

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-641

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA#: 21-641
Submission Date: 03/17/06
Brand Name: Azilect
Generic Name: Rasagiline Mesylate
Formulation: Tablets
Sponsor: TEVA Pharmaceuticals
Reviewer: John Duan, Ph.D.
Submission Type: Response to Approvable letter

BACKGROUND

The original NDA of rasagiline was submitted on September 3, 2003. An Approvable Letter was issued in 2004 and a second Approvable Letter was issued on August 4, 2005, in which the following requests were made.

“Although you have agreed to accept our proposed labeling language regarding the discrepant results for the effect of levodopa on rasagiline clearance, we had asked you to formally evaluate this effect. We continue to believe that an adequate characterization of this effect is necessary.”

We do not believe that you have adequately characterized the dose proportionality of rasagiline. Therefore, we ask you to perform a formal dose proportionality study. This Study should enroll at least 8 subjects (4 males, 4 females) in each age group (40-60; >65 years old) at each dose tested (the study should evaluate at least the following doses: 1mg, 2 mg, and 6 mg).

We note a doubling of the plasma levels of rasagiline in patients with mild renal dysfunction compared to normals. Because this finding was unexpected, we believe that patients with moderate to severe renal dysfunction should be formally evaluated (we recognize that you have done so, but we believe the data in these latter patients is unreliable because only a very few patients had adequate plasma sampling).”

The Agency expected that these studies would have been performed. However, the applicant, in the response letter dated January 20, 2006, concluded “that there are no safety concerns that would preclude this trial from being conducted post approval” for each of the 3 pharmacokinetic (PK) studies requested. This conclusion was reached without convincing arguments. Therefore, an incomplete response letter was issued on February 17, 2006. Thereafter, the applicant submitted a meeting request and met with the Agency on March 3, 2006. It was agreed that the Applicant would submit a response to the Agency summarizing and explicating the data contained in the pending application bearing on the PK issues identified. This submission constitutes the applicant’s responses.

MAJOR ISSUES ADDRESSED

Major topics addressed in this response are as follows.

1. Why the data adduced in the PK studies, full reports of which are available in the file of the pending NDA, are sufficient to provide valid and reliable estimates of the PK parameters for a 1 mg dose of rasagiline.
2. Why the data obtained from the renal impairment study are sufficient to persuasively document that renal impairment does not lead to an increase in rasagiline exposure.
3. Why Population PK models of rasagiline exposure in the presence and absence of levodopa/carbidopa (LD/CD), when taken in concert with clinical safety experience gained in over 400 PD patients exposed to a daily dose (2 mg) twice that being recommended for use, are sufficient to establish that the co-administration of LD/CD and rasagiline is highly unlikely to increase rasagiline exposure to an extent that will cause an increase in the incidence of clinically meaningful adverse events.

Although the submission is presented by the applicant in the way mentioned above, this review will focus on the three clinical pharmacology related issues identified in the Approvable Letter.

DRUG INTERACTION ISSUE

For the concern of the effect of levodopa/carbidopa on rasagiline clearance, the applicant made two arguments, one from the results of population pharmacokinetics and the other from the clinical experience.

Two Population Pharmacokinetic analyses for rasagiline were performed, one in the pivotal monotherapy study (TEMPO, TVP-1012/232) and the other in the pivotal adjunct therapy study (PRESTO, TVP-1012/133).

In the Population Pharmacokinetic analysis of the adjunct therapy study (PRESTO), all patients had rasagiline added to their chronic levodopa/carbidopa therapy. In this study (n=276; samples with quantifiable rasagiline level: 421), no effect of levodopa on rasagiline clearance was demonstrated.

In the monotherapy study (TEMPO), some patients (31 out of 352, [9%]) required additional PD therapy and were started on levodopa/carbidopa during the active treatment phase of the study (after the 6-month placebo-controlled phase). Based on these patients, the model suggested a decrease (31%) in rasagiline clearance.

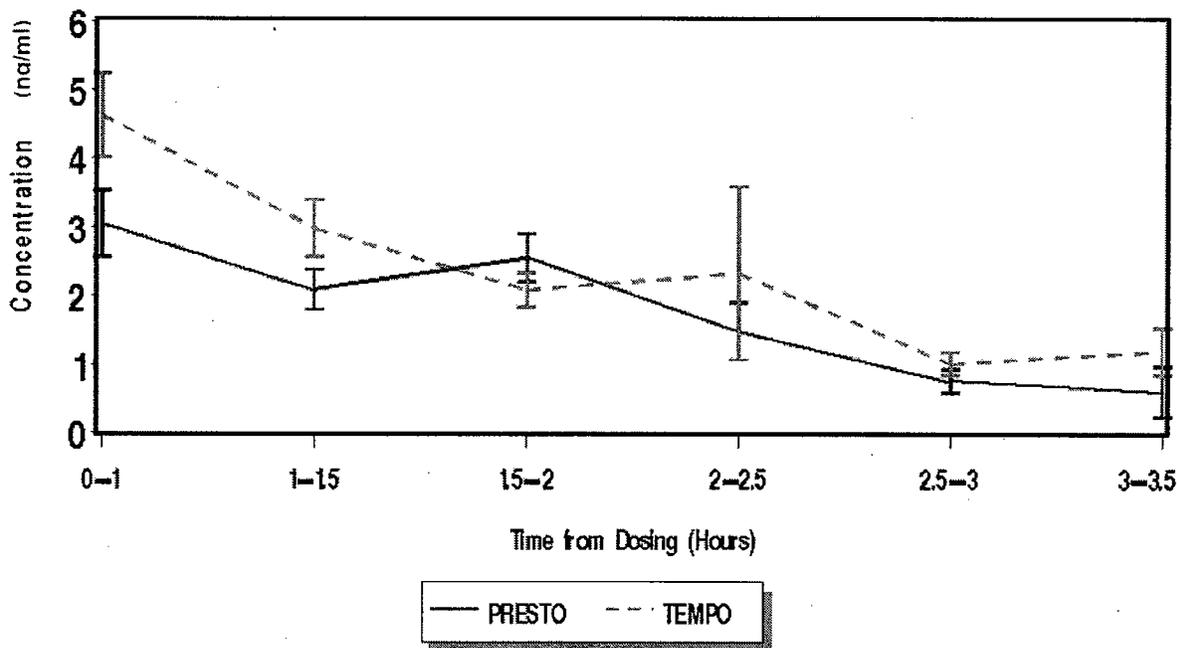
Looking further into the results of the TEMPO study, the applicant emphasized the following observations:

During the study, patients had 2 samples taken at week 14 and 26, and 1 sample taken at week 52. The week 52 sample was the only occasion where patients were sampled when co-medicated

with levodopa. For the levodopa covariate, therefore, the intra-individual variability was not ideally accounted for as would have been the case if more than one occasion had been sampled while patients were on concomitant LD/CD.

In the patients taking concomitant LD/CD at week 52, only a limited number of samples above the assay limit of quantitation were available for the Population PK model (7 samples with quantifiable rasagiline level and 31 samples with quantifiable aminoindan level).

Furthermore, when analyzing the mean rasagiline concentration in each time interval in the placebo-controlled phase of TEMPO (patients on 1 mg rasagiline, n=69) and comparing the concentrations to those in PRESTO (patients on 1 mg rasagiline and levodopa, n=72) by using t-test analysis, there is no statistically significant difference (see Figure below).



During the course of rasagiline's development, clinical experience was obtained for the concomitant administration of rasagiline and levodopa/carbidopa (LD/CD). Within the NDA database, 1361 PD patients accumulated 2646 patient years of exposure on rasagiline (with or without LD/CD). Out of the total rasagiline exposure, 987 patients used concomitant LD/CD for 1486 PYs. This experience includes both patients who had rasagiline added to chronic levodopa therapy as well as patients using rasagiline as monotherapy initiating levodopa/carbidopa therapy.

Additional clinical safety experience was gained in 406 PD patients (464 PYs) exposed to a daily dose of 2 mg, twice that being recommended for use. One-hundred PD patients (TEMPO/TEMPO EXT) on rasagiline 2 mg used concomitant LD/CD therapy for 90 PYs. According to the sponsor, the safety and tolerability of the 2 mg treated patients (with or without LD/CD) was comparable to the 1 mg dose.

Reviewer’s comments:

- Due to the lack of adequate dosing history information and limited sampling, in this case, the population study results are not reliable for detecting drug interactions, especially for supporting conclusion of negative interaction. Further, the two study results are not in agreement. Therefore, it is not conclusive regarding the drug interactions.
- The comparison across studies for detecting differences of concentrations is not sensitive due to confounding factors.
- The safety experience for the combination usage needs medical judgment.

If the medical reviewer deems the safety experience of the combination usage of levodopa/carbidopa and rasagiline is acceptable, the drug interaction study can be performed as a Phase IV commitment.

DOSE PROPORTIONALITY AND PK CHARACTERIZATION ISSUE

The Division’s concerns regarding adequacy and reliability of the PK data for 1 mg rasagiline/day arose for several reasons including uncertainties about assay reliability, the use of limited sampling schemes (sometimes only 3 time points) in some studies, and a limited number of studies that specifically evaluated the 1 mg dose (as opposed to the 2 mg dose).

Dose proportionality was demonstrated in three pharmacokinetic trials (CD596, TVP-1012/112, and TVP-1012/231) and was analyzed by a power model based on the Gough method.

In study CD596, dose proportionality was demonstrated for doses of 2, 5, and 10 mg/day (2, 5, and 10 fold higher than the dose recommended for use, respectively).

In the other two studies which support dose proportionality, TVP-1012/112 and TVP-1012/231, the 1 mg dose was evaluated. The Division was concerned that the sampling scheme in these studies was sparse, only 3 post-dose time points measured, and the first plasma sample obtained sometimes represented the highest rasagiline level among the samples obtained for the subject.

The applicant states that several Phase I studies were conducted which utilized adequate sampling and included the 1 mg dose. The sampling times for all multiple dose PK studies within the NDA are provided in table below.

Population	Study	N (Gender)	Dose Mg	Sampling times
Healthy	CD596 Pharmacokinetics	18 (M)	2, 5, 10	0 (pre-dose), 10, 20, 30, 45 min, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours
	P94159 Tyramine challenge study	12 (M)	1, 2	0 (pre-dose), 30 min, 1, 2, 3, 4, 8, and 12 hours
	TVP-1012/424 Hepatic impairment	8 (3F, 5M)	1	0 (pre-dose), 15, 30 min, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, and 48 hours

	TVP-1012/425 Renal impairment	8 (2F, 6M)	1	0 (pre-dose), 15, 30 min, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, and 48 hours
	TVP-1012/426 Ciprofloxacin interaction study	13 (M)	2	0 (pre-dose), 5, 10, 20, 30, 45 min, 1, 1.5, 2, 3, 4, 8, 12, and 24 hours
	TVP-1012/430 Theophylline interaction study	18 (1 F, 7M)	1	0 (pre-dose), 10, 20, 30, 45 min, 1 hour, 1.5, 2, 3, 4, 8, 12, and 24 hours
PD	TVP-1012/112 Phase II in LD/CD treated PD patients	23 (10F, 13 M)	0.5, 1, 2	0 (pre-dose), 30 min, 2 hours, and 4 hours
	TVP-1012/132 Tyramine interaction study in LD/CD treated PD patients	12 (4F, 8M)	1, 2	0 (pre-dose), 30 min, 1, 2, 4, 8, 12 and 24 hours.
	TVP-1012/231 Phase II study in monotherapy PD patients	42 (15F, 27M)	1, 2, 4	0 (pre-dose), 30 min, 2 hours, and 4 hours

Among the studies listed, the applicant selected the theophylline interaction study, TVP-1012/430, to address the Division's concern. This study thoroughly evaluates the exposure associated with oral administration of the 1 mg dose. Its 18 subjects, who were sampled frequently, provide data to calculate estimates of the PK parameters associated with the 1 mg dose. The applicant summarized the study briefly.

The demographic data are summarized in the following table.

Treatment	Gender (n)	Race (n)	Age (years) Mean \pm SD
Rasagiline 1 mg	Male (7)	Caucasian (17)	38.4 \pm 11.7
	Female (11)	Asian (1)	(21-55)

The mean pharmacokinetic results are summarized in the following table.

Parameter	Day 25
C _{max} (ng/ml)	8.82 \pm 2.98
AUC (0-t) (ng-h/ml)	8.72 \pm 2.32
t max (hr)	0.42

The applicant deems that study TVP-1012/430 adequately characterizes the exposure from a 1 mg dose and its data can be used to support the dose proportionality studies that used the 1 mg

dose. The applicant shows this by recalculating the mean AUC (0-t) in study TVP-1012/430 using the sampling times utilized by studies TVP-1012/112 and TVP-1012/231.

When the mean AUC (0-t) for study TVP-1012/430 is recalculated using sampling times of 0, 0.5, 2, and 4 hours, it is within 10 % of the mean AUC (0-t) when more frequent sampling times are used. The applicant concludes that the sampling times used in studies TVP-1012/112 and TVP-1012/231 provide reasonable representations of the mean AUC (0-t) compared to when more frequent sampling is utilized.

TVP-1012/430	AUC (0-t) (ng.h/ml)
Original: 0 (pre-dose), 10, 20, 30, 45 min, 1, 1.5, 2, 3, 4, 8, 12, and 24 hours	8.72 ± 2.32
Recalculated using 0 (pre-dose), 0.5 hr, 2 hr, and 4 hr	9.54 ± 3.04

The applicant also addresses the concerns that the first post-dose sample is obtained at the 0.5 hr time point and an early (< 0.5 hr) occurring C_{max} may be missed. Examination of studies that contained samples obtained earlier than 0.5 hr indicates C_{max} was observed prior to 0.5 hr in some cases. However, the applicant concludes that the values from earlier time points are comparable to those obtained where 0.5 hr was the first measurement and, therefore, the early partial AUC (0-0.5hr) is not influenced to a significant extent by the lack of samples prior to 0.5 hr.

