 | 27 | 210 | |
| 7 | F | 50 | 400 | 44 | 60 | 150 | 34 | 150 | 28 | 195 | 26 | 240 | |
| 8 | F | 50 | 600 | 32 | 55 | 200 | 37 | 180 | 15 | 195 | 33 | 240 | |
| Mean | | 47.5 | 475 | 38.2 | 40.6 | 250 | 36.6 | 175 | 20.7 | 178 | 21.1 | 186 | |
| SD | | 8.0 | 104 | 8.5 | 13.4 | 93 | 5.8 | 33.3 | 11.5 | 56.4 | 13.0 | 51.7 | |

- I am not aware of any study that directly compared (e.g. in the same study) the effect that a drug exerts on the TSF when tyramine is administered pre- and post- drug treatment with and without food. Such data could indicate whether the quantitative relationship regarding the tyramine potentiation as reflected by increased TSF is similar or not. If the TSF is similar under both testing designs (i. e. fasting and with food), then an assessment of tyramine potentiation might be demonstrated under either condition.

I was able to find one study (Bieck et al., *J Neural Transm*, Suppl 28: 21-31, 1989), however, that compared tyramine pressor responses to tyramine administered as a capsule and a similar amount of tyramine in cheese in subjects after treatment with an MAO inhibitor, brofaromine (150 mg QD). Figure 11 shows pressor responses of subjects administered a tyramine threshold dose (i.e. dose increasing systolic blood pressure by ≥ 30 mm Hg) with 100 ml water and English cheddar cheese supposedly containing a similar amount of tyramine as administered in a capsule (presumably under fasting conditions, although this was not explicitly stated). The pressor response for each subject was always greater for tyramine administered as a capsule without food. It is not known how reproducibly consistent or robust these results would be if one compared tyramine given as a capsule with a similar amount of tyramine administered in other tyramine containing products that are ingested (e.g. other tyramine containing foods or tyramine in wine). Neither is it clear what results would be observed if one investigated tyramine pressure responses using a similar experimental comparison of tyramine challenge both before and after treatment with a MAO inhibitor.

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Another study (Korn et al., *Psychopharmacol*, 88 : 153-157, 1986) utilized a tyramine challenge via 65 mg tyramine content in cheese along with 200 mg Chianti wine (without detectable tyramine). This tyramine challenge in food did not elicit a significant pressor response in subjects treated with a low daily dose of a MAO inhibitor, moclobemide (50 mg TID). However, 3 subjects treated with a potent MAO inhibitor, tranylcypromine (10 mg BID), that results in markedly increased tyramine sensitivity, did exhibit marked, sustained pressor responses. The maximal systolic blood pressure increment over baseline was 70, 75, and 100 mm Hg. The subject showing the greatest pressor response also had a severe headache and required urgent treatment with phentolamine. All subjects also showed a decrease in heart rate (up to 20 bpm below baseline). The ability of tyramine in food to evoke a significant pressor response seems likely to be directly related to the combination of the bioavailability of tyramine in the food product and the extent of MAO-A inhibition.

Figure 11 Pressor Effects of Tyramine Administered in Capsules and in Cheese in Subjects Treated with of Brofaromine (MAO Inhibitor)

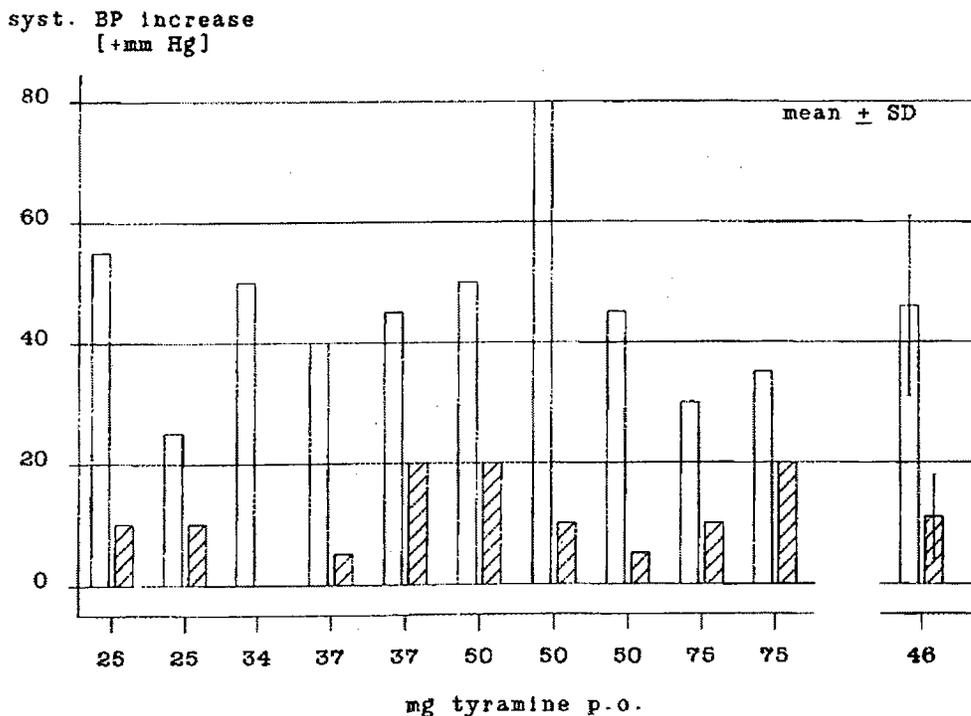


Fig. 3. Pressor effect of oral TYR in capsules □ or cheese ▨ in 10 subjects during treatment with brofaromine (150 mg/d, 14 d). Abscissa: individual PD₃₀ values of oral TYR in mg. Ordinate: increase of systolic BP

- My review of the data collected after tyramine administration (from day - 7 to day 70) focused on the mean maximal systolic blood pressure and the mean difference of this maximal systolic blood pressure from pre-tyramine (Table 25 - Table 29). There did not appear to be any clear pattern of an effect of rasagiline for producing higher blood pressure responses. Although the mean maximal systolic blood pressure difference was

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greater for the 2 mg rasagiline group vs placebo after 75 mg tyramine on day 24 (Table 28), this mean difference was not observed after administration of the same dose of tyramine on day 70 at the end of the study.

- In response to my request, the sponsor provided additional analyses of individual maximal systolic blood pressure and maximal systolic blood pressure increment above pre-tyramine systolic blood pressure and mean data according to treatment group for these all tyramine challenges. My review of these data did not suggest an effect of treatment on tyramine testing based upon mean maximal systolic blood pressure or mean maximal systolic blood pressure change. Mean ratios of maximal systolic blood pressure change for 75 mg at pre-treatment / day 70 did not suggest any treatment effect with mean ratio ranging between 2.1 – 2.5 for all 3 group. Neither was there any suggestion for an increased frequency of systolic blood pressure increments of ≥ 30 mm Hg after tyramine at any of the tyramine challenges.
- It appeared that patient # 206 may have experienced the hypertensive sustained threshold response (systolic blood increment > 30 mm Hg) to tyramine because of an increased exposure to 152 for rasagiline. This patient's PK data suggested that this patient was an outlier and generated a higher than expected exposure to plasma rasagiline. Conceivably this patient's response may have been a reflection of significant MAO-A inhibition. There was no clear explanation as to why the other patient (# 209) experienced the sustained hypertensive threshold response to tyramine.
- A review of the adverse events suggested that there may have been an increased frequency of AEs coded as hypertension related to rasagiline. Two patients treated with 2 mg rasagiline had 4 AEs, one patient treated with 1 mg rasagiline had 1 AE, and there were no such AEs in patients treated with placebo. The maximal severity of all these AEs was coded as moderate, the highest category available for coding.
- It is interesting to note that when one looks at potentially clinically significant (PCS) abnormal orthostatic vital signs that occurred after tyramine and study treatment that the frequency (Table 24) of hypertensive events (i.e. blood pressure increments > 30 mm Hg) is greatest in the 2 mg rasagiline group. The frequency of such events when occurring in the 1 mg group is typically greater than that in the placebo group.
- I reviewed data listings showing the occurrence of PCS blood pressure readings from home ambulatory recordings and did not find evidence suggesting a clear effect of rasagiline on outlier readings, particularly for hypertensive events. The sponsor also presented graphs of ambulatory blood pressure readings in individual. My review of these graphs did not suggest any clear pattern of abnormalities related to rasagiline. Because the instruction for the evening measurement after dinner was to obtain a reading after dinner without any time specification, there was no systematic collection of data at a particular time after eating.
- Mean systolic blood pressure difference during various orthostatic maneuvers (supine to sitting, sitting to standing, supine to standing) seemed increased in many instances with

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rasagiline treatment vs placebo (Table 23). Data for these calculations had been obtained by measuring orthostatic blood pressure responses at 0, 2, 4, 6, 8, and 12 hours after tyramine. At screening there were no clear or outstanding mean differences among the 3 treatment groups for the different orthostatic maneuvers. However, during study treatment and especially on days that tyramine was administered the mean values appeared to be greater for each rasagiline group compared to placebo on most days for supine to sitting and supine to standing. The difference I suggest did not seem as apparent for sitting to standing. In general, the treatment difference (i.e. mean rasagiline result – mean placebo result) seemed greater for 2 mg rasagiline vs 1 mg rasagiline. The effect that I suggest seems most striking if one compares treatment differences on day 70 after 75 mg tyramine. The mean treatment effect for supine to sitting, sitting to standing, and supine to standing respectively for the 1 mg rasagiline was 7.5, 0.6, and 8.1, and for the 2 mg rasagiline group was 19.4, 0.6, and 20.0.