Reviewer's Comments:

1. Dose proportionality from 2 mg to 10 mg has been established. Usually, the non-linearity would appear at high dose levels. Also, the predicted AUC values for 1 mg dose based on the study for 2-10 mg are similar to the measured values in another study. Therefore, dose proportionality will not be an issue. However, the characterization of pharmacokinetics of 1 mg dose did raise concerns as stated below.
2. The applicant stated in the submission dated November 18, 2004: "The plasma levels following 1 mg rasagiline dose are very low and the constraints of the bioanalytical limits of quantitation of rasagiline are preventing an accurate estimation of exposure at the relevant clinical dose. This limitation is apparent both after single or multiple doses, and on occasions it even led us to conduct clinical pharmacokinetic trials on a 2 mg dose instead of 1 mg, to allow better bioanalytical and pharmacokinetic assessment." Although it was declared that the above statements with respect to inaccurate assay were not true in subsequent submissions, the assay for 1 mg dose is problematic since levels can not be properly estimated after 1 mg dose. Even in study 430, the study report stated "plasma levels of rasagiline fell below the LOQ of the assay before the elimination phase was evident - hence the elimination pharmacokinetics of rasagiline could not be determined." Therefore, although the AUC_{0-t} can be calculated based on the profile, $AUC_{0-\infty}$ can not be estimated.

3. Due to this problem, the studies conducted using 1 mg contained limited concentration time points although the planned sampling scheme included more points (a lot of points were below detection limits) as the case in renal impairment study below.
4. Since LOQ (0.25ng/mL) of the assay is reasonably low, assay validation is appropriate and the sample size (18) is larger, this study is considered more reliable than other 1 mg studies. Based on the same consideration, the available data are sufficient to characterize overall PK of rasagiline provided the renal impairment study is conducted in Phase IV commitment (see next section).

RENAL IMPAIRMENT

The data obtained from the renal impairment study, TVP-1012/425, document that renal impairment does not increase rasagiline exposure.

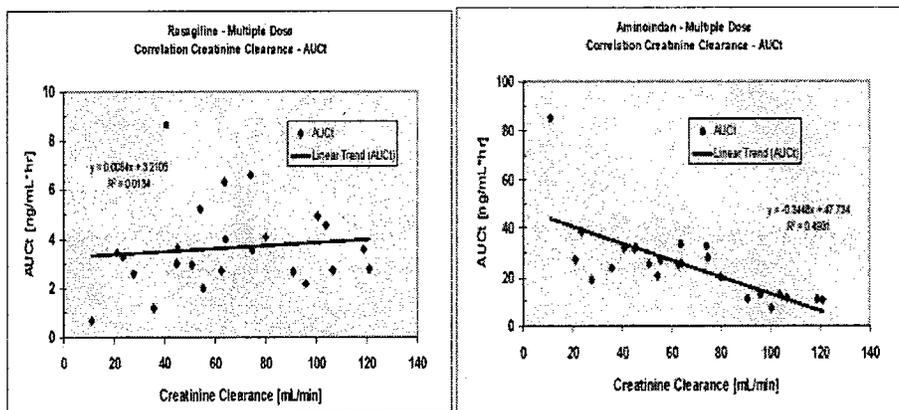
The study is based on a sufficient number of subjects with reasonably representative degrees of renal impairment (mild and moderate) to determine reliably whether or not renal impairment affects exposure to rasagiline.

Plasma samples were taken for rasagiline and AI at 0 (pre-dose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, and 48 hours. All subjects had at least 3 samples above the quantitation limit (QL) and most (91%) had 4 or more samples above the QL.

The data do not indicate a doubling of the plasma levels of the mild impairment group compared to the healthy group. The mean AUC (0-t) was 38% higher in the mild renal impairment group compared to normals after 7 days of repeated dosing and the mean AUC (0-t) for the moderate renal impairment group was 33% lower compared to normals.

There is no rasagiline detected in the mild or moderate renal impairment groups at the zero time point (pre-dose) on day 7 of dosing with rasagiline 1mg. The applicant deems that this indicates that there is no accumulation of rasagiline in subjects with mild or moderate renal impairment upon multiple dosing. In contrast, rasagiline's major metabolite, AI, which does undergo renal excretion, is detected in the mild and moderate renal impairment groups at the zero time point (pre-dose) on day 7. The applicant argues that this provides clear evidence of this study's capacity to detect the consequences of renal impairment for analytes that are cleared to a substantial extent by the kidney.

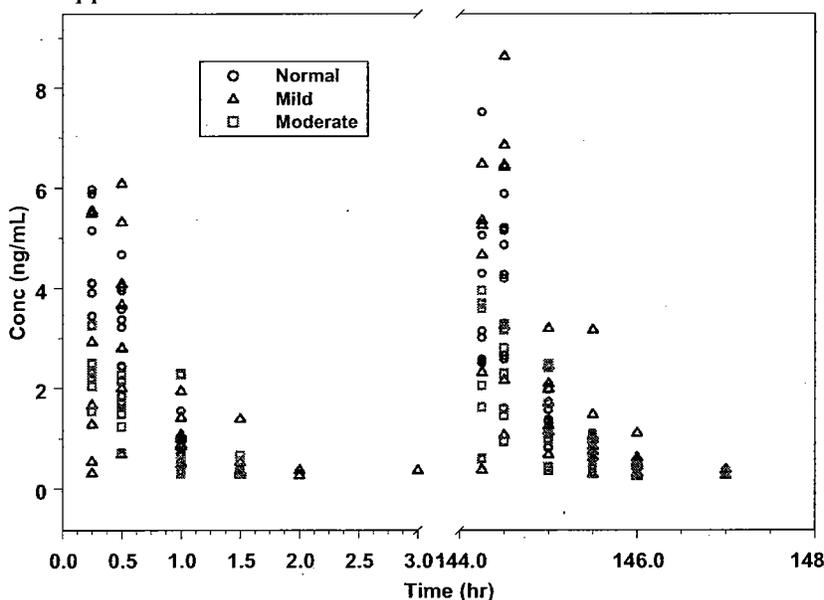
As displayed on the left in the following figure, there is no correlation between creatinine clearance and individual subjects' rasagiline exposure (AUCt). This supports the conclusion that decreasing renal function does not increase rasagiline exposure. However, there was evidence of increased AI exposure with decreasing renal function as shown on the right in figure below.



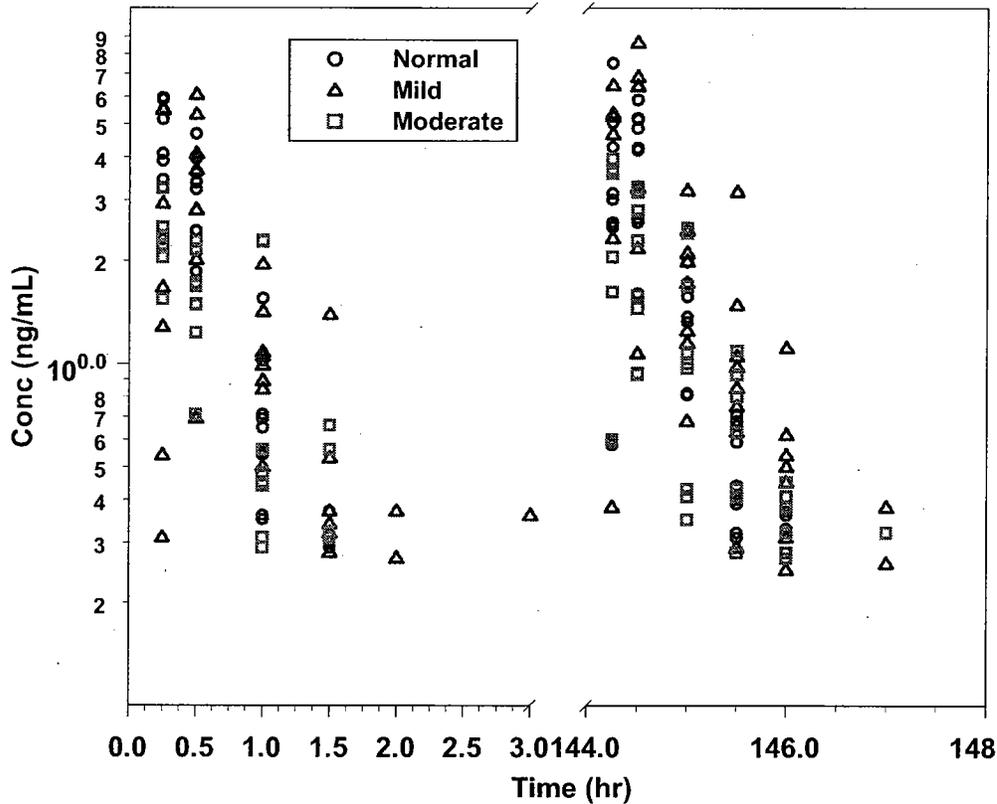
There is no signal present within the data to suggest that renal dysfunction increases exposure to rasagiline. Renal dysfunction does increase the exposure to AI, but this is a non-toxic metabolite, with a high safety ratio and no MAO-I activity.

Reviewer's Comments:

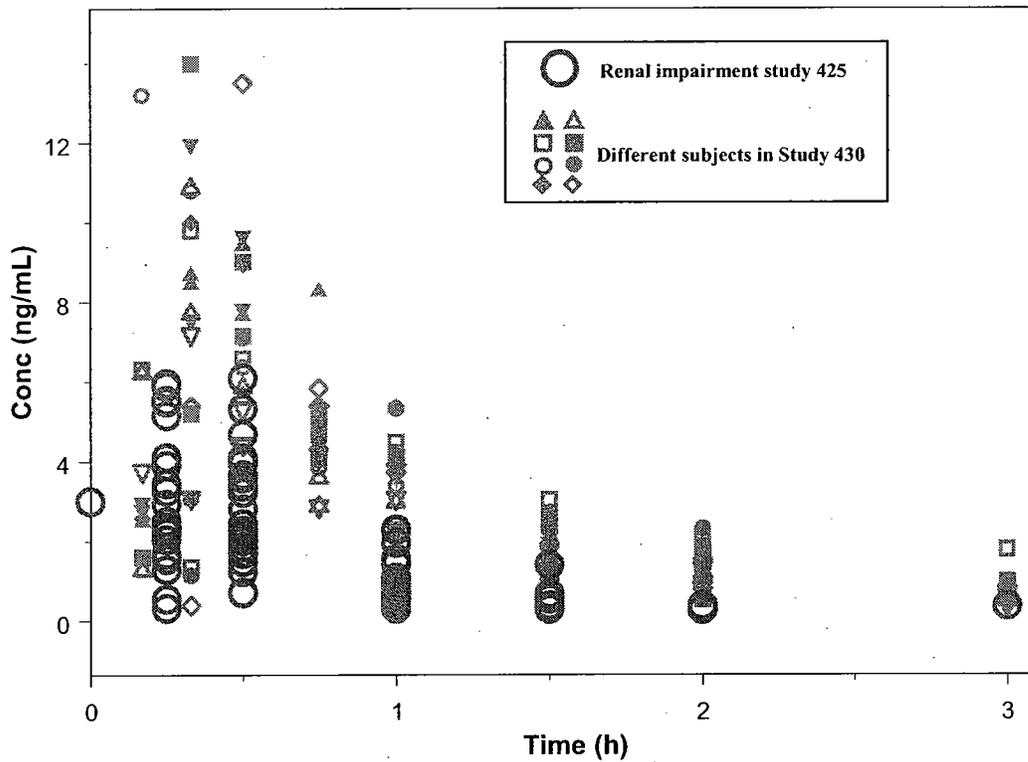
1. Due to the assay problem of 1 mg, there were not enough concentration time points to calculate AUC in a considerable number of patients. Therefore, the conclusion based on AUC is not reliable. In order to make full use of available data, a graphical approach is adopted by the reviewer. The purpose is to visually inspect the difference of pharmacokinetic profiles among three groups (Normal renal function, mild impaired renal function and moderate impaired renal function). Following is a concentration time plot including all time points in all patients.
2. As can be seen, the profiles of the three groups are overlapping after either single dose or 7-day dosing. This overlap indicates that there may not be dramatic differences of clearance among three groups. Therefore, it is not essential to conduct renal impairment study prior to approval.



- However, the figures do show a trend: the mild impairment is the highest, the normal lies in the middle and the moderate impairment is the lowest. Although this is consistent with the applicant's result, this trend lacks physiological basis, which may be attributed to the variability of the assay at lower concentrations. To clarify this issue and make a specific recommendation in the labeling, the applicant should conduct a renal impairment study as planned in Phase IV commitments.
- The following figure shows the same data plotted on the log scale, which supports the above interpretation.



- The assay method for this renal study is a little different from that in study 430. Although they use the same ANALYTICAL METHOD SOP 659. This study used VERSION B while study 430 used VERSION D. This difference may affect the PK results. The following figure is an overlap plot for both studies. The bigger circle in green is the concentration of renal study 425 and the smaller symbols in red are those in study 430. Although both studies used 1 mg dose, the concentrations were quite different. This may be the reason for the renal study to have very limited samples although the sampling scheme intended to have more samples. Three samples per subject can not define the profile and determine the AUC as was done in study 425, because it is difficult to determine the elimination phase with only 3 points (PK software Winnonlin showed an error as in the report of study 425: error 10207 "Lambda Z could not be estimated").



ADDITIONAL LABELING RELATED ISSUES

There is certain confusion about the information in the labeling based on the mass balance data. The current proposed version by the applicant and the version recommended by the Approvable letter are not consistent as summarized in the following table.

Excretion (% of dose)	Applicant	Approvable Letter
Total		84
Urine	/	62
Faeces		7

Although the total and urine parts are in agreement, the faeces part is different. The submission is revisited and the following table shows the original data these numbers were based on.

Collection period (hours/days)		Subject no./Sex		
		7M	8M	Mean
Urine	0-4			19.20
	4-8			6.54
	8-12			5.35
	12-24			11.19
	24-48			8.44
	48-72			3.18
	72-96			1.33
	96-120			0.81
	120-144			0.61
	144-168			0.51
	168-192			0.47
	192-216			0.35

	216-240	0.44
	240-264	0.37
	264-288	0.32
	288-312	0.28
	312-336	0.26
Total urine (Days 1-14)		59.61
	Day 18	0.18
	Day 21	0.15
	Day 24	0.13
	Day 27	0.10
	Day 30	0.10
	Day 34	0.08
	Day 38	0.07
Total urine		60.41
	0-24	0.13
	24-48	0.29
	48-72	2.67
	72-96	1.42
	96-120	1.27
	120-144	1.58
	144-168	0.98
	168-192	1.29
	192-216	0.57
	216-240	1.38
	240-264	0.77
	264-288	0.82
	288-312	0.83
Faeces	312-336	0.52
Total faeces (Days 1-14)		14.50
	Day 18	0.45
	Day 21	0.27
	Day 24	0.65
	Day 27	0.30
	Day 30	0.12
	Day 34	0.08
	Day 38	0.20
Total faeces		16.54
Total excretion		76.94

As can be seen, it was calculated that a total of 84% of the administered dose of ¹⁴C-rasagiline mesylate was excreted in urine and faeces during 38 days post-administration, based on direct measurements made during Days 1-14 and on interpolated data from Day 15 to Day 38. These results were derived as follows: During 7 days after administration to the six original subjects, a mean total of 60% of the radioactive dose was excreted in urine and 7% dose was excreted in the faeces, providing an overall recovery of 67% of the dose. When excreta were collected for 14 days post-administration in additional two subjects (as shown in the above table), again about 60% of the dose was recovered in the urine, but on this occasion 15% dose was recovered in the faeces. When 24-hour daily excreta collections were made at regular intervals until Day 38, radioactivity was still being excreted at a mean daily rate of about 0.25% dose per day at the end of this time. Calculations indicated that if excretion continued at the same rate, it would take about 5 to 6 weeks for 90% of the dose to be excreted.

Therefore, it is recommended the labeling state the 7-day data and the calculation results of a total of 84%.

COMMENTS

1. The available data show inconclusive and conflicting results regarding the drug interaction between levodopa and rasagiline. To elucidate this drug interaction and

provide clear instruction for the combination use, a drug interaction study between levodopa and rasagiline is recommended for Phase IV commitment. In the study, both the effect of rasagiline on levodopa and the effect of levodopa on rasagiline should be examined. As planned by the applicant, this study should involve young and elderly subjects to detect the age effect. In addition, the gender effect should be examined in this study by enrolling adequate number of males and females.

2. The renal impairment study results were not meaningful to allow a clear instruction for dosing in renal impairment patients. As a Phase IV commitment, the planned renal impairment study should first investigate the differences between the assay method used in study 430 (— SOP 659 Version D) and that used in study 425 (— SOP 659 Version B). If Version D used in study 430 is a more sensitive method, it should be used in the study to be conducted.
3. No additional dose proportionality study is necessary.

RECOMMENDATION

OCP found the applicant's responses acceptable to conduct the drug interaction study and renal impairment study as Phase IV commitments. The comments above should be incorporated in the letter to the applicant.

LABELING RECOMMENDATIONS

1. In CLINICAL PHARMACOLOGY section, the following changes should be made.

Pharmacokinetics

Rasagiline pharmacokinetics are linear with doses over the range of 1-10 mg. Its mean steady-state half life is 3 hours but there is no correlation of pharmacokinetics with its pharmacological effect because of its irreversible inhibition of MAO-B.

Absorption: Rasagiline is rapidly absorbed, reaching peak plasma concentration (C_{max}) in approximately 1 hour. The absolute bioavailability of rasagiline is about 36%.

Food does not affect the T_{max} of rasagiline, although C_{max} and exposure (AUC) are decreased by approximately 60% and 20%, respectively, when the drug is taken with a high fat meal. Because AUC is not significantly affected, AZILECT can be administered with or without food (See **DOSAGE AND ADMINISTRATION**).

Distribution: The mean volume of distribution at steady-state is 87 L, indicating that the tissue binding of rasagiline is in excess of plasma protein binding. Plasma protein binding ranges from 88-94% with mean extent of binding of 61-63% to human albumin over the concentration range of 1-100 ng/ml.

Metabolism and Elimination: Rasagiline undergoes almost complete biotransformation in the liver prior to excretion. The metabolism of rasagiline proceeds through two main pathways: N-dealkylation and/or hydroxylation to yield 1-aminoindan (AI), 3-hydroxy-N-propargyl-1-aminoindan (3-OH-PAI) and 3-hydroxy-1-aminoindan (3-OH-AI). *In vitro* experiments indicate

7 Page(s) Withheld

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 § 552(b)(5) Deliberative Process

 ✓ § 552(b)(4) Draft Labeling

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Ramana S. Uppoor
5/9/2006 09:51:10 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Agilect® (Rasagiline Mesylate) PRIMARY REVIEWER: Andre Jackson

NDA: 21641

TYPE: NDA

FORMULATION: Oral Tablet

STRENGTHS: 0.5 mg and 1 mg

APPLICANT: Teva Neuroscience

Submission Dates: November 4, 2004

April 22, 2005

1S

INDICATIONS: Mono and Adjunct Therapy Parkinson's Disease

Generic Name: Rasagiline Mesylate

**ADDENDUM TO THE JULY 12, 2005 AND NOVEMBER 4, 2004
REVIEWS**

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Background:

PART 1

OCPB issues related to the 1 mg dosage strength

The Clinical Pharmacology data at 1 mg for several studies submitted by the firm was reviewed by OCPB and it was concluded that the results indicated that all 1 mg study data in normals is of low quality due to the lack of sufficient samples to sufficiently define curve shape for the purposes of noncompartmental analysis (i.e., Cmax and AUC). A further analysis of the data submitted by the firm in their special population studies i.e., hepatic and renal did reveal some 1 mg data of higher quality that could be used to

indicate some trends for normals. In addition quality data from study CD 596 in normals (2m-10 mg) was examined to define dose proportionality. Summary of the data presented in Table A in the Appendix.

Several meetings have been held between the Medical Officers from the Division of Neuropharmacological Drug Products and OCPB related to the ongoing issues with the Rasagiline submission. Based upon these meetings it was decided that an addendum should be written for the review to include a more comprehensive design for the requested study to address several concerns related to age, dose effect and gender.

Original Study Design

Single dose study at doses of 1 mg, 2 mg and 6 mg in at least 24 normal subjects with the following demographics:

Dose	Males	Females
1 mg	4	4
2 mg	4	4
6 mg	4	4

The age range should be 30--80 yrs of age with at least 4 analyzable subjects in the following age groups:

Age	N
30-40	4
40-50	4
50-60	4
60-70	4
70-80	4

New Study Design

Single dose study at doses of 1 mg, 2 mg and 6 mg in at least 48 normal subjects with the following demographics:

Dose	Males		Females	
	40-60 yrs old	>65yrs old	40-60 yrs old	>65 yrs old
1 mg	4	4	4	4
2 mg	4	4	4	4
6 mg	4	4	4	4

Comment:

1. The new study design allows for age adults vs. elderly, gender, and dose effect to be addressed with sufficient N to have meaningful results.

PART 2

LEVODOPA

In the approvable letter sent to the firm the following item on levodopa was submitted from OCPB for a response by the firm.

Comment 1.

1. You need to formally evaluate the effect of levodopa on rasagiline clearance.

Firm's reply:

Teva accepts the current FDA proposed labelling on the effect of levodopa on rasagiline clearance, which indicates that one study (PRESTO) shows no effect and the other (TEMPO) shows an effect.

The firm's response is acceptable to OCPB

PART 3

DISSOLUTION

In the approvable letter sent to the firm the following item on dissolution was submitted from OCPB for a response by the firm.

2. The sponsor is requested to adopt the following dissolution method and specification for the 1mg strength of rasagiline tablets:

Equipment	USP, — Apparatus 2 (Paddles), Dissolution volume 500mL.
Medium	0.1N HCl (aq.)
Rotation speedrpm	50
Temperature	37 ⁰ C
Sampling time	15 minutes

Dissolution Specification Q= — in 15 min

Firm's reply:

The sponsor accepts the dissolution methodology and the 15 min sampling time point.

The firm's response is acceptable to OCPB

Part 4

Composition and dissolution data for the 0.5 mg strength

Table 1. Composition of the 0.5 mg ablet

The composition of the rasagiline mesylate tablets, the function of the components and a reference to the quality standards are summarized below:

Component	Amount (mg/tablet)	Function	Reference to Quality Standard
Rasagiline Mesylate (Drug Substance)		Drug Substance	In-house standard
Mannitol			USP, Ph. Eur.
Colloidal Silicon Dioxide			NF, Ph. Eur.
Starch			NF, Ph. Eur.
Pregelatinized Starch			NF, Ph. Eur.
Stearic Acid			NF, Ph. Eur.
Talc			USP, Ph. Eur.
Total Tablet Weight	105.0		

1. Equivalent to 0.5 mg of rasagiline base.

Table 2. Formulation for the 1.0 mg tablet.

Components	Reference to Quality Standards	Amount Per Batch	
		Amount Per Tablet [mg]	(tablets)
Rasagiline Mesylate	Teva In-House	/	/
Mannitol	USP, Ph. Eur.	/	/
Colloidal Silicon Dioxide	NF, Ph. Eur.	/	/
Starch ³	NF, Ph. Eur.	/	/
Pregelatinized Starch	NF, Ph. Eur.	/	/
	USP, Ph. Eur.	/	/

Stearic Acid

NF, Ph. Eur.

Talc

USP, Ph. Eur.

Theoretical End Weight

210.0

210

1. Equivalent to 1 mg of rasagiline base (N-Propargyl-1-(R)-aminoindan base).
2. Also named Colloidal Anhydrous Silica (Ph. Eur.).
3. Also named Maize Starch (Ph. Eur.).

Table 3. Dissolution data for the 0.5 mg tablet.

Dissolution Media (50 rpm, paddles)	Time Interval	10 minutes		15 minutes		20 minutes		30 minutes	
		Batch No	MIN062	MIN018	MIN062	MIN018	MIN062	MIN018	MIN062
0.1N HCL 500 ml	Mean %	96	98	96	98	95	99	96	98
	%RSD	1.9	2.2	2.9	1.6	1.4	2.2	1.8	2.0
0.1N HCL 900 ml	Mean %	89	100	97	100	97	100	97	100
	%RSD	8.9	1.6	1.8	2.0	1.7	1.7	2.0	2.0
Phthalate buffer at pH 4.5, 900 ml	Mean %	94	97	97	99	97	99	97	99
	%RSD	3.5	1.5	2.0	1.4	1.9	1.3	1.8	1.4
Phosphate buffer at pH 6.8, 900 ml	Mean %	93	96	95	99	98	98	96	99
	%RSD	1.1	1.0	1.0	1.3	1.2	1.5	1.3	1.2

MIN062 (0.5 mg Formulation II tablets with stearic acid)
 MIN018 (0.5 mg Formulation II tablets with stearic acid)

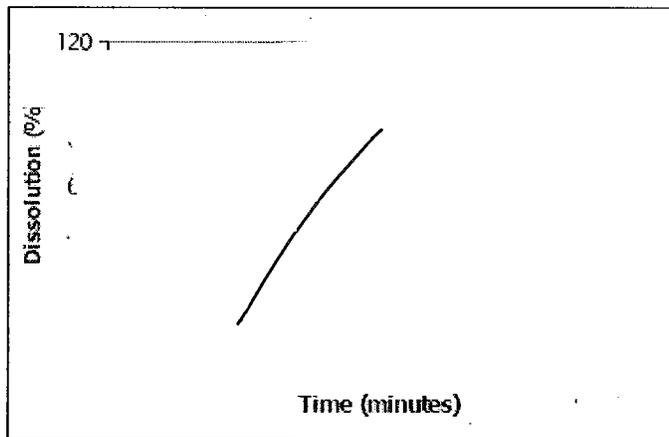


Figure 1. Comparative dissolution profile results of MIN062 vs. MIN018 in 500 ml 0.1N HCl

Comments:

1. The 0.5 mg tablet exhibits rapid dissolution and is compositionally proportional to the 1.0 mg tablet.

Comment To The Sponsor:

The sponsor is requested to adopt the accepted dissolution methodology and specification also for the 0.5 mg tablet strength:

Equipment	USP → Apparatus 2 (Paddles), Dissolution volume 500mL.
Medium	0.1N HCl (aq.)
Rotation speedrpm	50
Temperature	37°C
Sampling time	15 minutes
Dissolution Specification	Q= → in 15 min

SIGNATURES

Andre Jackson _____

RD/FT Initialed by Raman Baweja, Ph.D. _____
Team Leader

Cc-NDA 21641, HFD-860(Jackson, Baweja,Rahman,Mehta), Central Documents
Room(Biopharm-CDR)
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APPENDIX

Table A. STUDY SUMMARIES

STUDY DOSES	DATA QUALITY	SUBJECT POP	STUDY DEFICIENCY	COMPLETE PROFILES/N	WHAT WE KNOW	WHAT WE DON'T KNOW
CD 596 DAY 1 (2MG-10MG)	12-13 TIME PTS	18-30 MALES	NO FEMALES	4/6-2 MG 6/6-5 MG 6/6-10 MG	1)AUC NON-LINEAR ON DAY 1 2)C _{MAX} LINEAR ON DAY1	1)1MG DOSE 2)AGE 3)GENDER
CD 596 DAY 10 (2MG-10MG)	12-13 TIME PTS	18-30 MALES	NO FEMALES	5/6-2 MG 6/6-5 MG 6/6-10 MG	1)AUC LINEAR ON DAY 10 2) C _{MAX} LINEAR ON DAY 10 3)AUC INCREASES (2.17-3.4X DAY1-DAY10) 4)C _{MAX} INCREASES (1.5-1.8X DAY1-DAY10)	1)1MG DOSE 2)AGE 3)GENDER 4) HOW LONG DOES CL DECREASE W/TIME
TVP-424 DAY 1 1 MG	3-5 TIME PTS	5-MALES 3-FEMALES NORMALS	AGE(44-61)	6/8-1 MG	MALE AUC>FEMALE AUC 3.5>1.98 (TAB 33 PG93)	
TVP-424 DAY 7 1 MG	4-6 TIME PTS	5-MALES 3-FEMALES NORMALS	AGE(44-61)	6/8-1 MG	1) AUC INCREASES (1.39X DAY1- DAY 7) 2) C _{MAX} INCREASES (1.45X DAY1-DAY 7) ~TO YOUNG 3)MALE AUC>FEMALE AUC	1)WOULD IT BE HIGHER AT DAY 10 AND BEYOND