I question whether the observations I made might be general effects on blood pressure related to rasagiline or effects on blood pressure related to rasagiline treatment and tyramine administration. Thus, I check the Safety Review conducted by Dr. Lisa Jones. Of interest, the incidence of patients with PCS vital sign changes was higher for 1 mg rasagiline (vs placebo) for high systolic blood pressure (> 180) or diastolic blood pressure (> 100) (4.2 % vs 3.1 %) and for supine to standing systolic blood pressure (> 30) or diastolic blood pressure (> 20) (13.4 % vs 8.5 %). These data were related to Parkinson's Disease patients participating in adjunctive trials using concomitant LD. There was no similar presentation for 2 mg rasagiline. The incidence of similar changes was not higher for 1 mg rasagiline (vs placebo) in the monotherapy trial suggesting the possibility that this effect might be related to concomitant LD treatment. The incidence of adjunctive therapy patients showing any combination of these changes as a change from baseline was higher for 1 mg rasagiline (2.1 %) vs placebo (1.3 %). However, when mean data of changes from baseline were assessed, there were no clear differences in a host of mean blood pressure comparisons after different orthostatic maneuvers.

Although the mechanism of these apparent blood pressure changes at least in some individuals is not entirely clear, I do not think that one can exclude the possibility that there is some relationship to ingestion of tyramine and some MAO-A inhibition in some individuals. There may also be an increased risk for this hypertensive effect related to concomitant LD use.

- There are relatively few data that address the question of the effect of concomitant, adjunctive LD/CD treatment on PK parameters for rasagiline. This is an important issue because an increase of rasagiline exposure from concomitant LD could potentially increase MAO-A inhibition and thereby the risk for a hypertensive “cheese” reaction. The most important question, I suggest, is what does LD do to rasagiline exposure (i.e. plasma rasagiline AUC). There were no PK studies conducted in which the effect of LD was investigated as a potential drug interaction on rasagiline. When I compare AUC_{0-t} across studies for multidosing of 2 mg rasagiline, AUC_{0-24} was higher (26) in Parkinson's Disease patients treated with LD in this study than the AUC_{0-24} (20) in a PK

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study of relatively young, healthy males treated with 2 mg daily of rasagiline alone.

There were no data for $AUC_{0-\infty}$ for comparison nor for lower doses. Population PK analyses from Study 232 that were derived from a relatively limited number of samples of patients who began LD treatment suggested that there is a 31 % decrease in clearance of rasagiline when LD is used. However, a more precise estimate of what concomitant LD treatment does to rasagiline exposure for patients dosed with 0.5, 1, or 2 mg daily remains to be established. I think that it would be important determine more precisely how LD will impact on plasma rasagiline exposure, especially considering that increased exposure can increase MAO-A inhibition and risk for hypertensive “cheese” reaction.

- I have noted my concerns about the biological potency for tyramine in Study P94159 because the majority (18/29) of subjects exhibited a pressor threshold response at 800 mg or did not exhibit a threshold response. This is extremely unusual. The sponsor used tyramine from the same supplier / — for this study. Thus, the possibility exists that results observed in this study could underestimate the tyramine sensitivity if the tyramine used had a decreased potency than that which is normally expected.

8.3.6. Reviewer’s Conclusions

- **The potentially confounding effect of administering tyramine with food (i.e. applesauce) and also eating a few minutes after this does not allow one to draw any conclusions about the effect of tyramine exposure on blood pressure response in patients treated with 1 or 2 mg rasagiline daily. It is not possible to know whether the lack of significant pressor responses in most patients administered tyramine in this study design is a true negative or potentially a false negative because of the impact of the food on the plasma tyramine profile and corresponding pressor response.**
- **The sponsor has not validated its approach of assessing tyramine sensitivity (i.e. pressor responses after tyramine) when tyramine is administered with food and immediately before other food.**
- Based upon a variety of studies in the literature, there is clear evidence that food can markedly alter the plasma tyramine profile by diminishing C_{max} , AUC, and delaying T_{max} and also the pressor response to this altered plasma tyramine curve.
- The study design employed may have missed some tyramine-induced hypertensive reactions meeting the primary outcome measure and occurring relatively late (e.g. between 2– 4 hours) because of the confounding effect of food on the time to the response and the less frequent monitoring (e.g. every 15 minutes instead of every 5 minutes).
- There is a suggestion that 2 mg rasagiline treatment may be associated with an increased frequency of sustained, increased blood pressure responses in some patients administered

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tyramine (50 mg or 75 mg) and during orthostatic maneuvers (for both 1 and 2 mg rasagiline) especially changes from supine to sitting and supine to standing positions.

- There is a need to assess the effect of multidosing of LD on PK parameters for rasagiline, especially plasma rasagiline exposure (i.e. AUC) at daily doses ranging between 0.5 and 2 mg.
- It is not possible to know whether the tyramine used in this studied had a lower biological potency than that which is normally expected. If the biological potency of tyramine was diminished, results of this study may be an underestimate of the risk for rasagiline-induced tyramine sensitivity.

8.4. Study TVP-1012/232 TEMPO Tyramine Substudy

8.4.1. Description of Protocol TEMPO (#232) Tyramine SubStudy

Objective

The aim of this sub-study was to evaluate the effect of an oral dose of tyramine in PD patients chronically treated with rasagiline (1 mg or 2 mg/day) or placebo for six months.

Study Design

The study was conducted in 55 patients at 11 centers. The tyramine challenge was performed on the last day of the placebo-controlled phase of the study, before rolling over to the active-treatment phase. Following a light, low tyramine meal, patients had their baseline supine vital signs taken at 10-minute intervals for 30 minutes, at which point they received a capsule containing 75 mg of tyramine hydrochloride that was opened and mixed with applesauce. The tyramine dose used in this study was about two to three times higher than what might be ingested in a tyramine rich meal.

The patients were closely monitored for any potential hypertensive or bradycardic reaction: supine blood pressure and pulse were measured for 120 minutes at 5 minutes intervals. If there was either an elevation of systolic blood pressure by >30 mmHg compared to baseline for 3 consecutive measurements or a decrease in pulse to 40 bpm or less, then vital signs were taken for additional 60 minutes in 15 minutes intervals.

Study Population

Subjects with early untreated PD who are participating in TEMPO and who have completed the double-blind phase of the main study but have not begun the active treatment phase. Subjects who complete 26 weeks of the double-blind phase or subjects who reach the end point of needing additional therapy for PD are eligible. The maximum number of subjects includes those who completed 26 weeks of double-blind treatment in TEMPO, or who have reached the endpoint of needing additional therapy, and are willing to participate in the tyramine tolerance – up to 360 subjects.

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Main Inclusion Criteria :

- a) Men and women with idiopathic Parkinson's disease (PD) who have met inclusion criteria for TEMPO, and are currently enrolled in TEMPO.
- b) Subjects must have completed all procedures of the visit 5 (week 26) evaluation.

Exclusion Criteria :

- a) Subjects must not have begun the active treatment phase of TEMPO, or have started additional therapy for parkinsonism (i.e. LD, dopamine agonists).
- b) Subjects must not have a history of aneurysm or intracranial hemorrhage.
- c) Subjects should not have uncontrolled Hypertension BPs > 160/90.

Location and Investigators

The tyramine tolerance was to be conducted at a site, such as a clinical research center, that was equipped for intensive cardiovascular monitoring, and the administration of intravenous medications. The location was to have convenient access to an emergency room. The tyramine tolerance was to be conducted by an independent investigator and coordinator (different than the investigator and coordinator of TEMPO). The tyramine tolerance coordinator was to be immediately available to the subject throughout the study visit, and the investigator was to be available so that he/she could be at the subject's bedside within 5 minutes of being called by the coordinator. The TEMPO site investigator and coordinator was to remain blinded to the results of the tyramine tolerance until all subjects at their site had completed the double-blind phase of TEMPO study. The site investigator of TEMPO was to be informed only in cases of Serious Adverse Experiences or clinically significant adverse experiences that would have an impact on participation of the subject in the active treatment extension.

Specific Study Procedures

Following a regular meal, subjects were to have baseline hemodynamic monitoring, then receive a standard dose of tyramine and then be closely monitored for a possible tyramine MAO reaction (this could include headache and bradycardia).

Baseline: Supine blood pressure and heart rate were to be measured by an automated device every ten minutes for a 30 minute baseline period before tyramine is administered (t - 30 min, - 20 min, -10 min, 0 min). Baseline blood pressure and pulse were defined as the average of the four readings obtained before administration of tyramine.

Tyramine administration: Tyramine was to be administered immediately following the baseline period.

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Active monitoring: The active monitoring period began immediately after the subject had received the dosage of tyramine. Supine blood pressure and heart rate were to be measured every five minutes for 120 minutes. Continuous 3 lead ECG were also to be recorded during the initial 120 minutes of active monitoring. If there had been neither : 1) a > 20 mm Hg rise in SBP from baseline over 3 consecutive measurements; 2) significant bradycardia (< 40 BPM); or 3) significant ECG changes during the initial 120 minutes of monitoring following the tyramine dosing, the frequency of heart rate and blood pressure monitoring were to be changed to every 15 minutes for 60 additional minutes. Subjects who did not show a significant reaction were to be observed in clinic for an additional hour (total of 4 hours).

Additional monitoring in case of reaction: If there was, at any time during the 4 hours of active monitoring, a significant reaction (as described above), supine blood pressure and heart rate should have been monitored every five minutes until the cardiovascular changes had resolved, and then for one additional hour. Continuous 3 lead ECG should also have been monitored during this period. Pulse and blood pressure were to be obtained every 15 minutes for one hour. These subjects should then be observed for at least an additional hour (total duration of observation was to be at least four hours).

For subjects who experienced a severe reaction to the tyramine such that they required pharmacological intervention to lower blood pressure, blood pressure and pulse should have been monitored every 5 minutes and continuous three lead ECG obtained during the duration of hemodynamic abnormality and period of treatment, and for one hour following the return of blood pressure and pulse to baseline levels at that visit. Blood pressure and pulse should then have been monitored every 15 minutes for two additional hours. For the second hour, subjects were to be clinically observed, one vital sign measure was to be taken at the end of the second hour.

Twelve lead ECG: For subjects participating in the tyramine tolerance the ECG performed just prior to the subject's participation in the tyramine tolerance could also be used for the Visit 5 (week 26) ECG required for TEMPO. For all subjects, standard twelve-lead ECG was to be performed once during the 30 minute baseline period before the tyramine dosing and then 4 hours after the meal. Twelve lead ECGs should also have been performed at the onset and conclusion of any cardiovascular reaction.

Orthostatic measurements: For all subjects, standing and supine vital signs were to be obtained 30 minutes prior and immediately before administering the tyramine in applesauce, and then 2 and 4 hours after tyramine administration. Subjects who experienced a cardiovascular reaction were to remain supine for the duration of the reaction. Measurement of standing blood pressure was to be postponed until the resolution of the reaction.

Adverse events were to be recorded as they occurred.

Subjects who experienced a clinically significant change in cardiovascular parameters were to be placed on a tyramine restricted diet for the remainder of the TEMPO study.

Procedure for treatment of severe or clinically significant hypertension.

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If systolic blood pressure is ≥ 60 mm Hg higher than baseline or > 190 mm Hg, if diastolic blood pressure is ≥ 30 mm Hg higher than baseline or > 115 mm Hg, or if the investigator believes that the subject experienced a clinically significant tyramine reaction that requiring anti- intervention therapy, anti-hypertensive therapy was to be initiated according to the following protocol:

1. Labetolol, an alpha-beta adrenergic blocking agent, could be given as an intravenous injection using an initial dose of 5 mg over 1-2 minutes. If there was no response (i.e., at least a 10-20 mm Hg decrease in systolic BP or a 5-10 beat/minute increase in heart rate) within 5-7 minutes, a repeat dose of 10 mg of labetolol should have been administered over 1-2 minutes. This process should have been repeated in 10 minutes if the clinical response was unsatisfactory. The subject was 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 labetolol (i.e., history of bronchial asthma, sick sinus syndrome, first degree atrioventricular block with PR interval > 0.24 seconds), phentolamine, an alpha-1 blocker could be used. This drug should have been administered intravenously at a dosage of 2 mg over 15-30 seconds. If there was an inadequate response within 2-7 minutes, a second intravenous injection of 5 mg should have been given over 30-60 seconds.

3. If neither therapy yielded acceptable clinical results, the subject should have been 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.

Outcomes Measurements :

1. Primary Outcome Measures :

Number of subjects in each group who experienced one or more of the following cardiovascular events:

a) A ≥ 30 mm Hg increase in systolic blood pressure from baseline (documented by at least 3 consecutive measurements)

b) Bradycardia with a heart rate below 40 beats per minute (documented by at least 3 measurements over 10 minutes)

c) Clinically significant ECG changes

2. Secondary Outcome Measures :

a) Change in systolic blood pressure

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- b) Change in diastolic blood pressure
- c) Change in pulse
- d) Frequency of adverse events
- e) Frequency of abnormal ECG findings
- f) Number of subjects in each group requiring treatment with antihypertensives

Materials and Supplies

1. Study Medication

- a) Rasagiline: Subjects were to receive their assigned dosage of rasagiline dispensed as per protocol TVP-1012/232. Subjects were to take study medication as usual in the morning on the day of the tyramine tolerance.
- b) Tyramine: Subjects were to receive 75 mg of tyramine as a capsule of tyramine HCl. Tyramine capsule was to be opened and mixed into applesauce. Storage conditions for tyramine HCl : room temperature (15-25°C 59-77°F).

2. Study Meal

The study meal was meant to simulate the subject's normal dietary habits. The subject was to be provided with a reasonable stipend (e.g., ten dollars) to purchase amounts and types of food of his/her choice at the hospital or clinic cafeteria. Tyramine containing foods were to be avoided and subjects were to be provided with a list of excluded food items (e.g., certain cheese, liver). The subject could consume the meal either outside of or at the research center. Alternatively, the study coordinator could arrange for a meal of the subject's choice to be brought to the research center. No more than one hour was to elapse between the completion of the meal and administration of tyramine. Subjects were to confirm that none of the listed high-tyramine foods were consumed at this meal.

3. Monitoring Devices:

- a) Blood pressure and heart rate were to be measured by semi-automatic or automatic monitor.
- b) ECG was to be obtained using standard 12 lead electrocardiography.
- c) Continuous 3 lead ECG was to be obtained using standard cardiac telemetry monitor capable of making paper print-outs.

Analysis Plan

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Distributions of relevant demographic and clinical variables at enrollment into TEMPO were to be compared for subjects participating in the tyramine tolerance and those not participating (for any reason). Reasons for non-participation were to be tabulated by TEMPO treatment group.

Comparisons of the numbers of subjects experiencing the primary outcome event (increase in systolic blood pressure, bradycardia, significant ECG change) in each active treatment group versus the number experiencing the outcome in the placebo group were to be made using a one-sided test based on the binomial distribution, or if the outcome was rare, the Poisson distribution. One-sided 95% confidence intervals for the population risk in each active treatment group were also to be calculated. For example, if 100 subjects in an active treatment group underwent the tyramine tolerance and no primary outcome events were experienced, the expectation was that there could be 95% confidence that the population risk of such events would be < 3%. These analyses were to be repeated for component events (increase of 30 mm Hg in systolic blood pressure, bradycardia, clinically significant ECG changes).

Changes from baseline (tyramine tolerance) in the blood pressure (systolic and diastolic) and pulse measurements were to be compared among the three treatment groups. Changes from baseline to each subsequent evaluation and the total “area under the curve” were to be evaluated.

Sample Size Considerations: Because the occurrence of the primary outcome was expected to be rare, the sponsor did not expect to find statistically significant differences between the treatment groups. As stated above, the sponsor expected to be able to place upper confidence limits on the population rates of occurrence based on the numbers of events seen. For example, zero outcomes among a sample of 100 subjects would give 95% confidence that the true rate of occurrence was < 3%.

Conventional small size calculations could be performed for the secondary variables. For example, if it was assumed that the standard deviation of the difference between two repeated measurements of systolic or diastolic blood-pressure taken on the same subject 10 minutes apart was 5 mm Hg, samples of size 84 per group were expected to give > 90% power of detecting a differential mean change of 2.5 mm Hg between two groups, using a 0.05 level two-sided test.

8.4.2. Presentation of Results of TEMPO (#232) Tyramine SubStudy

Baseline Characteristics

Of the 55 patients that participated in the sub-study, 19 patients were drawn from each of the rasagiline groups and 17 from the placebo group. All were Caucasians except for one Black patient in the 2 mg/day rasagiline group. There were 7%, 47% and 59% males in the 1 mg/day, 2 mg/day and placebo groups, respectively. The majority of patients were hospitalized prior to study entry. The mean disease duration was 0.8 ± 0.7 , 1.31 ± 1.6 and 0.88 ± 0.7 for the 1 mg, 2 mg and placebo groups, respectively. Two patients in the placebo group demonstrated a need for additional anti-PD therapy. The baseline characteristics of patients who chose to participate in the sub-study were similar to those who did not participate.

Eligibility Criteria

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All patients (excluding one patient in each of the 2 mg and placebo groups who completed meal within 30 minutes prior to tyramine intake) met the eligibility criteria for participating in the sub-study as Study TVP-1012/232 (TEMPO), the study under which they had already been enrolled and were still under treatment. Two patients (3.6%) in the placebo group demonstrated a need to additional anti-PD therapy.

Table 33 Distribution of Patients by Eligibility Criterion

| TVP -1012/232 Tyramine Sub-Study | All | 1 mg | | 2 mg | | PLACEBO | |
|---|-----|------|-------|------|-------|---------|-------|
| | N | N | % | N | % | N | % |
| All | 55 | 19 | 100.0 | 19 | 100.0 | 17 | 100.0 |
| Sign Tyramine Tolerance Consent Form | 55 | 19 | 100.0 | 19 | 100.0 | 17 | 100.0 |
| Completed Placebo-controlled Phase of TEMPO | 55 | 19 | 100.0 | 19 | 100.0 | 17 | 100.0 |
| Blood Pressure <= 160/90 | 55 | 19 | 100.0 | 19 | 100.0 | 17 | 100.0 |
| No Aneurysm/intra -cranial hemorrhage history | 55 | 19 | 100.0 | 19 | 100.0 | 17 | 100.0 |
| Completed meal within the previous 30 min | 53 | 19 | 100.0 | 18 | 94.7 | 16 | 94.1 |
| Consumed lunch w/o high tyramine foods | 55 | 19 | 100.0 | 19 | 100.0 | 17 | 100.0 |

Cross Reference: Appended Table: Distribution of Eligibility Criteria, Section xx.

Adverse Experiences

One patient in the 2 mg/day rasagiline group and one patient in the placebo group experienced headache. Another patient in the 2 mg/day group felt nervous.

Vital Signs

All post-tyramine consumption measurements in each parameter were pooled. As demonstrated, means of vital sign results were comparable across treatment groups (Table 34, Table 35 and Table 36). None of the site investigators reported vital sign reactions.

Upon a specific request from the Sponsor, the data obtained from the tyramine sub-study had been reviewed by the Safety Monitoring Committee (SMC) for the TEMPO study in a conference held on 23rd February 2000. Based on its observations, the SMC had some concern regarding the blood pressure of 2 patients (out of 55). Because at that time the study codes had not yet been broken, the SMC requested the treatment assignment for these two patients.