TVP-424 DAY 1 1 MG	4-5 TIME PTS	5-MALES 3-FEMALES MILD LIVER	AGE(45-61)	2/8- 1MG	5.53>4.15 (TAB 45 PG 105)	1) MALE AUC>MALE AUC 4.05>3.09 (TAB 35 PG 95) 2) AUC INCREASES(1.0X FROM NORMALS ON DAY 1)	
TVP-424 DAY 7 1 MG	5-11 TIME PTS	5-MALES 3-FEMALES MILD LIVER	AGE(45-61) MALE SUB 11 AUC=23.76 2X OTHERS	4/8-1 MG	1) AUC INCREASES(2.75 X DAY 1- DAY 7) 2) CMAX INCREASES (1.73X DAY 1- DAY 7) 3) MALE AUC>FEMALE AUC 11.33>7.49 W/O 11(8.22) (TAB 47 PG 107) 4) AUC INCREASES (1.9X FROM NORMALS ON DAY 7)	SHOULD MILD HEPATIC BE CONTRAINDICA TED?	
TVP-424 DAY 1 1 MG	5-7 TIME PTS	MALES FEMALES MODERATE LIVER	AGE(41-63)	1/8-1 MG	1) AUC INCREASES (1.9X FROM NORMALS ON DAY 1)		
TVP-424 DAY 7 1 MG	7-12 TIME PTS	MALES FEMALES MODERATE LIVER	AGE(41-63)	2/8-1 MG	1) AUC INCREASES(4.7X DAY 1-DAY 7) 2) CMAX INCREASES(1.2X DAY 1- DAY 7) 3) AUC INCREASES (6.7X FROM NORMALS ON DAY 7)		
TVP-425 DAY 1 1 MG	3-4 TIME PTS	6-MALES 2-FEMALES NORMALS	AGE(49-63)	2/8 NO FEMALES	1) FEMALE AUC-MALE AUC 2.47=2.45 (TAB 35 PG 97)		
TVP-425 DAY 7	4-5 TIME PTS	6-MALES 2-FEMALES	AGE(49-63)	6/8	1) AUC INCREASES(1.47X DAY 1-DAY 7)		

1 MG		NORMALS				2) CMAX INCREASES(1.15X DAY1-DAY 7) 3)FEMALE AUC>MALE AUC 3.31=3.74 (TAB 47 PG 109)	
TVP-425 DAY 1 1 MG	2-6 TIME PTS	6-MALES 2-FEMALES MILD RENAL	AGE(29-65)	4/8 1 FEMALE	1) AUC INCREASES (1.0X FROM NORMALS ON DAY 1) 2)MALE AUC>FEMALE 2.73>1.53 (TAB 37 PG 99)		
TVP-425 DAY 7 1 MG	4-6 TIME PTS	6-MALES 2-FEMALES MILD RENAL	AGE(29-65)	6/8	1) AUC INCREASES(2.0X DAY1-DAY 7) 2) CMAX INCREASES(1.3X DAY1-DAY 7) 3)FEMALE AUC>MALE AUC 7.23>4.13 (TAB 49 PG 111) 4) AUC INCREASES (2.0X FROM NORMALS ON DAY 7)		
TVP-425 DAY 1 1 MG	3-4 TIME PTS	6-MALES 2-FEMALES MODERATE RENAL	AGE(40-64) SUB 25 IN MODERATE NOT IN DEMO USED 6 DIFF SUB DAY1 VS DAY 7	2/6 NO FEMALE	DATA IS QUESTIONABLE SHOWS A DECREASE IN AUC	SHOULD MODERATE RENAL BE CONTRAINED?	
TVP-425 DAY 7 1 MG	3-6 TIME PTS	MALES FEMALES MODERATE RENAL	AGE(40-64)	3/8	DATA IS QUESTIONABLE SHOWS A DECREASE IN AUC		

CONCLUSIONS: HEPATIC

1. AUC INCREASES 2.17-3.4 IN NORMAL MALES FROM DAY1-DAY10.

2. AUC INCREASES 2.75X IN MILD HEPATIC SUBJECTS DAY 1 -DAY 7.
3. AUC INCREASES 1.9X IN MILD HEPATIC ON DAY 7 COMPARED TO NORMALS

CONCLUSIONS: RENAL

4. AUC INCREASES 2.17-3.4 IN NORMAL MALES FROM DAY 1-DAY 10.
5. AUC INCREASES 2.0 X IN MILD RENAL SUBJECTS DAY 1 -DAY 7.
6. AUC INCREASES 2.0 X IN MILD RENAL SUBJECTS ON DAY 7 COMPARED TO NORMALS
7. AUC FOR MODERATE RENAL SUBJECTS COMPARABLE TO NORMALS ON DAY 7
BUT DATA MAY BE QUESTIONABLE SINCE THEY USED DIFF SUBS DAY 1 VS DAY 7

CONCLUSION: GENDER

8. MALES TEND TO HAVE SLIGHTLY HIGHER OR COMPARABLE LEVELS TO FEMALES ON DAYS 1 AND 7

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/s/

Andre Jackson
7/29/05 12:09:01 PM
BIOPHARMACEUTICS

Raman Baweja
7/29/05 12:36:05 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW**DRUG: Agilect® (Rasagiline Mesylate) PRIMARY REVIEWER: Andre Jackson**

NDA: 21641

TYPE: NDA

FORMULATION: Oral Tablet

STRENGTH: 1 mg

APPLICANT: Teva Neuroscience

Submission Date: April 22, 2005

1S

INDICATIONS: Mono and Adjunct Therapy Parkinson's Disease

Generic Name: Rasagiline Mesylate

ADDITIONAL RESPONSE TO APPROVABLE LETTER

The firm responded to questions from the FDA related to assay quality for their NDA. The firm's response to this inquiry in their current April 14, 2005 submission is that indeed their assay was valid. However they still stated some reservations related to the quality of the 1 mg PK data especially for the study P94159 which indicated non linearity above the 1 mg dose. This observation is an issue for the Medical Reviewer in his clinical assessment of Tyramine in this study.

Subsequent to the current submission, OCPB has looked at all studies for this NDA to identify potential problems with the Clinical Pharmacology data. The following Table summarizes the Clinical Pharmacology data according to study details and a brief narrative related to the quality of the data.

Table 1. Summary of Clinical Pharmacology data submitted for the NDA 21-641. Study details and the number of samples taken per subject is presented with a brief commentary on study quality.

STUDY #	DOSE	SAMPLED TIMES	N SUBJECTS	COMMENTS
P94159	1MG	0.5 AND 1 HR	6 (DAY1)	CURVES ARE ALL DECREASING ¹
	1 MG	0.5, 1 AND 2 HRS	6(DAY 10)	5 CURVES DECREASING 1 CURVE PROFILE ²
TVP-1012/424 Hepatic Impairment Study- HEALTHY	1 MG	0.25,0.5,1,1.5, 2 0.25,0.5,1,1.5 0.25,0.5,1	1 1 6	2 CURVES ³ DECREASING 6 PROFILES
TVP-1012/424 Hepatic Impairment Study- MILD	1 MG			6 CURVES DECREASING
TVP-1012/424 Hepatic Impairment Study- MODERATE	1 MG			7 CURVES DECREASING 1 PROFILE ³

TVP-1012/425 Renal Impairment Study- MILD	1 MG	0.25,0.5,1,1.5, 2,3 0.25,0.5,1,1.5,2 0.25,0.5,1,1.5 0.25,0.5,1 0.5,1	1 2 4 1 1	4 CURVES DECREASING 4 PROFILES
CC547 SINGLE RISING DOSES 1-20 MG	1 MG	0.5,1 0.5	5 1	DATA OF NO VALUE
CC547 SINGLE RISING DOSES 1-20 MG	2 MG	0.5,1,2 0.5,1	3 3	DATA OF NO VALUE 3 PROFILES DECREASE
TVP1012/112 PATIENTS ON CHRONIC LEVO DOPA DATA USED FOR DOSE PROPORTIONALITY	0.5 MG	0.5,2,4 0.5,2 0.5,2,4	7 FEMALE 2 MALE 1 MALE	FEMALE 0.5 MG ALL CURVES DECREASING 2 MALES CURVES DECREASING
TVP1012/112 PATIENTS ON CHRONIC LEVO DOPA DATA USED FOR DOSE PROPORTIONALITY	1.0 MG	0.5,2,4 0.5,2,4	2 FEMALE 4 MALES	CURVES DECREASING CURVES DECREASING
TVP1012/112 PATIENTS ON CHRONIC LEVO DOPA DATA USED FOR DOSE PROPORTIONALITY	2.0 MG	0.5,2,4 0.5,2,4	6 MALES 2 FEMALES	5 DECREASING 2 DECREASING
TVP1012/231 GENDER EFFECT	1.0 MG	VISIT 10 0.5,2,4	5 FEMALES 10 MALES	4 DECREASING 10 DECREASING
TVP1012/231 GENDER EFFECT	2.0 MG	DAY 10 0.5,2,4	4 FEMALES 9 MALES	4 DECREASING 8 DECREASING
TVP1012/231 GENDER EFFECT	4.0 MG	DAY 10 0.5,2,4	6 FEMALES 8 MALES	5 DECREASING 6 DECREASING

1. CURVES DECREASING RESEMBLE INTRAVENOUS INPUT-NO ABSORPTION CMAX
2. PROFILES SHOW AN ABSORPTION MAXIMUM
3. Representative curves attached to the review

Comments:

1. These results indicate that all 1 mg study data in normals is of low quality due to the lack of sufficient samples to sufficiently define curve shape for the purposes of noncompartmental analysis (i.e., Cmax and AUC). In several studies the 1st sample is Cmax which makes it difficult to know if the maximum actually preceded this sampling time. These have been designated as descending curves. In many cases the firm collected only two samples per subject which makes the data totally unacceptable.

2. Two studies done in PD patients: TVP1012/112 was used to determine dose proportionality while TVP1012/231 was used for gender effect. The quality of the data does not allow any meaningful conclusions related to C_{max} since most data was decreasing (ie, failure to observe a “true “ absorption maximum-See graphs in Appendix). The area under the curve can be used to determine “pseudo dose proportionality” but there is no rigorous data on maximal exposure since C_{max} could not be accurately estimated in most normal subjects. The dose proportionality study needs to be repeated using a better assay and more frequent sampling perhaps earlier than 0.5 hrs. Furthermore, the age range of study subjects rarely included subjects >70 yrs of age.

3. OCPB recommends that the firm conduct the following study.

Single dose study at doses of 1 mg, 2 mg and 6 mg in at least 24 normal subjects with the following demographics:

Dose	Males	Females
1 mg	4	4
2 mg	4	4
6 mg	4	4

The age range should be 30--80 yrs of age with at least 4 analyzable subjects in the following age groups:

Age	N
30-40	4
40-50	4
50-60	4
60-70	4
70-80	4

COMMENT TO THE CLINICAL DIVISION

The OCPB ongoing issue with the Rasagiline submission has been the inconsistent results related to any apparent dose effect. Following several questions to the firm related to this matter the firm has finally responded in their November 18, 2004 submission related to the assay problems at the 1.0 mg dose, ” The plasma levels following 1 mg rasagiline dose are very low and the constraints of the bioanalytical limits of quantitation of PAI are preventing an accurate estimation of exposure at the relevant clinical dose. This limitation is apparent both after single or multiple doses, and on occasions it even led us to conduct clinical pharmacokinetic trials on a 2 mg dose instead of 1 mg, to allow better bioanalytical and pharmacokinetic assessment.” Therefore, based upon the firm’s own admission related to the low quality of any 1.0 mg data, OCPB recommends that the firm improve the assay sensitivity, conduct a new dose proportionality study which should include proper subject representation for age and gender with more frequent sampling

since the determination of maximum exposure i.e., C_{max} was not possible from the previous studies results. The data in the Appendix shows the problem of obtaining C_{max} data from plasma curves without a maximum (i.e., a curve without a measured concentration prior to the highest concentration exclusive of the measurement at time=0). The unresolved issue of a dose effect should be addressed by doing the following study.

Recommended Study:

Single dose study at doses of 1 mg, 2 mg and 6 mg in at least 24 normal subjects with the following demographics:

Dose	Males	Females
1 mg	4	4
2 mg	4	4
6 mg	4	4

The age range should be 30--80 yrs of age with at least 4 analyzable subjects in the following age groups:

Age	N
30-40	4
40-50	4
50-60	4
60-70	4
70-80	4

The pharmacokinetic data submitted by the firm was done primarily at doses greater than 1 mg. However, since the 1 mg dose has been shown to be the effective clinical dose it is important that issues related to dose effect and its pharmacokinetics be resolved.

THE FIRM SHOULD RECEIVE COMMENTS 1, 2 and 3 , TABLE #1 AND THE REPRESENTATIVE GRAPHS IN THE APPENDIX.

SIGNATURES

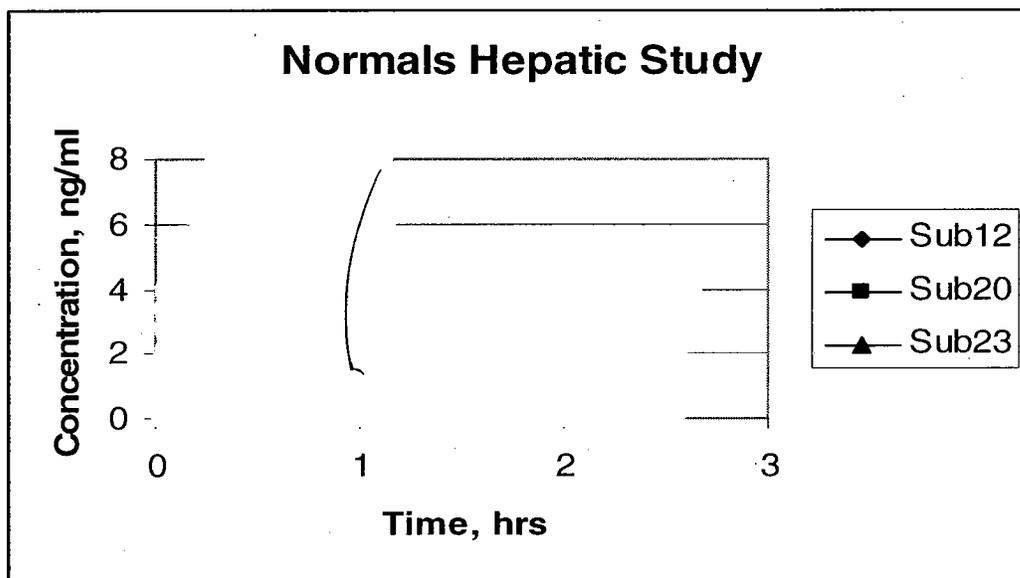
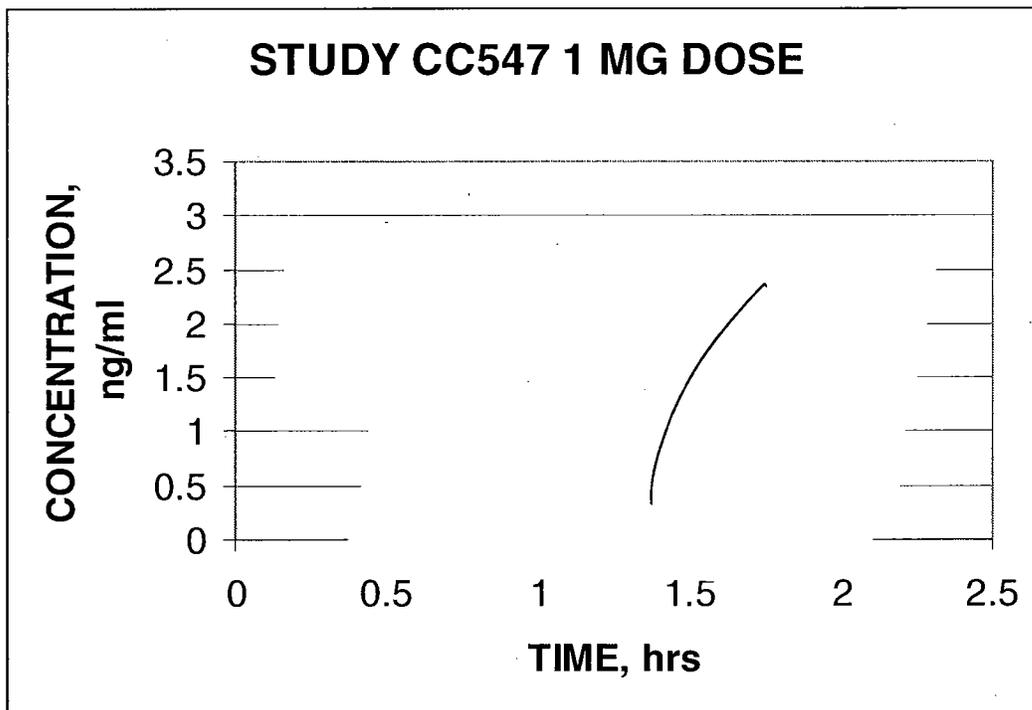
Andre Jackson _____

RD/FT Initialed by Raman Bawaja, Ph.D. _____
Team Leader

Cc-NDA 21641, HFD-860(Jackson, Bawaja,Rahman,Mehta), Central Documents Room(Biopharm-CDR)

**APPEARS THIS WAY
ON ORIGINAL**

APPENDIX



FIGURES ARE FOR SINGLE DOSE ESCALATION STUDY CC547, 3 TYPICAL SUBJECTS 1 MG DOSE AND FOR THE 1 MG DOSE FOR THE NORMALS IN THE HEPATIC STUDY,

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/s/

Andre Jackson
7/12/05 09:23:25 AM
BIOPHARMACEUTICS

Raman Baweja
7/12/05 10:05:51 AM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Agilect® (Rasagiline Mesylate) PRIMARY REVIEWER: Andre Jackson

NDA: 21641

TYPE: NDA

FORMULATION: Oral Tablet

STRENGTH: 1 mg

APPLICANT: Teva Neuroscience

Submission Date: April 14, 2005

1S

INDICATIONS: Mono and Adjunct Therapy Parkinson's Disease

Generic Name: Rasagiline Mesylate

MEMO TO FILE

The firm responded to this review on April 14, 2005 that indeed their assay was valid. However they still stated some reservations related to the quality of the 1 mg PK data especially for the study P94159 which indicated non linearity above the 1 mg dose. This observation is an issue for Dr. Kapcala in his clinical assesment of the Tyramine in this study.

The details of this apparent discrepancy between a valid assay and the "low plasma concentrations following a 1 mg dose" needs to resolved by the firm to Dr. Kapcala's satisfaction.

SIGNATURES

Andre Jackson _____

RD/FT Initialed by Sally Yasuda, Pharm.D. _____
Acting Team Leader

Cc-NDA 21641, HFD-860(Jackson, Yasuda,Rahman,Mehta), Central Documents
Room(Biopharm-CDR)

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CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW**DRUG: Agilect® (Rasagiline Mesylate) PRIMARY REVIEWER: Andre Jackson**

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INDICATIONS: Mono and Adjunct Therapy Parkinson's Disease

Generic Name: Rasagiline Mesylate

ADDITIONAL RESPONSE TO APPROVABLE LETTER

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The details of this apparent discrepancy between a valid assay and the "low plasma concentrations following a 1 mg dose" needs to resolved by the firm to Dr. Kapcala's satisfaction.

Subsequent to this submission OCPB looked at all studies for this submission to identify potential problems with the Clinical Pharmacology data. The following Table summarizes the Clinical Pharmacology data according to study details and a brief narrative related to the quality of the data.

Table 1. Summary of Clinical Pharmacology data submitted for the NDA 21-641. Study details and the number of samples taken per subject is presented with a brief commentary on study quality.

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TVP-1012/424 Hepatic Impairment Study- MILD	1 MG			6 CURVES DECREASING
TVP-1012/424 Hepatic Impairment Study- MODERATE	1 MG			7 CURVES DECREASING 1 PROFILE
TVP-1012/425	1 MG	0.25,0.5,1,1.5, 2,3	1	4 CURVES

Renal Impairment Study-MILD		0.25,0.5,1,1.5,2 0.25,0.5,1,1.5 0.25,0.5,1 0.5,1	2 4 1 1	DECREASING 4 PROFILES
CC547 SINGLE RISING DOSES 1-20 MG	1 MG	0.5,1 0.5	5 1	DATA OF NO VALUE
CC547 SINGLE RISING DOSES 1-20 MG	2 MG	0.5,1,2 0.5,1	3 3	DATA OF NO VALUE 3 PROFILES DECREASE
TVP1012/112 PATIENTS ON CHRONIC LEVO DOPA DATA USED FOR DOSE PROPORTIONALITY	0.5 MG	0.5,2,4 0.5,2 0.5,2,4	7 FEMALE 2 MALE 1 MALE	FEMALE 0.5 MG ALL CURVES DECREASING 2 MALES CURVES DECREASING
TVP1012/112 PATIENTS ON CHRONIC LEVO DOPA DATA USED FOR DOSE PROPORTIONALITY	1.0 MG	0.5,2,4 0.5,2,4	2 FEMALE 4 MALES	CURVES DECREASING CURVES DECREASING
TVP1012/112 PATIENTS ON CHRONIC LEVO DOPA DATA USED FOR DOSE PROPORTIONALITY	2.0 MG	0.5,2,4 0.5,2,4	6 MALES 2 FEMALES	5 DECREASING 2 DECREASING
TVP1012/231 GENDER EFFECT	1.0 MG	VISIT 10 0.5,2,4	5 FEMALES 10 MALES	4 DECREASING 10 DECREASING
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TVP1012/231 GENDER EFFECT	4.0 MG	DAY 10 0.5,2,4	6 FEMALES 8 MALES	5 DECREASING 6 DECREASING

1. CURVES DECREASING RESEMBLE INTRAVENOUS INPUT-NO ABSORPTION CMAX
2. PROFILES SHOW AN ABSORPTION MAXIMUM

Comments:

1. These results indicate that all 1 mg study data in normals is of low quality due to the lack of sufficient samples to sufficiently define curve shape for the purposes of noncompartmental analysis (i.e., Cmax and AUC). In several studies the 1st sample is Cmax which makes it difficult to know if the maximum actually preceded this sampling time. These have been designated as descending curves. In many cases the firm collected only two samples per subject which makes the data totally unacceptable.

2. Two studies done in PD patients TVP1012/112 was used to determine dose proportionality while TVP1012/231 was used for gender effect. The quality of the data

does not allow any meaningful conclusions related to Cmax since most data was decreasing (ie, failure to observe a "true" absorption maximum. The area under the curve can be used to determine dose proportionality. These studies need to be repeated using either a better assay or sampling earlier than 0.5 hrs.

3. The sponsor should comment on these results (i.e., no defined maximum in curves) and their potential to impact the label in the areas of hepatic impairment, renal impairment, dose proportionality, gender effects and other relevant areas.

THE FIRM SHOULD RECEIVE COMMENTS 1-3 AND Table #1.

SIGNATURES

Andre Jackson _____

RD/FT Initialed by Sally Yasuda, Pharm.D. _____
Acting Team Leader

Cc-NDA 21641, HFD-860 (Jackson, Yasuda, Rahman, Mehta), Central Documents
Room (Biopharm-CDR)

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/s/

Andre Jackson
4/15/05 09:25:42 AM
BIOPHARMACEUTICS

Sally Yasuda
4/15/05 11:26:24 AM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Agilect® (Rasagiline Mesylate) PRIMARY REVIEWER: Andre Jackson

NDA: 21641

TYPE: NDA

FORMULATION: Oral Tablet

STRENGTH: 1 mg

APPLICANT: Teva Neuroscience

Submission Date: November 18, 2004

1S

INDICATIONS: Mono and Adjunct Therapy Parkinson's Disease

Generic Name: Rasagiline Mesylate

Review of Amendments to a Pending Application

THE FOLLOWING COMMENTS WERE FAXED TO THE FIRM October 27, 2004:

QUESTION:

1. You should do a formal log dose regression on the tyramine study P94159 to clearly establish if the PK is indeed nonlinear for AUC between the 1 mg and 2 mg
2. You should present detailed calculations showing the individual data for all pharmacokinetic calculations in Appendix 2 Tables 1 and 2. These tables should be annotated for easy identification with their EDR origin or the original tables can be presented in proximity to the newly calculated mean values.
3. You should make pharmacokinetic comparisons only to subjects whom exhibit the same pharmacokinetics. For example, males in study CD596 (1-20 mg) exhibit nonlinear pharmacokinetics following single dosing, but linear kinetics after multiple dosing (2-10 mg/day). However in study P94159 at multiple doses of 1 mg and 2 mg/day, the pharmacokinetics appears to be nonlinear on Day 9. Therefore it would not be meaningful to compare the multiple dose data from studies CD596 and P94159. This principle should be followed in all of your comparisons across treatment groups.

THE FIRM'S RESPONSES TO THE QUESTIONS FOLLOW:

1. Firm's Response to Question 1:

A power model analysis based of the Gough K. et al. 1995 paper was performed on the tyramine study P94159, using the following model characteristics:

$$\text{Log}(Y_{ijk}) = s_i + p_j + \beta \cdot \log(D_k) + \varepsilon_{ijk}$$

Where:

___ Y_{ijk} is the AUC of the i subject in the j period on the k dose.

___ s_i is the random subject effect,

___ p_j is the period effect

___ D_k is the k dose.

After exponentiation: $Y_{ijk} = \alpha * (D_k)^\beta$ (i)

Dose proportionality requires that $\beta = 1$ for dose-dependent parameters and $\beta = 0$ for dose independent-parameters. In our case AUC is dose-dependent parameter so if 1 is within the CI of the estimate of β then we can conclude proportionality. Else:

From (i) we can obtain:

The increase in AUC for an R-fold increase in dose: $AUC_2/AUC_1=R^\beta$

Or as given in the results, the increase in dose required to double the AUC:

$R= 2^{1/\beta}$ (ii)

Results:

The subjects and their AUC values of PAI –Rasagiline on Day 9 and 10 are presented in Table 1.

Table 1. Study P94159 – Individual Subjects Data

Subject No.	Dose (mg)	PAI AUC (ngxh/ml)	
		Day 9	Day 10
601	1	6.57	6.56
602	1	4.37	2.95
603	1	6.56	6.65
605	1	5.33	3.72
606	1	6.87	7.63
607	1	5.35	5.55
610	2	22.33	18.45
612	2	34.36	22.24
613	2	24.16	24.24
615	2	28.62	24.56
617	2	22.20	28.11
618	2	16.44	20.47

The power-model analysis which included all available data where PAI AUC's were reported, was fitted using the analysis of variance model (SAS PROC GLM). The linear relationship between Log(AUC) and Log(Dose) was fitted by incorporating into the model Log(Dose), as well as the random subject effect. It included dose levels of 1 and 2 mg.

The table below (Table 2) presents estimates and confidence intervals (CI) of β from the analysis of AUC, and estimated R values with CI's for PAI.

Table 2. Study P94159 - Summary Results of the Assessment of PAI Dose Proportionality Using the Power Model Analysis

Day	AUC	β Estimate (95% CI)	Estimate of the Increase in Doses Required for Doubling the AUC (95% CI)
9	AUC _{0-t}	2.06 (1.66,2.46)	1.40 (1.33,1.52)
10	AUC _{0-t}	2.13 (1.60,2.65)	1.39 (1.30,1.54)

* ANOVA (SAS GLM Procedure) - SAS output is given in Attachment 1.

** Obtained using the estimate of β and (ii)

The results of the analysis demonstrate departure from dose proportionality in AUC for PAI, with 95% CI values of 1.66-2.46 and 1.60-2.65 on Day 9 and 10, respectively.

The clinical significance of the results is limited however, for reasons that were discussed in previous 'dose proportionality' correspondence with the FDA (Amendment to a pending application, February 12, 2004, study CC547 Question 3 and study CD596 Question 4), as follows:

The plasma levels following 1 mg rasagiline dose are very low and the constraints of the bioanalytical limits of quantitation of PAI are preventing an accurate estimation of exposure at the relevant clinical dose. This limitation is apparent both after single or multiple doses, and on occasions it even led us to conduct clinical pharmacokinetic trials on a 2 mg dose instead of 1 mg, to allow better bioanalytical and pharmacokinetic assessment.