Both patients who exhibited increases in systolic BP had been randomized to 2 mg/day rasagiline. One patient (#40) had a consistent increase in systolic blood pressure of 27 mmHg at around 60 minutes post tyramine administration without pulse changes or accompanying symptoms (Figure 12). In the other case (patient #605), there was a moderate but not sustained increase in systolic blood pressure 65 minutes after tyramine administration and then again between 95-105 minutes (Figure 13). The blood pressure values did not rise above 165 mmHg at any point in time. There was no associated bradycardia. The patient remained asymptomatic and did not require intervention. Review of the medical history of these two patients revealed that both had a history of mild and controlled hypertension. The absolute values of blood pressure measured in these patients did not meet the pre-defined criteria for tyramine-MAO inhibitor reaction. It should be noted that these two patients had maintained a non-restricted diet during both study phases (until the point at which the data was reviewed by the DSMB) without any complication that could be attributed to tyramine effect.

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Figure 12 Systolic Blood Pressure of Patient # 40 (2 mg Rasagiline) After 75 mg Tyramine

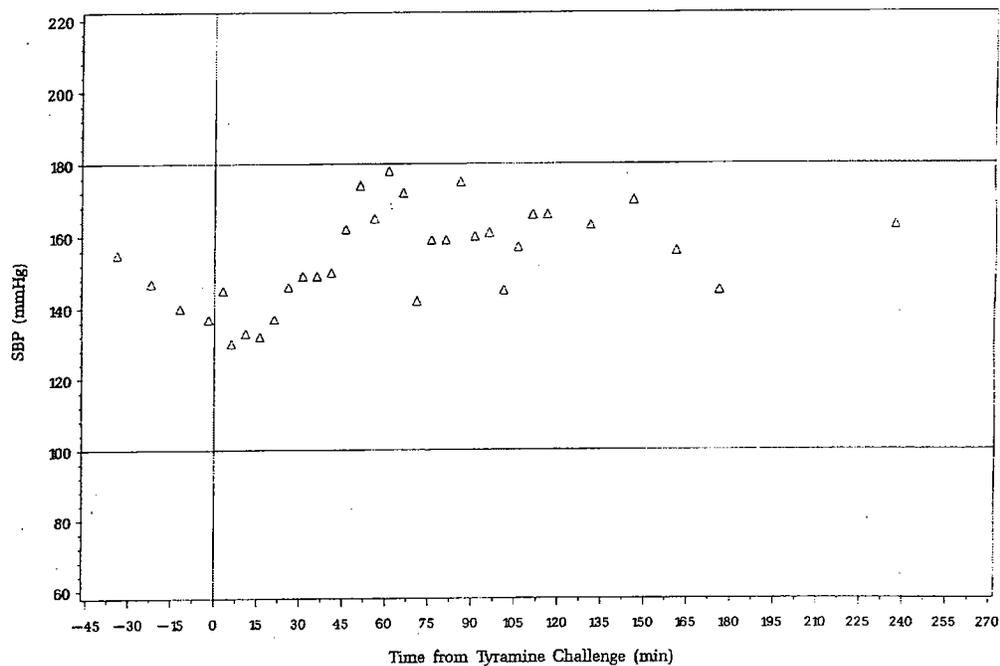
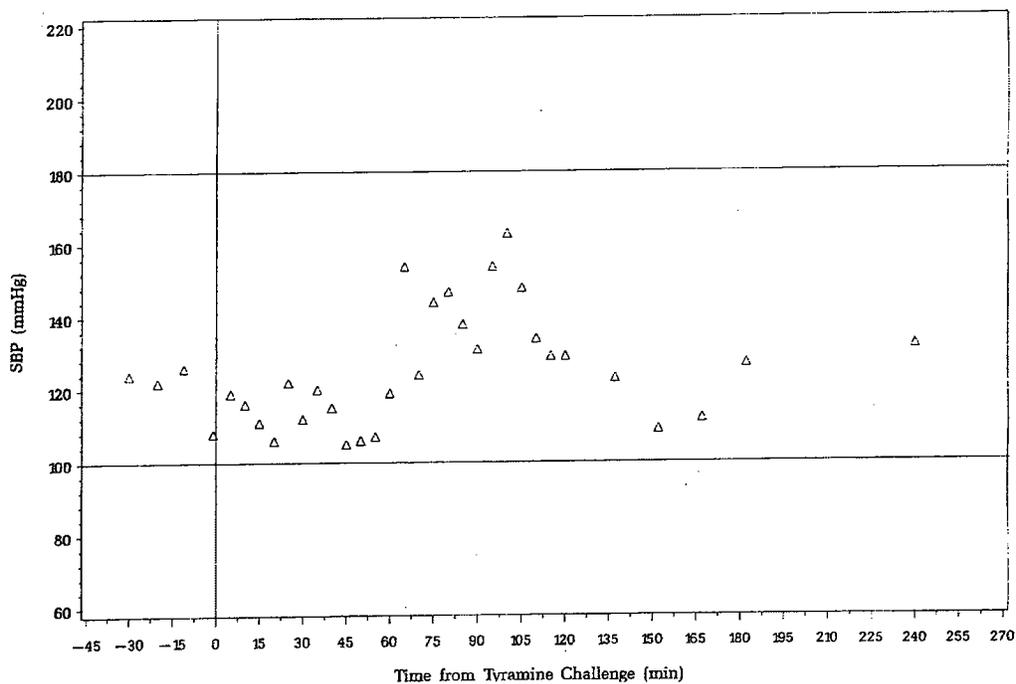


Figure 13 Systolic Blood Pressure of Patient # 605 (2 mg Rasagiline) After 75 mg Tyramine



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Table 34 Descriptive Statistics of Supine SBP (mmHg) prior to and after Tyramine Challenge

| TVP -1012/232 Tyramine Sub-Study | | 1 mg | 2 mg | PLACEBO | All |
|--|------|-------|-------|---------|-------|
| Mean SBP at Baseline (mmHg) | N | 19 | 19 | 17 | 55 |
| | Mean | 128.9 | 131.2 | 121.4 | 127.4 |
| | Std | 12.3 | 14.3 | 12.2 | 13.4 |
| | Min | 104.5 | 108.8 | 98.3 | 98.3 |
| | Max | 151.0 | 155.8 | 146.3 | 155.8 |
| Mean SBP (mmHg) after Tyramine Challenge | N | 19 | 19 | 17 | 55 |
| | Mean | 129.9 | 132.4 | 119.3 | 127.5 |
| | Std | 13.9 | 14.1 | 12.5 | 14.5 |
| | Min | 96.2 | 110.5 | 99.8 | 96.2 |
| | Max | 150.7 | 156.9 | 140.9 | 156.9 |
| Mean Change from Baseline of SBP (mmHg) | N | 19 | 19 | 17 | 55 |
| | Mean | 1.0 | 1.2 | -2.2 | 0.1 |
| | Std | 6.8 | 4.9 | 8.3 | 6.8 |
| | Min | -15.9 | -9.3 | -13.2 | -15.9 |
| | Max | 12.9 | 10.7 | 12.5 | 12.9 |

Table 35 Descriptive Statistics of Supine DBP (mmHg) prior to and after Tyramine Challenge

| TVP -1012/232 Tyramine Sub-Study | | 1 mg | 2 mg | PLACEBO | All |
|--|------|-------|-------|---------|-------|
| Mean DBP at Baseline (mmHg) | N | 19 | 19 | 17 | 55 |
| | Mean | 76.9 | 74.8 | 71.9 | 74.6 |
| | Std | 7.8 | 7.3 | 6.1 | 7.3 |
| | Min | 65.5 | 54.8 | 52.3 | 52.3 |
| | Max | 91.3 | 85.0 | 82.5 | 91.3 |
| Mean DBP (mmHg) after Tyramine Challenge | N | 19 | 19 | 17 | 55 |
| | Mean | 76.6 | 74.9 | 69.9 | 73.9 |
| | Std | 8.8 | 8.5 | 8.0 | 8.8 |
| | Min | 57.9 | 58.9 | 47.1 | 47.1 |
| | Max | 91.3 | 89.8 | 81.2 | 91.3 |
| Mean Change from Baseline of DBP (mmHg) | N | 19 | 19 | 17 | 55 |
| | Mean | -0.3 | 0.1 | -2.0 | -0.7 |
| | Std | 5.1 | 4.7 | 4.1 | 4.6 |
| | Min | -11.9 | -10.5 | -7.4 | -11.9 |
| | Max | 7.4 | 5.6 | 7.2 | 7.4 |

Table 36 Descriptive Statistics of Supine Pulse (bpm) prior to and after Tyramine Challenge

| TVP -1012/232 Tyramine Sub-Study | | 1 mg | 2 mg | PLACEBO | All |
|---|------|------|-------|---------|-------|
| Mean Pulse at Baseline (bpm) | N | 19 | 19 | 17 | 55 |
| | Mean | 68.1 | 71.1 | 69.7 | 69.6 |
| | Std | 8.7 | 8.9 | 15.9 | 11.3 |
| | Min | 56.0 | 54.8 | 46.0 | 46.0 |
| | Max | 95.8 | 92.0 | 104.8 | 104.8 |
| Mean Pulse (bpm) after Tyramine Challenge | N | 19 | 19 | 17 | 55 |
| | Mean | 66.0 | 67.7 | 65.6 | 66.4 |
| | Std | 9.5 | 7.4 | 12.8 | 9.9 |
| | Min | 52.4 | 54.9 | 49.1 | 49.1 |
| | Max | 97.7 | 80.0 | 99.5 | 99.5 |
| Mean Change from Baseline of Pulse (bpm) | N | 19 | 19 | 17 | 55 |
| | Mean | -2.1 | -3.4 | -4.2 | -3.2 |
| | Std | 3.7 | 5.0 | 6.0 | 5.0 |
| | Min | -6.6 | -18.1 | -14.3 | -18.1 |
| | Max | 5.3 | 5.4 | 7.1 | 7.1 |

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8.4.3. Sponsor's Conclusions of the Tyramine-Challenge Sub-Study

In the opinion of the Independent SMC, no finding in the sub-study suggested any safety concern associated with the use of 1 mg/day rasagiline administered without tyramine restriction (including as an adjunct to LD). Therefore, no restrictions were advised for patients known to be on 1 mg/day rasagiline. Based on the above mentioned results, on data obtained from study TVP-1012/132 and in order to maintain the study blind during the active-treatment phase of the TEMPO study, the sponsor adopted a very conservative precautionary approach and initiated a tyramine-restricted diet for all study participants. At that time only 28 patients were still in study (active-treatment phase). The decision to mandate a tyramine-restricted diet in all study participants should not imply that such a restriction is necessary with the 1 mg /day in the future. It should be noted that non-selective MAO-Is administered with 5-20 mg tyramine are able to evoke a classical tyramine reaction (i.e. extreme values of systolic BP with or without changes in diastolic BP and pulse). In contrast, 75 mg tyramine administered to patients treated with 2 mg rasagiline induced only mild elevation in BP. Such administration to patients treated with 1 mg rasagiline did not result in any change in BP.

8.4.4. Reviewer's Comments

- I consider the lack of significant blood pressure responses after tyramine administration in most rasagiline-treated patients to be of indeterminate significance because of the potential confounding effects of administering tyramine with food (e.g. applesauce) and relatively soon after a meal). I have outlined my many reasons for concern about food altering the plasma tyramine profile and corresponding pressor response in the Reviewer's Comment section of my review of tyramine challenge Study 132. The positive responses by 2 patients in the 2 mg group could be evidence for tyramine sensitivity in selected patients.
- Patients were supposed to receive tyramine with applesauce within 60 minutes of the completion of their meal. Approximately half of the patients began consuming tyramine at or within 30 minutes of the completion of their meal. It was not clear that there was documentation based upon the CRFs that the remaining half of patients began consuming tyramine within 60 minutes of the completion of their meal (as specified within the protocol).
- The study permitted the potential for additional heterogeneity of pressor responses because there was no standardized meal given to all patients. Patients could eat outside the hospital or in the hospital cafeteria or snack bar as long as they consumed food that met the low tyramine content restrictions. I consider this design as potentially contributing to the possibility of different plasma tyramine profiles related to the specific, different meals and related to this, potentially different pressor responses.
- Two patients (# 40 and 605 came very close to meeting the primary outcome endpoint (i.e. > 30 mm Hg systolic blood pressure increment above baseline –average of 4 pre-tyramine recordings). Patient # 40 had a mean pre-treatment systolic blood pressure of 145 mm Hg and needed 3 consecutive measurement to be \geq 175 mm Hg. Between 51 and 66 minutes after tyramine, this patient had readings of 174, 165, 178, and 172 (Figure 12). Thus, this patient can be viewed as having a borderline response just beneath the specific protocol-define

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outcome. Patient # 605 had a mean pre-treatment systolic blood pressure of 120 mm Hg and needed 3 consecutive measurement to be ≥ 150 mm Hg. Between 95 and 105 minutes after tyramine, this patient had readings of 154, 163, 148, and 172 (Figure 13). Thus, this patient can also be viewed as having a borderline response just barely beneath the specific protocol-defined outcome. If the 148 reading was 150, this patient would have met the protocol defined outcome. Both of these patients had been treated with 2 mg tyramine and likely exhibited increased pressor sensitivity to tyramine.

- I had requested additional analyses of individual maximal systolic blood pressure and maximal systolic blood pressure increment above pre-tyramine systolic blood pressure because the sponsor had only provided analyses showing the mean VS changes from baseline. Such analyses could potentially mask peak pressor response for the group and would not permit a look at individual responses. Based upon these new analyses, mean data according to treatment group for these 75 mg tyramine challenges suggested a dose-dependent effect of rasagiline vs placebo. Mean maximal systolic blood pressure was 137, 148, and 153 mm Hg for placebo, 1 mg rasagiline and 2 mg rasagiline, respectively. Mean maximal systolic blood pressure increment was 15, 19, and 21 mm Hg for placebo, 1 mg rasagiline and 2 mg rasagiline, respectively. In addition, there was an increased frequency of subjects showing a systolic blood pressure increment of ≥ 30 mm Hg in 1 mg (21 %) and 2 mg (16 %) rasagiline groups compared to placebo (6 %). Only one subject (2 mg group) exhibited a systolic blood pressure increment ≥ 50 mm Hg (i.e. 51). Altogether, these results suggest an effect of rasagiline on increasing tyramine sensitivity.
- Considering that food can delay the plasma tyramine T_{max} and the corresponding pressor response, it is possible that some hypertensive reactions could have been missed between 3 and 4 hours after tyramine administration because blood pressure measurements were made at 15 minute intervals from hour 2-3 and also between 3- 4 hours.

I have provided example of 2 types of patients (both treated with 1 mg rasagiline) for whom the primary outcome measure may not have been demonstrated because of the design of the study in which blood pressure monitoring decreased in the second half of the monitoring period. Figure 16 is an example of a patient who could possibly have met the primary outcome if blood pressure had been monitored at 5 minute intervals between 2 -3 hours. This patient had a mean baseline systolic blood pressure of 132.25 mm Hg and required 3 consecutive readings of ≥ 153 . At 115 , 120, and 140 minutes after tyramine this patient had readings of 153, 158, and 151, respectively. It is clearly conceivable that a reading between 120 and 140 minutes could have been ≥ 153 and would have been evidence for this patient meeting the primary outcome measure. Figure 15 is an example of another type of patient who could possibly have met the primary outcome if blood pressure had been monitored at more frequent intervals between 3 - 4 hours. This patient had a mean baseline systolic blood pressure of 127 mm Hg and required 3 consecutive readings of ≥ 157 . The last systolic blood pressure at 240 minutes (60 minutes after the previously last recording of 134) was 158. It also seems conceivable that 2 other readings at close intervals around the last reading could have been ≥ 157 and would have been evidence for this patient meeting the primary outcome measure.

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Figure 14 Systolic Blood Pressure of Patient # 434 (1 mg Rasagiline) After 75 mg Tyramine

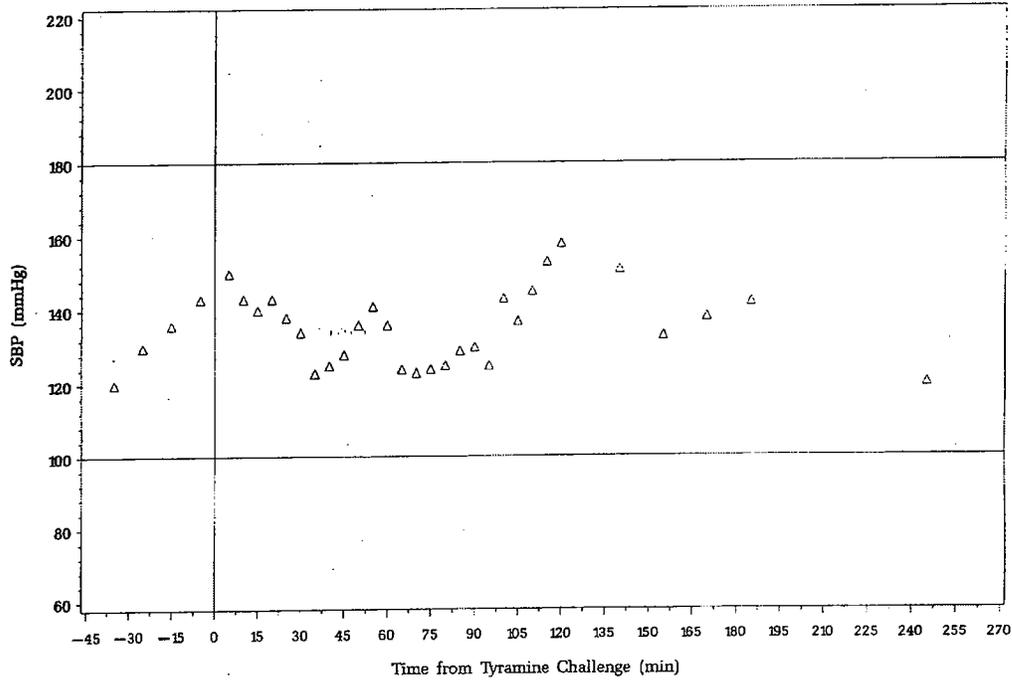
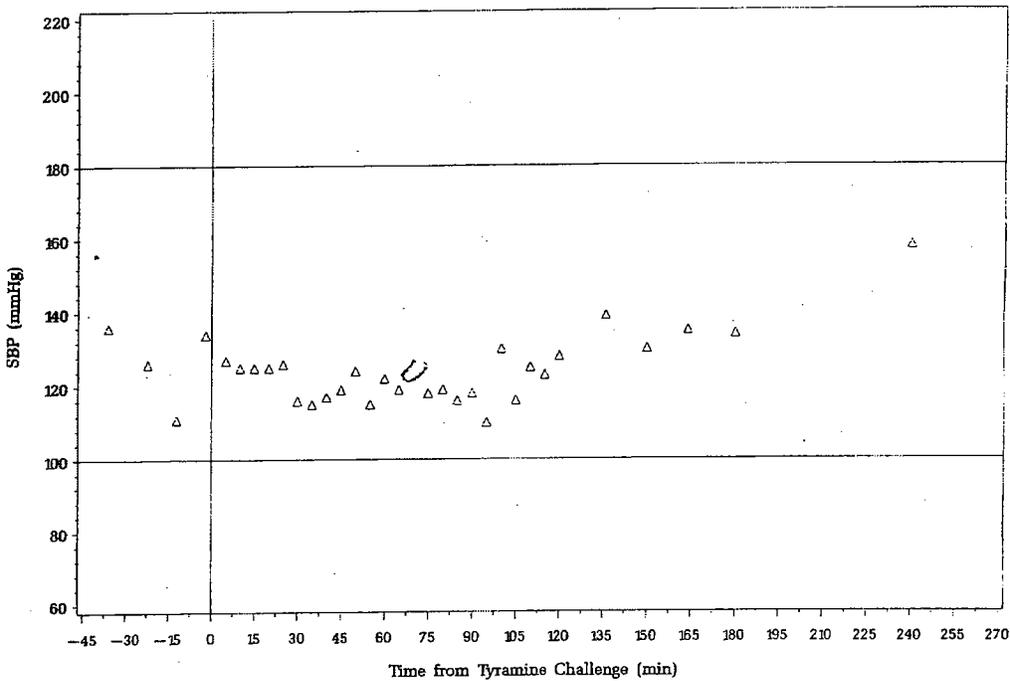


Figure 15 Systolic Blood Pressure of Patient # 45 (1 mg Rasagiline) After 75 mg Tyramine



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- I have noted my concerns about the biological potency for tyramine in Study P94159 because the majority (18/29) of subjects exhibited a pressor threshold response at 800 mg or did not exhibit a threshold response. This is extremely unusual. The sponsor used tyramine from the same supplier (_____) for this study. Thus, the possibility exists that results observed in this study could underestimate the tyramine sensitivity if the tyramine used had a decreased potency than that which is normally expected.