Moreover, the plasma sampling of rasagiline in the tyramine study was mainly aimed at verifying adequate exposure to rasagiline, and hence few samples were taken (pre-dose, 30 min, 1, 2, 3 and 4 hours post dose). Study CD596 on the other hand, was designated as a pharmacokinetic study, and therefore more concentrated sampling was employed, including timepoints around t_{max}. This study is therefore enabling a more accurate estimate of PK parameters, and is more adequate for the estimation of dose linearity and proportionality. The results of the power-model analysis in the CD596 study (according to the method described by Gough et al. 1995), indeed demonstrated dose proportionality in AUC for PAI at the dose range of 2-10 mg following repeated dosing).

FDA Reply:

The following table for rasagiline analysis for study P94159 was submitted in the original application.

Parameter	Rasagiline	Aminoindan
Method	GC/MS	GC/MS
Sensitivity/LOQ	0.25 ng/ml	0.5 ng/ml

Linearity (Standard curve samples)	0.25-10 ng/ml	0.5-10 ng/ml
Quality Control (QC) Samples	0.4 ng/ml 2.50 ng/ml 7.5 ng/ml	0.75 ng/ml 2.50 ng/ml 7.5 ng/ml
Precision of Standards (%CV)	<u>7.37% @ 0.25ng/ml</u> <u>2.50% @ 10.0 ng/ml</u>	6.14% @ 0.5 ng/ml 2.67% @ 10 ng/ml
Precision of QC Samples (%CV)	9.8 @ 0.4 ng/ml 7.52 @ 7.5 ng/ml	8.05% @ 0.75 ng/ml 4.56% @ 7.5 ng/ml
Accuracy of Standards (%)	93% @ 0.25ng/ml 99.3% @ 10ng/ml	99.3% @ 0.5 ng/ml 99.0% @ 10 ng/ml
Accuracy of QC Samples (%)	99% @ 0.4 ng/ml 99% @ 7.5 ng/ml	99% @ 0.75 ng/ml 103% @ 7.5 ng/ml

This table indicates that your assay was reliable, however you are currently stating that “The plasma levels following 1 mg rasagiline dose are very low and the constraints of the bioanalytical limits of quantitation of PAI are preventing an accurate estimation of exposure at the relevant clinical dose.” You need to explain what you mean by “The plasma levels following 1 mg rasagiline dose are very low and the assay not being accurate.” Is the problem related to stability, assay sensitivity, recovery etc. You must be very clear since this is pivotal information for all studies at the 1 mg dose.

Further, there were several studies, P94159, CC547, CC596, TVP-1012/424, TVP-1012/425, TVP-1012/426, TVP-1012/430, TVP-1012/112, TVP-1012/132, and TVP-1012/231 where a 1 mg dose was studied either under single or multiple dose conditions. Based upon your claimed assay unreliability at the 1 mg dose are the aforementioned study results to be viewed as reliable by OCPB. If the answer is yes the firm should explain why.

2.Firm’s Response to Question 2.

Data listings of pharmacokinetic parameters of individual patients by study, which were used to calculate data presented in Appendix 2, Tables 1 and 2 (Amendment #8), are attached (Attachment 2).

The means and standard deviations presented in Tables 1 and 2 (Appendix 2, Amendment #8) were calculated from these individual data.

Following is a table which annotates the pharmacokinetic data to the clinical trial reports within the submission (Table 3).

Table 3. Annotation of PK Data to the Clinical Trial Reports in the Submission

Study	Page in submission (PDF page no.)
CD596	5.3.3.1.2 /hpbio/hupharm/CD596.pdf App. II pages 412, 416, 420 of 1020
P94159	5.3.4.1.1 /hpbio/hupharm/P94159.pdf pages 1455-1456, 1459-1460 of 1834

**APPEARS THIS WAY
ON ORIGINAL**

Study	Page in submission (PDF page no.)
TVP-1012/424	5.3.3.3.1 /hpbio/hupharm/TVP1012424.pdf Section 9.18 table 45 page 105 of 587
TVP-1012/425	5.3.3.3.2 /hpbio/hupharm/TVP1012425.pdf Section 9.19 table 47 page 109 of 551
TVP-1012/426	5.3.3.4.1 /hpbio/hupharm/TVP1012426.pdf App. 5, tables 14.1-14.2 pages 338-339 of 640
TVP-1012/430	5.3.3.4.2 /hpbio/hupharm/TVP1012430.pdf App. 4, table 4.1.3 page 850 of 1062
TVP-1012/112	5.3.1.4.8 /hpbio/hupharm/112/TVP1012112a.pdf page 1933 (662 of 730)-1948 (677 of 730)
TVP-1012/132	5.3.4.2.1 /hpbio/hupharm/132/132app_15.4.pdf pages 378-384 of 410 of App 15.4 in submission
TVP-1012/231	5.3.3.2.1 /hpbio/hupharm/231/TVP1012231.pdf pages 1825-1826 of 2030

FDA Reply:

The firm's response is acceptable.

3.Firm's Response to Question 3.

Dose proportionality was assessed as part of the dose ranging studies in healthy subjects and PD patients. Rasagiline AUC and Cmax increased more than proportionally with increasing dose following single oral rasagiline doses of ≥ 5 mg. However, steady-state Cmax and AUC in subsequent multiple-dose studies increased approximately proportionally with increasing dose over a dose range of 1 mg to 10 mg rasagiline administered q.d. to healthy subjects. Dose proportionality in early PD patients was apparent over the dose range of 1 to 4 mg/day rasagiline,

and in patients on chronic levodopa therapy, over the dose range of 0.5 to 2 mg/day rasagiline (Module 2.7.2.3.2). In previous correspondence with the Division, further clarifications regarding dose proportionality were made, based on the Single and Multiple dose data (Amendment to a pending application, February 12, 2004, study CC547 Question 3 and study CD596 Question 4; Response to analysis request, April 29, 2004). The conclusions drawn from these analyses were that where applicable, i.e., at the dose range of 2-10 mg for studies CC547 and CD596 (all male subjects), and at the dose range of 0.5-2 mg and 1-4 mg (male and female) patient studies TVP-1012/112 and TVP-1012/231, respectively, the model showed dose-proportionality in AUC for PAI following repeated dosing. The tyramine study P94159 was not included or used for dose proportionality assessments for reasons stated below.

__The plasma levels following 1mg rasagiline dose are very low and the constraints of the bioanalytical limits of quantitation of PAI are preventing an accurate estimation of exposure at the relevant clinical dose.

__In the tyramine study, the plasma levels of rasagiline following 1mg dose were even slightly lower compared to other studies with similar subject populations. Exposure following 1 mg was 5.8 ± 1 , and 5.5 ± 1.8 ng.h/mL on Day 9 and 10, respectively in the tyramine study compared to all other phase I - normalized exposure of 8.8 ± 3.5 ng.h/mL, and 'all phase II' - normalized exposure of 9.5 ± 4.2 ng.h/mL of males at steady state (Table 2, Appendix 2, in the response to the tyramine question of the approvable letter). Following 2 mg dose however, the exposure to rasagiline in the tyramine study was representative of all other trials.

__The objective of the tyramine study was to evaluate the potential pharmacodynamic interaction between rasagiline and tyramine, and to define the sensitivity to tyramine with rasagiline compared to placebo. Pharmacokinetic sampling was therefore mainly aimed to verify adequate exposure to rasagiline, and hence PK sampling was sparse (pre-dose, 30 min, 1, 2, 3 and 4 hours post dose). The multiple dose study CD596 on the other hand is more relevant for PK assessment than the tyramine study since its major objective was to gain complete pharmacokinetic profile of rasagiline following multiple dose administration at various doses, and for this end the PK sampling was relatively dense, including time points at: pre dose, 10, 20, 30, 45 min and, 1, 1.5, 2, 3 and 4 hours post dose. Also, the distribution of sampling times around t_{max} (~0.5-1h) allows better characterization of the PK profile. No such specific attempt was made in the tyramine study for the reason stated above. In conjunction with these premises, pharmacokinetic comparisons in our response to FDA Action letter of July 2, 2004 (Amendment to a pending application, November 4, 2004) were applied to subjects whom exhibit the same pharmacokinetics, accepting the Division's observation that comparison should be made only for data with linear pharmacokinetics. Also, being aware of the apparent time dependent exposure at all dose levels between single and multiple dosing, the

Aug 2004 response provided only multiple-dose data.

The dose dependent kinetics following a single dose administration, and the time depended kinetics have been referred to in the submission Clinical Overview. Irreversible binding to MAO in the gastrointestinal tract (a large reservoir of MAO) may contribute to the low (36%) absolute bioavailability observed in a single dose study, and saturation of Gastro-Intestinal Tract (GIT) MAO over time may be another factor contributing to the time dependent pharmacokinetics. Slow turnover of MAO bound rasagiline in the body may also explain the prolonged recovery of ¹⁴C after a single radio-labeled dose.. The irreversible binding of rasagiline to MAO-B may be responsible for some of its atypical PK properties, the most important of which is time dependent pharmacokinetics. The clinical relevance of this dependence after a single dose administration, is however limited. Rasagiline is intended for chronic dosing, and therefore the multiple dose setting is clinically more relevant.

FDA Reply:

You state” The conclusions drawn from these analyses were that where applicable, i.e., at the dose range of 2-10 mg for studies CC547 and CD596 (all male subjects), and at the dose range of 0.5-2 mg and 1-4 mg (male and female) patient studies TVP-1012/112 and TVP-1012/231, respectively, the model showed dose-proportionality in AUC for PAI following repeated dosing.” This response is troubling since you previously stated that your assay for the 1 mg dose was low and not reliable. Are you now stating that in some studies the assay was reliable. You must clarify this point.

Given the level of concern by Dr. Kapcala related to gender and age effects on Tyramine levels, one must be clear on the exposure levels at the 1 mg dose which has been seriously challenged by your statement related to the 1 mg dose and moreover the impact has serious consequences since you stated the assay was not reliable at the 1 mg dose following multiple dosing.

The firm needs to clarify these issues or all study results may be subject to scientific challeng.

THE FIRM SHOULD RECEIVE THE 3 FDA REPLIES TO THEIR ANSWERS

SIGNATURES

Andre Jackson _____

RD/FT Initialed by Sally Yasuda,Pharm.D. _____

Acting Team Leader

Cc-NDA 21641, HFD-860(Jackson, Yasuda,Rahman,Mehta), Central Documents
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/s/

Andre Jackson
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CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Agilect® (Rasagiline Mesylate) PRIMARY REVIEWER: Andre Jackson

NDA: 21641

TYPE: NDA

FORMULATION: Oral Tablet

STRENGTH: 1 mg

APPLICANT: Teva Neuroscience

Submission Date: August 27, 2004

INDICATIONS: Mono and Adjunct Therapy Parkinson's Disease

Generic Name: Rasagiline Mesylate

Review of Meeting on Firm's Planned Response to FDA Approvable Letter

Background

The firm submitted some preliminary replies to the comments sent by the Division of Neuropharmacology related to their approvable letter dated July 2, 2004. The purpose of the meeting was to discuss and clarify the FDA concerns and the firm's proposed responses.

Meeting Objectives

The purpose of the meeting is to discuss several of the concerns listed in the clinical section of the FDA's approvable letter dated July 2, 2004. The topics to be discussed are the Division's recommendations related to tyramine, melanoma, and the use of concomitant antidepressants.

The questions submitted by the firm were:

1. Teva believes that the results of the tyramine challenge studies together with the phase III experience (total of 58% (1072/1849.5 patient years) of exposure to rasagiline 0.5mg, 1 mg, and 2 mg were without tyramine restriction: 660 patient years on adjunct therapy and 412 patient years on monotherapy) indicate that rasagiline under usual real-life conditions is selective for MAO-B inhibition and can be used safely without dietary restrictions as monotherapy and as add-on therapy to levodopa at the doses recommended in the prescribing information (see attached summary). The attached summary addresses the Agency's concern that the selectivity of rasagiline 1 mg/day for MAO-B has not been adequately demonstrated in the 4 tyramine challenge studies. The Division's approvable letter and proposed labeling indicates that the labeling would need to be revised with respect to tyramine in the absence of an additional confirmatory trial. Teva would like the Division to clarify the wording for the labeling in the absence of this additional trial.

2. The Division acknowledged in the approvable letter an apparent increase of risk for melanoma in patients with Parkinson's disease compared to that in the general population. However, the observation of this apparent increased risk was made in patients being treated with dopaminergic therapy which did not include rasagiline. The company has briefly summarized the melanoma issue (summary attached) based on the rasagiline clinical development program and information from other

sources, including some recent unpublished results (by Dr Jorgen Olsen), which strengthens the connection between melanoma and Parkinson's disease. Also A North American epidemiological cohort study that assessed the prevalence of melanoma in PD patients (EPOO-2, submitted in the application) which showed that the prevalence of melanoma in PD patients is much higher than in a comparable age and sex-matched population. Based on the above, we believe that a statement in the rasagiline labeling that informs health care professionals of the apparent increased risk of melanoma with dopaminergic therapy and/or Parkinson's disease should be included. Does the Division agree?

3. The Agency stated in their proposed labeling that the concomitant use of antidepressants was not recommended. In addition, there is wording that states that although a small number of patients were concomitantly treated with antidepressants, the numbers were not adequate. This wording has a comment from the Division to verify the numbers cited (tricyclics n= 1, SSRI n= 1, in the FDA proposed labeling. In the rasagiline clinical program, about 1, see attached table) rasagiline treated patients received antidepressants (tricyclics n= 1, SSRI n= 1, and trazadone n= 45). We believe

Does the Division agree?

Comments: TO BE SUBMITTED TO THE FIRM

1. The firm should do a formal log dose regression on the Tyramine study P94159 to clearly establish if the PK is indeed nonlinear for AUC between the 1 mg and 2 mg doses.
2. The firm should present detailed calculations showing the individual data for all Pharmacokinetic calculations in Appendix 2 Tables 1 and 2. These Tables should be annotated for easy identification with their EDR origin or the original tables can be presented in proximity to the newly calculated mean values.
3. The firm should make pharmacokinetic comparisons only to subjects whom exhibit the same pharmacokinetics. For example males in study CD596 (1-20 mg) exhibit nonlinear pharmacokinetics following single dosing but linear kinetics after multiple dosing(2-10 mg/day). However in study P94159 at multiple doses of 1mg and 2mg/day, the pharmacokinetics appear to be nonlinear on day 9. Therefore it would not be meaningful to compare the multiple dose data from studies CD596 and P94159. This principle should be followed in all of the firm's comparisons across treatment groups.