8.4.5. Reviewer's Conclusions

- **The potentially confounding effect of administering tyramine with food (i.e. applesauce) and also eating a few minutes after this does not allow one to draw any conclusions about the effect of tyramine exposure on blood pressure response in patients treated with 1 or 2 mg rasagiline daily. It is not possible to know whether the lack of significant pressor responses in most patients administered tyramine in this study design is a true negative or potentially a false negative because of the impact of the food on the plasma tyramine profile and corresponding pressor response.**
- **The sponsor has not validated its approach of assessing tyramine sensitivity (i.e. pressor responses after tyramine) when tyramine is administered with food and immediately before other food.**
- Based upon a variety of studies in the literature, there is clear evidence that food can markedly alter the plasma tyramine profile by diminishing C_{max}, AUC, and delaying T_{max} and also the pressor response to this altered plasma tyramine curve.
- The study design employed may have missed some tyramine-induced hypertensive reactions meeting the primary outcome measure and occurring relatively late (e.g. between 2-3 hours or between 3 – 4 hours) because of the confounding effect of food on the time to the response.
- It is not possible to know whether the tyramine used in this studied had a lower biological potency than that which is normally expected. If the biological potency of tyramine was diminished, results of this study may be an underestimate of the risk for rasagiline-induced tyramine sensitivity.

8.5. Study TVP-1012/133 PRESTO Tyramine Substudy

8.5.1. Description of Protocol PRESTO (#133) Tyramine SubStudy

This study was generally conducted similarly as Tyramine Substudy 232 (TEMPO) with a major study design difference being that tyramine was administered immediately at the end of the meal during the dessert phase. Tyramine was also added to one of several dairy desserts instead of to applesauce as was done in the TEMPO Tyramine Substudy. Thus, I will not describe this study in the same detail as the TEMPO substudy was described. I will summarize major parts of the protocol.

Objective

The aim of this substudy was to evaluate the effect of an oral dose of tyramine in PD subjects chronically treated with rasagiline (0.5 mg or 1 mg/day) or placebo for six months.

Study Design – Tyramine Sub-study

Subjects enrolled into this substudy were those who completed all procedures at Visit 06 (week 26) of study TVP-1012/133 (PRESTO). Subjects were excluded if they had a history of intracranial or systemic aneurysm or intracranial hemorrhage. Subjects were also excluded if they had uncontrolled hypertension defined as systolic BP > 160 mmHg or diastolic BP >90 mmHg.

A 12-lead ECG was obtained, and then seated blood pressure and heart rate were measured by an automated device every ten minutes for a 30 minute baseline period. The baseline measurements were made before the meal and before tyramine was administered (t=-30 min, -20 min, -10 min, 0 min). Baseline blood pressure and pulse were defined as the average of the four readings obtained before administration of tyramine.

After baseline ECG was completed, blood pressure and pulse were recorded and subjects consumed a low tyramine containing meal that they had brought from home. The light meal consisted of a sandwich, a beverage and a piece of fruit, or the equivalent. This was followed by dessert consisting of 6 to 8 ounces of yogurt, frozen yogurt or ice cream (according to the subject's preference) which was mixed with the contents of a 50 mg capsule of tyramine hydrochloride. The meal and dessert + tyramine were to be finished within 15 minutes of the last baseline blood pressure reading.

The active monitoring period began immediately after the ingestion of tyramine, 50 mg. Seated blood pressure and heart rate were measured every 5 minutes for 120 minutes, then every 15 minutes for 60 additional minutes. At the end of this period, subjects who did not experience significant events such as: elevations of systolic blood pressure (> 30 mmHg increase from the mean baseline value), reductions in heart rate below 40 beats per minute lasting 10 minutes or more, or adverse events (e.g., headache) were discharged from the clinic.

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Subjects who experienced significant elevations of blood pressure, reductions of heart rate or adverse events as specified above at any time during the active monitoring period had their blood pressure and heart rate measured every five minutes until the cardiovascular changes or adverse events resolved, for a minimum of 120 minutes after the onset of the reaction. Blood pressure and heart rate continued to be measured every 15 minutes for 60 additional minutes. A continuous 3-lead ECG was to be recorded during this period. The total duration of observation was at least 180 minutes after tyramine administration.

Subjects who experienced a reaction to tyramine requiring pharmacological intervention (see below), had their blood pressure and heart rate monitored every 5 minutes and a continuous 3-lead ECG obtained during the duration of hemodynamic abnormality and treatment period, for a minimum of 120 minutes after the onset of the reaction. Then blood pressure and heart rate monitoring were continued every 15 minutes for 120 minutes. The total duration of observation was at least 240 minutes after tyramine administration.

If systolic BP rose more than 60 mmHg above baseline or above 190 mmHg, or if the diastolic BP was 30 mmHg higher than baseline or greater than 115 mmHg, or if the investigator believed that the subject was experiencing a clinically significant tyramine reaction that required intervention, anti-hypertensive therapy could be initiated according to the following protocol: Labetalol, an alpha-beta adrenergic blocking agent, could have been given as an intravenous injection using an initial dose of 5 mg over 1-2 minutes. If there was no response (i.e., at least a 10 to 20 mmHg decrease in systolic BP or a 5 to 10 beat per minute increase in heart rate) within 5 to 7 minutes, a repeat dose of 10 mg of labetalol was to be administered over 1 to 2 minutes. This process was to be repeated after 10 minutes if the clinical response was unsatisfactory. The subject was to remain in the supine position to avoid orthostatic hypotension for at least 30 minutes (or until the reaction was over).

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), phentolamine, an alpha-1 blocker could have been used. This drug was to be administered intravenously at a dosage of 2 mg over 15 to 30 seconds. If there was an inadequate response within 2 to 7 minutes, a second intravenous injection of 5 mg was to be given over 30 to 60 seconds. If phentolamine was unavailable at the hospital formulary, the subject was to receive sodium nitroprusside intravenously according to standard guidelines in a clinical unit capable of continuous cardiac and BP monitoring.

If neither therapy yielded acceptable clinical results, the subject was to be transferred to the nearest emergency department for further evaluation and treatment. Ganglionic blocking agents, including guanethidine, guanadrel and reserpine were not to be given.

For all subjects, a standard 12-lead ECG was recorded once during the 30 minute baseline period before the tyramine dosing and then 180 minutes after the end of the meal. A 12-lead ECG was also recorded at the onset and conclusion of any cardiovascular reaction. As described in the previous section continuous 3-lead ECG monitoring may also have been done, as required. Adverse events were recorded as they occurred.

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The research staff, investigator and coordinator, conducting this substudy were not the same individuals who were responsible for PRESTO. The PRESTO site investigator and coordinator remained blinded to the results of this tyramine sub-study until all subjects at their site completed PRESTO. The site investigator for PRESTO was to be informed only in the event of serious adverse events.

Safety Measurements

The primary outcome measure was the occurrence of one or both of the following cardiovascular events:

- An increase in systolic BP of > 30 mmHg from the mean baseline value, documented by at least 3 consecutive measurements.
- Heart rate below 40 beats per minute, documented by at least 3 consecutive measurements over 10 minutes.

Secondary outcome measures were :

- Clinically significant 12-lead and/or 3-lead ECG changes
- Changes from baseline in vital signs throughout the challenge period, individual graphical presentation
- Subjects requiring antihypertensive therapy.
- Adverse events: The incidence and the frequency of adverse events were summarized. AEs with the same COSTART term and onset date for an individual subject were counted as separate events each time there was a change in severity.

Statistical Analysis – Tyramine Sub-study

The occurrence of the primary outcome was expected to be rare. Therefore, no statistically significant differences between treatment groups were expected. No power calculations or formal statistics were made or planned. Only patients that gave their consent participated in this sub-study. All presentations were descriptive in nature. Patients meeting the primary outcome were discussed on a case by case basis.

The number of subjects with each of the primary and secondary outcome measures listed in the preceding section were counted and presented by treatment group. Changes in systolic and diastolic BP and heart rate were presented graphically for individual subjects and examined on a case-by-case basis.

Baseline was calculated as the mean of the four measurements taken before tyramine administration. Descriptive statistics of mean changes from baseline considered all observations made after baseline for each subject and the change from baseline for each of these post-tyramine observations.

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Distributions of relevant demographic and clinical variables at enrollment into PRESTO were qualitatively compared for subjects who participated in the tyramine challenge sub-study and for those who did not participate (for any reason).