SIGNATURES

Andre Jackson _____

RD/FT Initialed by Raman Baweja, Ph.D. _____

Cc-NDA 21641, HFD-860(Jackson, Baweja,Rahman,,Mehta), Central Documents Room(Biopharm-CDR)

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/s/

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BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Agilect® (Rasagiline Mesylate) PRIMARY REVIEWER: Andre Jackson

NDA: 21641

TYPE: NDA

FORMULATION: Oral Tablet

STRENGTH: 1 mg

APPLICANT: Teva Neuroscience

Submission Date: September 5, 2003

1S

INDICATIONS: Mono and Adjunct Therapy Parkinson's Disease

Generic Name: Rasagiline Mesylate

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EXECUTIVE SUMMARY

RECOMMENDATIONS

1. The Clinical Pharmacology and Biopharmaceutics section of NDA 21-641 is acceptable to OCPB.

COMMENTS TO THE MEDICAL OFFICER

1. The firm has stated that the reason for not including other racial groups in the study population was due to the inclusion criteria in protocols CC547, as well as CD596, TVP-1012/421, TVP-1012/422, and TVP-1012/426 are reflecting the population pool available for the studies at the time and site of the study. The sponsor also mentions that all the above protocols were finalized prior to the release of the FDA draft guidance "Collection of Race and Ethnicity Data in Clinical Trials" on Jan 2003.

COMMENTS TO THE SPONSOR

1. Please incorporate the OCPB labeling on page 34 of this review.
2. The sponsor is requested to adopt the following dissolution method and specification for the 1mg strength of rasagiline tablets:

Equipment	USP, — Apparatus 2 (Paddles), Dissolution volume 500mL.
Medium	0.1N HCl (aq.)
Rotation speed	50rpm
Temperature	37 ⁰ C
Sampling time	15 minutes

Dissolution Specification Q= — in 15 min

SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Agilect (rasagiline mesylate) is a propargylamine-based drug indicated for the treatment of idiopathic Parkinson's disease.

Rasagiline (N-propargyl-1(R)-aminoindan)-PAI has been developed by Teva Pharmaceutical Industries Ltd. Rasagiline is a potent, selective, non-reversible inhibitor of MAO-B. In addition, in contrast to selegiline, Rasagiline is not metabolized to amphetamine or methamphetamine. Rasagiline is being developed for use both as monotherapy and as adjunct therapy to levodopa in Parkinson's disease. The drug demonstrated efficacy and a good safety profile, both in de novo Parkinsonian patients, given as monotherapy in the dose range of 1-4 mg/day and in fluctuating Parkinsonian patients, as an adjunctive to levodopa at doses of up to 2 mg/day.

The precise mechanisms of action of rasagiline are unknown. One mechanism is believed to be related to its MAO-B inhibitory activity, which causes an increase in extracellular levels of

dopamine in the striatum. The elevated dopamine level and subsequent increased dopaminergic activity are likely to mediate rasagiline's beneficial effects seen in models of dopaminergic motor dysfunction. The protective activity of rasagiline on neurons is independent of its MAO inhibitory activity, and may be mediated by other mechanisms. This activity may contribute to its putative effect on disease progression.

The clinical development program for rasagiline mesylate included a series of Phase I and II studies and 3 pivotal Phase III studies. One phase III monotherapy study, TVP-1012/232 (TEMPO), used "ON" time as the key efficacy measure whereas the other 2 Phase III adjunct studies, TVP-1012/122 (LARGO) and TVP-1012/133 (PRESTO), used "OFF" time as the main efficacy parameter.

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.

The focus of this NDA is the active moiety, i.e., the parent drug.

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 metabolite AI, is found in the urine and accounts for about 20% of the dose (less than 0.5% of the administered dose is 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.

Multiple dosing studies in PD patients not on levodopa 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 levodopa/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 $t_{1/2}$ is between 2.1 ± 1.1 and 3.5 ± 1.5 hours and that of AI $t_{1/2}$ is between 10.4 ± 2.2 and 11.6 ± 1.3 hours. The estimate of accumulation via $(1/1-e^{-k \cdot \tau})$ 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 apparent gender differences following 1 mg once daily dosing. 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 τ 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 in the monotherapy PD subjects resulted in a 31% decrease in rasagiline CL/F. However when levodopa was the substrate, there was no effect of rasagiline on levodopa or vice versa.

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 PD subjects in the monotherapy clinical study who were currently smoking tobacco however this effect was not apparent in PD patients on chronic Levodopa 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.

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 specification are being set in this NDA.

QUESTION BASED REVIEW

General Attributes

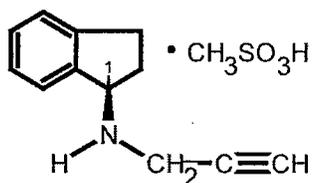
What is the proposed mechanism of drug action and therapeutic indications?

The precise mechanisms of action of rasagiline are unknown. One mechanism is believed to be related to its MAO-B inhibitory activity, which causes an increase in extracellular levels of

dopamine in the striatum. The elevated dopamine level and subsequent increased dopaminergic activity are likely to mediate rasagiline's beneficial effects seen in models of dopaminergic motor dysfunction. The protective activity of rasagiline on neurons is independent of its MAO inhibitory activity, and may be mediated by other mechanisms. This activity may contribute to its putative effect on disease progression.

What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product? What is the proposed dosage and route of administration?

Structural Formula (Absolute Configuration R):



Rasagiline Mesylate

Molecular Formula: (C₁₂ H₁₃ N)•CH₄SO₃

Relative Molecular Mass: 267.34

Relative Molecular Mass (base): 171.23

Chirality: The carbon atom at position 1 of the indan ring is the asymmetric center of the N-propargyl-1-(R)-aminoindan.

Compositional Formula for the 1 mg rasagiline tablet.

	Reference to	Amount Per	Amount Per Batch
	Quality	Tablet [mg]	(tablets)
	Standards		
Rasagiline Mesylate	Teva In-	—	1

	House		
Mannitol	USP, Ph. Eur.		
Colloidal Silicon Dioxide	NF, Ph. Eur.		
Starch ³	NF, Ph. Eur.		
Pregelatinized Starch	NF, Ph. Eur.		
Stearic Acid	NF, Ph. Eur.		
Talc	USP, Ph. Eur.		
Theoretical End Weight		210.0	210

1. Equivalent to 1 mg of rasagiline base (N-Propargyl-1-(R)-aminoindan base).
2. Also named Colloidal Anhydrous Silica (Ph. Eur.).
3. Also named Maize Starch (Ph. Eur.).

Appearance: White to off- white crystalline powder

Solubility in Representative Solvents (at 25°C): Freely soluble in water (1.6 g/ml; 617 mg/ml)

Freely soluble in ethanol (9.3g/ ml; 108 mg/ml) Sparingly soluble in isopropanol (56.1 g/ml; 18 mg/ml)

The proposed route of administration is oral.

What are the overall solubility, permeability and dissolution characteristics of the formulation?

Dose/Solubility Volume (at 37 ± 0.5°C / pH 7.4) in water:

High solubility drug

Dose solubility volume: 1 mg/ 103 mg/ml=0.01 ml

Where:

1 mg = largest dose strength

The absolute bioavailability is 36% and it exhibits dissolution of or greater at several different pH values within 15 min. Therefore the classification of this drug would be highly soluble with low permeability.

Rasagiline is a potent, selective, non-reversible inhibitor of MAO-B. In addition, in contrast to selegiline, Rasagiline is not metabolized to amphetamine or metamphetamine. Rasagiline is being developed for use both as monotherapy and as adjunct therapy to levodopa in Parkinson's disease. The drug demonstrated efficacy and a good safety profile, both in de novo Parkinsonian patients, given as monotherapy in the dose range of 1-4 mg/day and in fluctuating Parkinsonian patients, as an adjunctive to levodopa at doses of up to 2 mg/day.

What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology and biopharmaceutics study data ?

There were three primary clinical Phase III studies conducted. One was a phase III monotherapy study, TVP-1012/232 (TEMPO), while the other 2 Phase III adjunct studies were TVP-1012/122 (LARGO) and TVP-1012/133 (PRESTO).

The principal statistical analysis compared the mean change from baseline to termination in total Unified Parkinson's Disease Rating Scale UPDRS for each of the active-treatment groups to placebo (two contrasts) using ANCOVA adjusted for baseline UPDRS, treatment, center and treatment-by-center interaction.

The primary endpoint for both studies LARGO (TVP-1012/122) and PRESTO (TVP-1012/133) was the change from baseline to treatment in the mean total daily OFF time. For LARGO the mean total daily OFF time during treatment was the mean value of the total daily OFF time recorded from the 12, 24-hour diaries while for PRESTO it was the mean total daily OFF time recorded from the 9, 24-hour diaries.

Secondary End-Points were UPDRS Motor, UPDRS Activities of Daily Living ADL, UPDRS Mental -

A safety endpoint was the interaction of rasagiline with Tyramine based upon the tyramine 30 assay (i.e., dose of tyramine 50, 100, and 400 mg that is required to increase blood pressure 30 mm Hg in subjects /dose of tyramine required in the presence of Rasagiline in the same subjects).

GENERAL CLINICAL PHARMACOLOGY

What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

OFF time, 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 (ON1), ON with troublesome dyskinesia (ON2), OFF , or asleep . UPDRS was chosen since the scores assess not only motor skills but also mental state, behavioral aspects and the general mood of PD patients.

Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Rasagiline's metabolite AI, is found in the urine and accounts for about 20% of the dose (less than 0.5% of the administered dose is excreted unchanged in the urine). There is no direct proof of AI activity in man. The potential contribution of AI to rasagiline effectiveness in humans is estimated on the basis of pre-clinical studies. Rasagiline's primary pharmacodynamic activity is selective MAO-B inhibition. AI did not exhibit MAO inhibitory activity either in *in vitro* or *in vivo* assays, and therefore does not contribute to MAO inhibition by rasagiline.

DOSE PROPORTIONALITY

What is the degree of linearity or nonlinearity in the dose-concentration relationship?

Study TVP-231-PD patients not on levodopa 1-4 mg /day

Table 1: TVP-1012/231 - Dose Proportionality Assessment Results Summary Using the Power Model Analysis

PK Parameter	Sex	β Estimate	R- Estimate of the Increase in
		(95% CI)*	Doses Required for Doubling the AUC (95% CI)**
PAI AUC(0-t)	All (N=41)	0.96 (0.64,1.28)	2.06 (1.72,2.94)
	Female (N=15)	1.07 (0.63,1.52)	1.91 (1.58,3.00)
	Male (N=26)	0.86 (0.42,1.30)	2.24 (1.70,5.28)
PAI AUC(0-Inf)	All (N=42)	1.06 (0.84,1.29)	1.92 (1.71,2.29)
	Female (N=15)	1.08 (0.68,1.48)	1.90 (1.60,2.76)
	Male (N=27)	1.02 (0.73,1.32)	1.97 (1.69,2.59)
AI AUC(0-t)	All (N=42)	1.05 (0.87,1.24)	1.93 (1.75,2.22)
	Female (N=15)	1.03 (0.69,1.37)	1.96 (1.66,2.74)
	Male (N=27)	1.03 (0.84,1.22)	1.96 (1.77,2.27)

The results of the analysis demonstrate dose proportionality in AUC for PAI and AI on week 10 for both males and females and overall. All 95% Confidence Intervals for both males and females and overall included the value of 1 which is an evidence of dose proportionality. This proportionality is also demonstrated by the estimates of the increase in doses required for doubling the AUC (R) and their Confidence Intervals which included the value of 2 for both PAI and AI and for both males and females and overall.

Study TVP-112-PD patients on levodopa, rasagiline dose 0.5-2 mg /day

Table 2: TVP-1012/112 - Dose Proportionality Assessment Results Summary Using the Power Model Analysis

PK Parameter	Sex	β Estimate	R- Estimate of the Increase in
		(95% CI)*	Doses Required for Doubling the AUC (95% CI)**
PAI AUC(0-4h) (ng.h/ml)	All (N=23)	0.95 (0.67,1.24)	2.07 (1.75,2.81)
	Female (N=10)	1.09 (0.67,1.51)	1.89 (1.58,2.81)
	Male (N=13)	1.13 (0.78,1.47)	1.85 (1.60,2.43)

* ANOVA (SAS GLM Procedure)

** Obtained using the estimate of β and (ii)

The results of the analysis demonstrate dose proportionality in AUC for PAI on week 12 for both males and females and overall. All 95% Confidence Intervals for both males and females and overall included the value of 1, which is an evidence of dose proportionality. This proportionality is also demonstrated by the estimates of the increase in doses required for doubling the AUC (R) and their Confidence Intervals which included the value of 2 for PAI and for both males and females and overall.

For the dose range tested (1-20mg) study CC547 in normals, the results of the analyses demonstrate departure from dose proportionality in AUC for PAI and AI following a single dose administration which indicates that clearance decreases with dose.

GENERAL PHARMACOKINETICS AND CHRONIC DOSING

Do PK parameters change with time following chronic dosing?

Study CD 596 done in normals –single dosing.

	2 mg	5 mg	10 mg
C_{max} D1 (ng.ml ⁻¹)	2.92 (0.40)	7.81 (1.02)	19.24 (2.91)
C_{max} # D1 (ng.ml ⁻¹)	-	3.12 (0.41)	3.85 (0.58)
C_{max} D10 (ng.ml ⁻¹)	5.12 (0.83)	14.86 (5.50)	27.00 (4.17)
C_{max} # D10 (ng.ml ⁻¹)	-	5.94 (2.20)	5.40 (0.83)

The estimate of accumulation via $(1/1-e^{-k \cdot \tau})$ was 1.0, assuming a half-life of 3 hrs. Calculated accumulation based upon C_{max} (i.e., Day10/Day 1)= 1.4. Therefore, there appears to be little to no accumulation of Rasagiline following multiple dosing. However, the pharmacokinetics are nonlinear between single doses of 2 and 10 mg, with a 8 fold increase in C_{max}

Multiple dosing Day 1 vs Day 10 –Study CD596 -2-10 mg/day.