8.5.2. Sponsor's Presentation of Results of PRESTO (#133) Tyramine SubStudy

The data from this sub study were reviewed by the Safety Monitoring Committee and Teva Director of Drug Safety under blinded conditions prior to code opening of the PRESTO study for the assessment of increases in blood pressure that may signal concern. Patients that are discussed in this report were already marked before code opening and before their treatment assignment was revealed.

Subject Disposition

The study was conducted at 16 centers, corresponding to 28% of sites conducting PRESTO. Altogether 57 subjects signed an IRB/REB-approved consent form to participate. Two out of 57 subjects had elevations of blood pressure (systolic BP > 160 mmHg or diastolic BP > 90 mmHg) in the baseline measurements that excluded them from further participation in the substudy. The remaining 55 subjects received tyramine: 22 from the 0.5 mg rasagiline treatment group, 13 from the 1 mg rasagiline treatment group and 22 from the placebo treatment group. All of these subjects had a least 3 hours of monitoring, as required by the protocol and are considered completers.

Demographics and Other Baseline Characteristics

Table 37 shows the distribution of subjects by gender in each treatment group. The 1 mg/day treatment group was slightly under represented relative to the number of patients in each of the other two treatment groups. The distribution of gender was similar in each the 1 mg group but was predominantly males in the placebo and 0.5 mg groups. There were no remarkable differences in age, or duration of Parkinson's Disease among the groups.

Table 37 Distribution of Subjects by Gender

| TVP-1012/133a Tyramine Sub-Study | 0.5 mg | | 1 mg | | Placebo | | All | |
|-------------------------------------|-----------|--------------|-----------|--------------|-----------|--------------|-----------|--------------|
| | N | % | N | % | N | % | N | % |
| Gender | | | | | | | | |
| Female | 6 | 27.3 | 7 | 53.8 | 4 | 18.2 | 17 | 29.8 |
| Male | 16 | 72.7 | 6 | 46.2 | 18 | 81.8 | 40 | 70.2 |
| All | 22 | 100.0 | 13 | 100.0 | 22 | 100.0 | 57 | 100.0 |

Baseline and Post-Tyramine Blood Pressure and Pulse

Mean values for baseline systolic BP, diastolic BP and pulse for subjects in the tyramine challenge substudy are shown in Table 38, Table 39, and Table 40. There are no apparent differences among treatment groups for systolic blood pressure, diastolic blood pressure, or pulse.

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Table 38 Descriptive Statistics of Systolic Blood Pressure Prior to (Baseline) and After 50 mg Tyramine Challenge

| TVP-1012/133a Tyramine Sub-Study | | 0.5 mg | 1 mg | Placebo | All |
|---|--------|--------|-----------------|-----------------|-------|
| Mean Systolic BP (mmHg) at Baseline | N | 22 | 13 [‡] | 22 [§] | 57 |
| | Mean | 118.2 | 127.3 | 124.4 | 122.7 |
| | Std | 14.5 | 29.5 | 14.7 | 19.0 |
| | Median | 116.3 | 123.0 | 123.8 | 122.3 |
| | Min | 88 | 88 | 94 | 88 |
| | Max | 147 | 204 | 148 | 204 |
| Mean Systolic BP (mmHg) After Tyramine Administration | N | 22 | 12 | 21 | 55 |
| | Mean | 120.0 | 118.9 | 119.3 | 119.5 |
| | Std | 13.2 | 12.3 | 11.3 | 12.1 |
| | Median | 121.1 | 120.6 | 118.6 | 119.0 |
| | Min | 98 | 103 | 95 | 95 |
| | Max | 148 | 136 | 144 | 148 |
| Mean Change from Baseline of Systolic BP (mmHg) | N | 22 | 12 | 21 | 55 |
| | Mean | 1.7 | -2.0 | -4.2 | -1.3 |
| | Std | 13.0 | 11.1 | 12.3 | 12.4 |
| | Median | 0.3 | -1.4 | -4.4 | -2.1 |
| | Min | -24 | -21 | -29 | -29 |
| | Max | 39 | 19 | 29 | 39 |

[‡] 12 subjects received tyramine, 50 mg

[§] 21 subjects received tyramine, 50 mg

Cross-reference: Individual data listing of Tyramine Challenge: All Vital Sign Measurements in Appendix 16.2.6.24

Table 39 Descriptive Statistics of Diastolic Blood Pressure Prior to (Baseline) and After 50 mg Tyramine Challenge

| TVP-1012/133a Tyramine Sub-Study | | 0.5 mg | 1 mg | Placebo | All |
|--|--------|--------|-----------------|-----------------|------|
| Mean Diastolic BP (mmHg) at Baseline | N | 22 | 13 [‡] | 22 [§] | 57 |
| | Mean | 71.4 | 73.2 | 76.6 | 73.8 |
| | Std | 12.1 | 15.9 | 11.2 | 12.7 |
| | Median | 70.3 | 72.0 | 77.6 | 75.0 |
| | Min | 48 | 48 | 54 | 48 |
| | Max | 93 | 114 | 100 | 114 |
| Mean Diastolic BP (mmHg) After Tyramine Administration | N | 22 | 12 | 21 | 55 |
| | Mean | 70.2 | 68.0 | 71.5 | 70.2 |
| | Std | 9.5 | 6.8 | 10.9 | 9.5 |
| | Median | 72.5 | 70.3 | 74.5 | 71.9 |
| | Min | 47 | 50 | 54 | 47 |
| | Max | 82 | 75 | 95 | 95 |
| Mean Change from Baseline of Diastolic BP (mmHg) | N | 22 | 12 | 21 | 55 |
| | Mean | -1.2 | -1.8 | -4.0 | -2.4 |
| | Std | 8.4 | 5.6 | 7.7 | 7.6 |
| | Median | -3.0 | -1.2 | -4.1 | -2.8 |
| | Min | -13 | -11 | -19 | -19 |
| | Max | 24 | 9 | 18 | 24 |

[‡] 12 subjects received tyramine, 50 mg

[§] 21 subjects received tyramine, 50 mg

Cross-reference: Individual data listing of Tyramine Challenge: All Vital Sign Measurements in Appendix 16.2.6.24

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Table 40 Descriptive Statistics of Pulse Prior to (Baseline) and After 50 mg Tyramine Challenge

| TVP-1012/133a Tyramine Sub-Study | | 0.5 mg | 1 mg | Placebo | All |
|--|--------|--------|-----------------|-----------------|------|
| Mean Pulse (bpm) at Baseline | N | 22 | 13 [‡] | 22 [§] | 57 |
| | Mean | 65.9 | 68.5 | 70.1 | 68.1 |
| | Std | 11.2 | 8.5 | 10.7 | 10.4 |
| | Median | 63.5 | 72.0 | 70.0 | 66.0 |
| | Min | 54 | 54 | 50 | 50 |
| | Max | 101 | 77 | 89 | 101 |
| Mean Pulse (bpm) After Tyramine Administration | N | 22 | 12 | 21 | 55 |
| | Mean | 68.7 | 69.4 | 74.8 | 71.2 |
| | Std | 8.9 | 7.3 | 12.5 | 10.4 |
| | Median | 67.8 | 70.7 | 71.7 | 69.8 |
| | Min | 57 | 58 | 57 | 57 |
| | Max | 88 | 81 | 106 | 106 |
| Mean Change from Baseline of Pulse (bpm) | N | 22 | 12 | 21 | 55 |
| | Mean | 2.9 | 1.4 | 4.0 | 3.0 |
| | Std | 6.7 | 3.3 | 8.8 | 7.0 |
| | Median | 1.8 | 1.0 | 2.1 | 1.8 |
| | Min | -13 | -3 | -6 | -13 |
| | Max | 17 | 8 | 36 | 36 |

[‡] 12 subjects received tyramine, 50 mg

[§] 21 subjects received tyramine, 50 mg

Cross-reference: Individual data listing of Tyramine Challenge: All Vital Sign Measurements in Appendix 16.2.6.24

Primary Outcome Measures

Systolic BP increases > 30 mmHg

Four subjects (7%) had an increase in BP that met the predefined endpoint of systolic BP of > 30 mmHg above the mean baseline value for at least 3 consecutive measurements. Three of these subjects (# 4, 118, 266) had received 0.5 mg/day rasagiline and one had received placebo (# 411). None of the subjects who received 1 mg/day rasagiline had a clinically significant blood pressure increase during the tyramine challenge substudy.

Table 41 Distribution of Subjects with Clinically Significant Increase in Systolic Blood Pressure - Tyramine Sub-Study

| TVP-1012/133a Tyramine Sub-Study | 0.5 mg | | 1 mg | | Placebo | | All | |
|--|--------|-------|------|-------|---------|-------|-----|-------|
| | N | % | N | % | N | % | N | % |
| All | 22 | 100.0 | 13 | 100.0 | 22 | 100.0 | 57 | 100.0 |
| Clinically Significant Increase in Blood Pressure* | 3 | 13.6 | . | . | 1 | 4.5 | 4 | 7.0 |
| Non Significant Increase in Blood Pressure | 19 | 86.4 | 13 | 100.0 | 21 | 95.5 | 53 | 93.0 |

* Defined as systolic BP of > 30 mmHg above the mean baseline value for at least 3 consecutive measurements.

Cross-Reference: Tyramine Challenge - All Vital Sign Measurements in Appendix 16.2.6.24

In addition, 2 patients (# 362 and 736) who were identified prior to code opening, had increases in systolic blood pressure of > 30 mmHg over baseline for 2 consecutive measurements. Both patients were on placebo.

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Brief descriptions of patients who met the primary outcome measure are provided below along with a figure showing the vital signs after 50 mg tyramine for each patient.

Patient # 4 (0.5 mg Rasagiline)

This patient reported right arm tingling 70 minutes after tyramine intake (usually associated with the subject's "OFF" state). Thirty five (35) minutes later the subject turned "OFF", feeling "panicky", with poor mobility and unclear speech. This incident was accompanied with increase in blood pressure from 119/69 mmHg to 140/83-179/90 at 110-250 minutes after tyramine administration (Figure 16).

From 250 minutes after administration, blood pressure decreased (to 126/80-106/64), movement improved and subject returned to "ON" state.

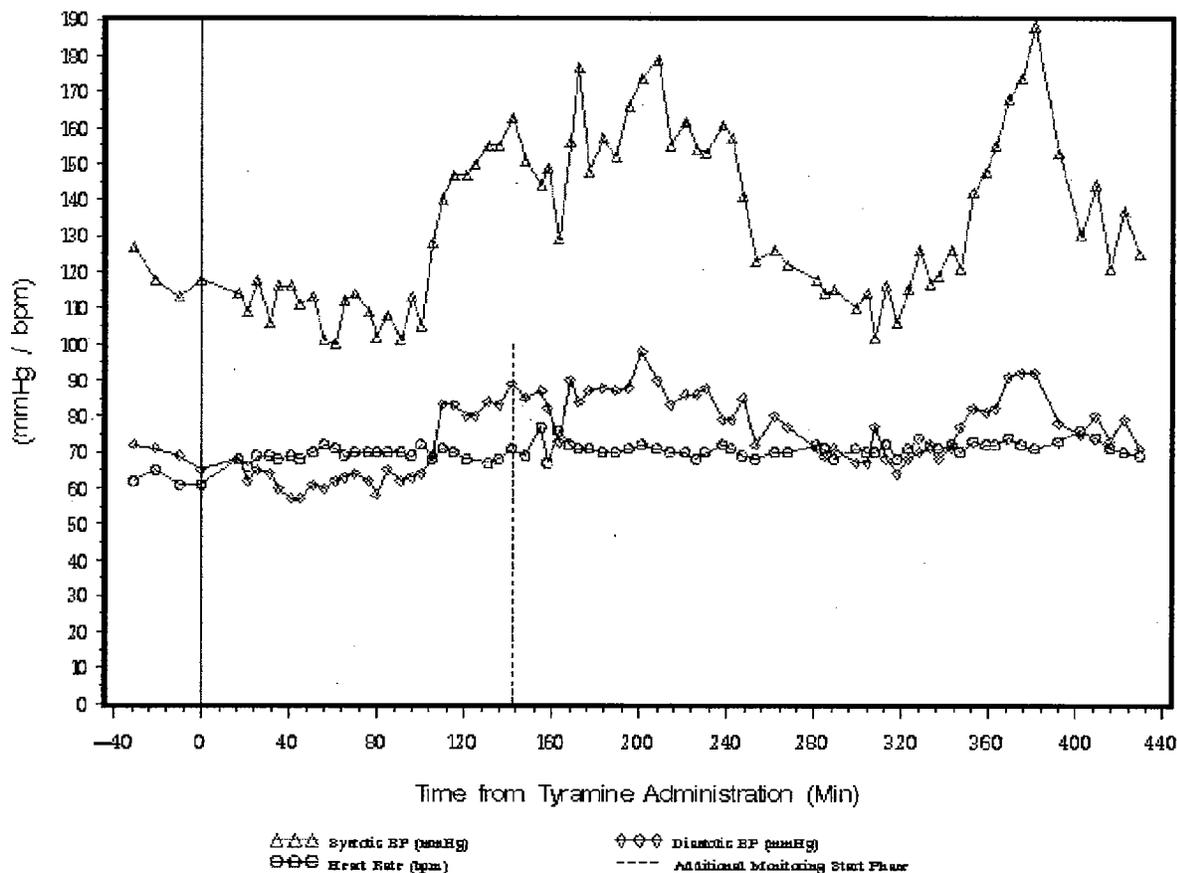
The subject began turning "OFF" again (slurred speech, slowed movement) 340 minutes after tyramine administration. Blood pressure increased simultaneously again to 190/90. LD/carbidopa was taken 360 minutes after tyramine administration. Blood pressure decreased to 121/73 60 minutes later (420 minutes after administration), with the subject turning "ON".

The subject's heart rate remained stable during this trial. No anti-hypertensive medication was administered during the trial period and the investigator attributed these blood pressure elevations to the "OFF state". It is well documented that in patients with dose-related response fluctuations the mean systolic-diastolic blood pressure, both supine and standing, is significantly higher during the "OFF" phase as compared to the "ON" phase¹. Home BP measurements of this patient were unremarkable.

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Figure 16 Vital Sign Changes Over Time in Patient # 4 (0.5 mg Rasagiline) After 50 mg Tyramine



Patient # 118 (0.5 mg Rasagiline)

This patient's baseline blood pressure was 124/70 mmHg and began increasing 110 minutes after administration, to a peak of 200/95, 170 minutes after administration of tyramine (Figure 17).

There was a gradual decrease in blood pressure that brought systolic blood pressure to 120mmHg, 295 minutes after tyramine administration.

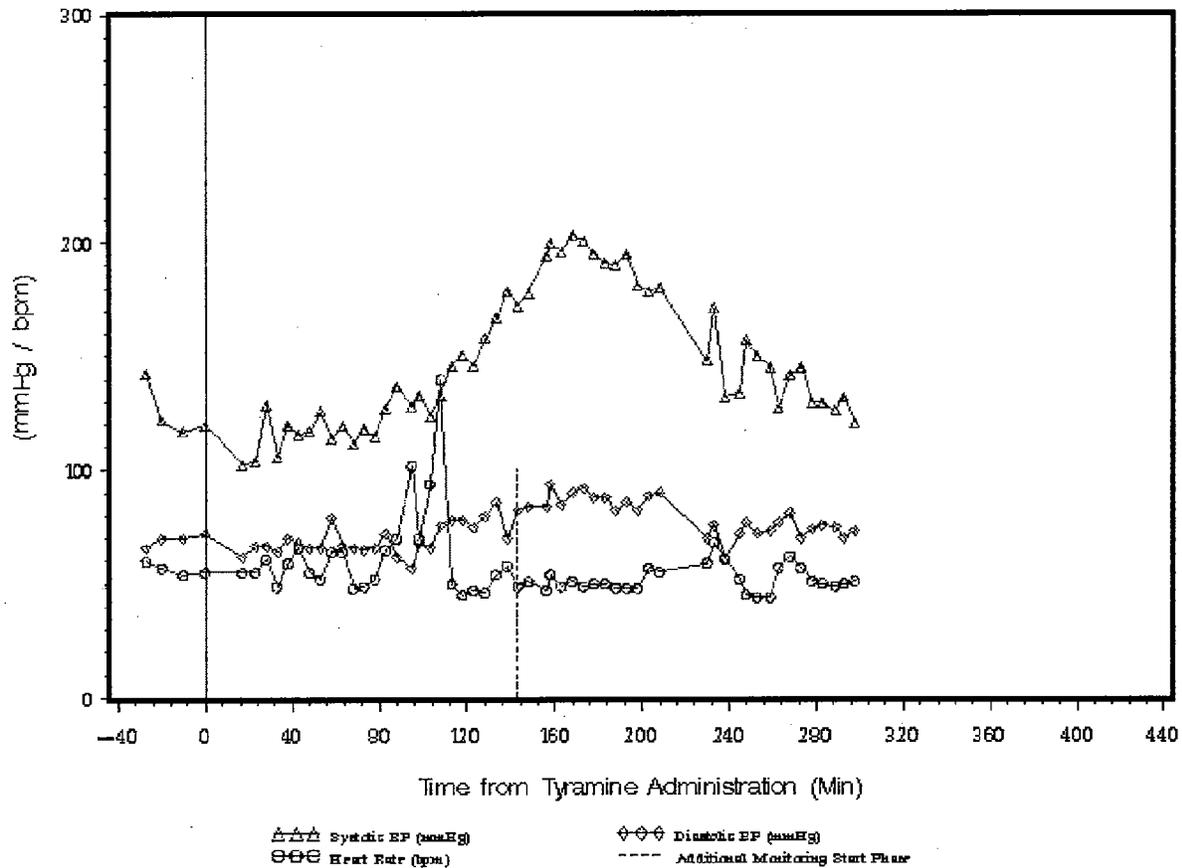
Diastolic BP remained almost unchanged during the tyramine challenge. No ECG changes noted at 3 and 5 hours post-meal compared to baseline. The subject did not report any symptoms during the trial.

Subject continued into the extension study, with normal blood pressure and no AE but insomnia.

The subject performed multiple home blood pressure measurements before and after meals, during TVP-1012/133. A non-severe increase in post-meal blood pressure was recorded at baseline, at visit 1 and at visit 6.

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Figure 17 Vital Sign Changes Over Time in Patient # 118 (0.5 mg Rasagiline) After 50 mg Tyramine



Patient # 266 (0.5 mg Rasagiline)

This patient's mean baseline blood pressure at the tyramine challenge visit was 88/50 mmHg, the mean baseline heart rate at that visit was 57 bpm.

During the first 135 minutes blood pressure was approximately 105/65 mmHg, then increased to around 145/80 mmHg, at 165 minutes after tyramine administration, with a peak of 155/100 mmHg (200 minutes after tyramine administration) (Figure 18). The blood pressure remained at these levels until the end of the trial, 385 minutes after tyramine administration. This pattern is not consistent with potential tyramine reaction

No medications were administered during the sub-study period. The subject reported no symptoms during that period.

The trial staff was under the impression that the baseline blood pressure was below the subject's average and that the increase in blood pressure therefore might not be clinically significant. At Termination visit of TVP-1012/133 performed on the same day, supine BP was 134/76; during the whole study duration mean supine BP was 123/72 mmHg.