Table 2. Study CD596 - Summary Results of the Assessment of Dose Proportionality Using the Power Model Analysis

PK Parameter	Day	AUC	β Estimate (95% CI)*	R- Estimate of the Increase in Doses Required for Doubling the AUC (95% CI)**
AI	1	AUC0-Inf	1.22 (1.07,1.37)	1.76 (1.66,1.91)
AI	10	AUC0-24	1.08 (0.94,1.21)	1.90 (1.77,2.09)
PAI	1	AUC0-Inf	1.38 (1.17,1.59)	1.65 (1.55,1.81)
PAI	10	AUC0-24	1.10 (0.95,1.26)	1.88 (1.74,2.08)

* ANOVA (SAS GLM Procedure)

The results of the analysis demonstrate dose proportionality in AUC for PAI and AI on Day 10, with 95% CI values of 0.95-1.26 for PAI and 0.94-1.21 for AI. The overall trend was for clearance to decrease with length of exposure. This was also apparent in the population analysis of Presto (Study #133) where the oral clearance was decreased following the 10th consecutive dose on day 10 relative to the first dose on study day 1.

S AND R INTERCONVERSION

Was there any evidence of in vivo interconversion between R and S Rasagiline ?

Three subjects from the 10 day dosing study CD596 were studied to determine if Rasagiline mesylate which is the R-enantiomer of N-propargyl-1-aminoindan (R-PAI) biotransforms to the S-enantiomer of N-propargyl-1-aminoindan (S-PAI) in the plasma samples of healthy volunteers that were dosed with 5mg (group B) or 10mg (group C) of rasagiline mesylate per day.

Table 3. Response ratios 12C/13C in the plasma samples.

Patient no.	201	202	303
Response ratio	0.257	0.298	0.369
	0.295	0.278	0.158
	0.208	0.235	0.221
	0.258	0.240	0.219
Mean*	0.254	0.263	0.242
% from noise (0.270)	-6%	-3%	-10%

The mean was calculated for the responses even though they came from different time points since they are all below the noise (i.e., below 0.270) level. The mean and the corresponding %RSD show that these are in fact noise responses detected from the R-PAI concentrations in the sample.

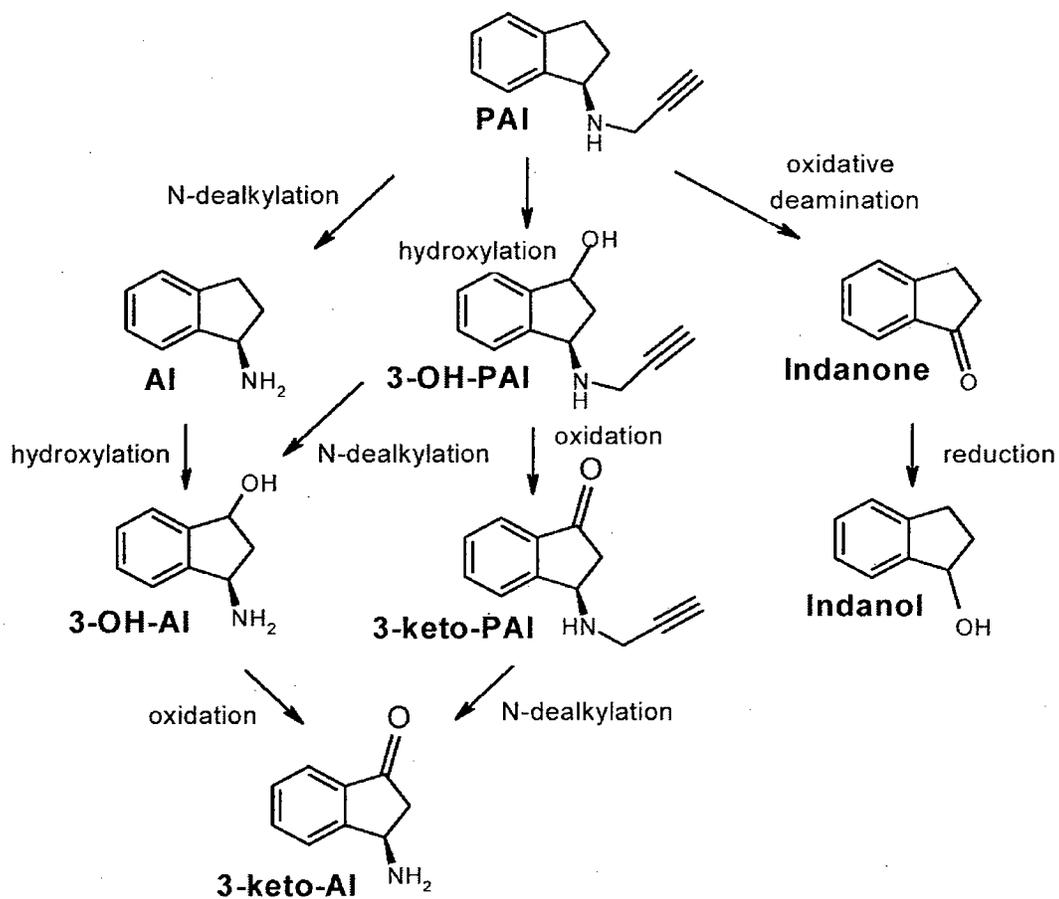
It appears that bioenantiomeric conversion did not occur *in-vivo* in volunteers dosed with 5 or 10 mg rasagiline per day. S-PAI was not detected (Detection Limit approximately 3.3ng/mL). All the values were below the upper noise level.

MAJOR ROUTES OF ELIMINATION

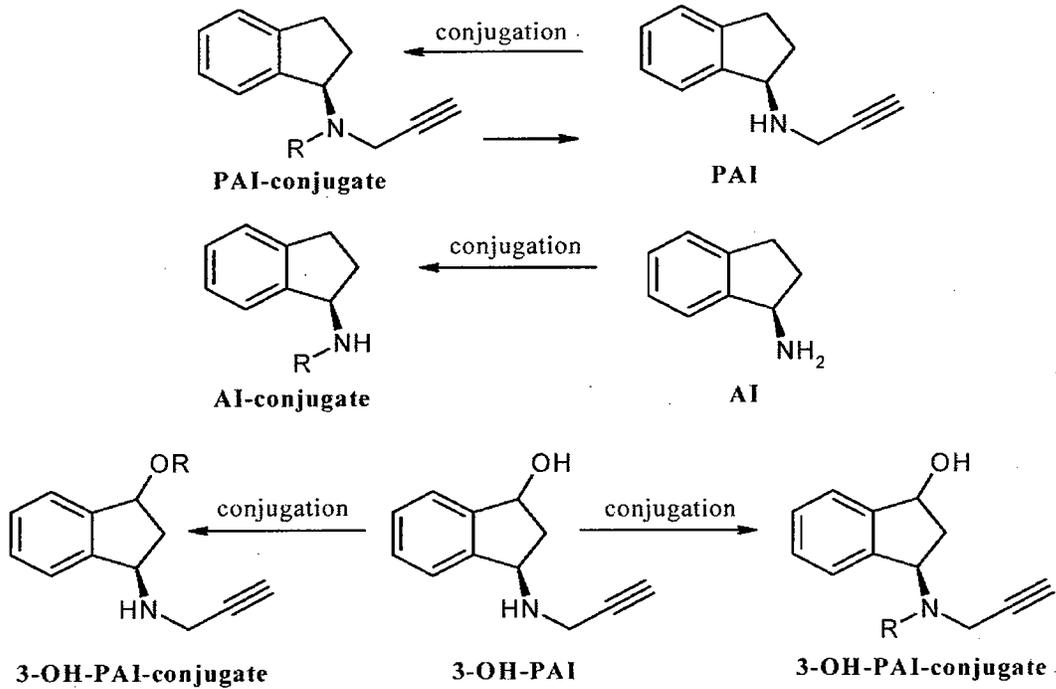
**What is the proposed metabolic scheme for Rasagiline?
PAI's Human Metabolic Pathways**

1A2 is the enzyme responsible for the conversion of PAI to AI.

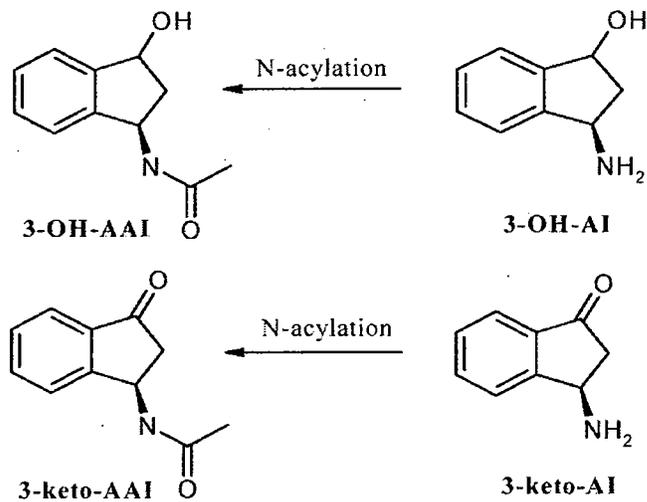
Phase I biotransformations



Phase II biotransformations



Where: R = sulfate or glucuronide



Do Mass Balance studies suggest renal or hepatic route as the major route of elimination?

The human metabolic pathway scheme is shown on pages 13-14 of this review.

A total of eight healthy adult male human subjects were studied. Subjects remained resident in the Clinic for 168 hrs of blood sampling and 24-hour urine and fecal collections were made until Day 15 (336 hours post-dose). Subjects returned to the Clinic on Days 18, 21, 24, 27 and 30 for daily residency periods when 24-hour urine and feces output were collected.

Concentrations declined with a mean terminal phase half-life of about 23 hours, and were below the limit of detection at 96 hours post-administration for all six subjects indicating that this terminal phase is solely due to metabolites. During 3 to 12 hours after dosing, AI represented about 20% of the total drug-derived material (radioactivity) in plasma, thereby confirming it as a major metabolite of rasagiline in humans. However, parent drug and the metabolite together never accounted for more than about half of the total radioactivity in the systemic circulation, indicating the rapid and extensive formation of other metabolites.

It was calculated that a mean total of 84.38% of the radioactive dose of ¹⁴C-rasagiline mesylate to eight human subjects was excreted in urine and feces during 38 days after administration. Measured excretion data are summarized in the following table:

Days after dosing	Urine	Feces	Total
1-7	60.15	7.06	67.21

The results showed that biotransformation of the drug was very extensive and essentially complete prior to excretion, but at least 80% of the radioactivity in urine was associated with ten main radioactive components, each of which accounted for 2% of the dose or more. On the basis of their chromatographic retention properties, with mass spectroscopic confirmation in some cases, the more important of these components were tentatively identified as 3 OH-PAI and 3-keto-PAI, AI and 3-OH-AI, which were also present in urine as conjugates, together with an *N*-glucuronide (or possibly *N*-carbamoyl glucuronide) conjugate of rasagiline which was very abundant in urine shortly after dosing, but much less so afterwards.

IN VITRO PERFORMANCE

What are the important in vitro intrinsic factors related to the exposure of rasagiline?

PROTEIN BINDING AND RED CELL PARTIONING

What was the protein binding and red cell partitioning for rasagiline?

The extent of binding of ¹⁴C-TVP101 at 1, 10 and 100 ng/ml was determined in 4 male and 4 female subjects. In male subjects the extent of binding ranged from 90.4% to 93.7% and in female subjects from 88.7% to 92.8%. There were no notable changes in the extent of binding with increasing plasma concentrations of ¹⁴C-TVP101. The mean extent of binding of ¹⁴C-TVP101 to male human plasma proteins was 92.3% and to female human plasma proteins was 91.1%.

Over the same concentration range the extent of binding to human albumin ranged from 61.3-66.2%. Radioactivity levels in blood cells of rasagiline were calculated from the corresponding plasma and whole-blood values and the blood packed cell volumes. The cells : plasma ratio, ranged from a minimum of 0.1, to a maximum of 1.2 during the period when both concentrations were measurable. In general the mean blood cell : plasma ratio was ~ 0.5 (range 0.21 – 0.66) indicating that association of radioactivity with the erythrocytes was not extensive.

IN VITRO DRUG INTERACTIONS

Is the drug an inhibitor and/or an inducer of CYP enzymes?

Study Design: The potential inhibitory effect of 1 µg/mL rasagiline mesylate on the metabolism of human CYP model substrates was measured using microsomes from a pool of 4 individual human livers (HHM-0219). The selected dose represents a concentration which is approximately 50-fold higher than the maximum human plasma concentration measured following treatment at the intended therapeutic doses of rasagiline. The model substrates used and the isoforms which these assessed are as follows: ethoxyresorufin (CYP1A2), coumarin 7-hydroxylase (CYP2A6), tolbutamide (CYP2C9), *S*-mephenytoin (CYP2C19), bufuralol (CYP2D6), chlorzoxazone (CYP2E1) testosterone (CYP3A4) and lauric acid (CYP 4A).

Results: In comparison to 'vehicle incubations', rasagiline mesylate caused no significant inhibition (< 25% in all cases) of ethoxyresorufin *O*-deethylase, coumarin 7-hydroxylase, tolbutamide 4-hydroxylase, *S*-mephenytoin 4-hydroxylase, bufuralol 1'-hydroxylase, chlorzoxazone 6-hydroxylase, testosterone 6β-hydroxylase or lauric acid 12-hydroxylase activities in the presence of human liver microsomes. In addition, no significant inhibition (< 25% in all cases) was measured following a 10 minute pre-incubation in the presence of the metabolic cofactors.

Conclusions: Since rasagiline mesylate caused no inhibition of the model substrates, rasagiline mesylate has no potential for interference with substrates of CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2C19, CYP2E1, CYP3A4, CYP4A.

Did any in vitro hepatocyte studies indicate which CYP enzyme systems would be involved in rasagiline metabolism?

- Experiments with supersomes expressing various CYP isoforms, and studies with various inhibitors have indicated that CYP1A2 is the predominant P450 isoform involved in the metabolic elimination of TVP-1012.

EXTRINSIC FACTORS

What type of drug-drug interactions were investigated for Rasagiline?

The following drug-drug interaction studies were done for rasagiline with dense sampling:

Drug	Study #
Ciprofloxacin	TVP-1012/426
Theophylline	TVP-1012/430
Carbidopa/levodopa	TEMPO(TVP1012/232)

PRESTO(TVP1012/133)-Population Analysis

	Count	Per Cent of population
Concomitant medication, beta blockers	12	4%
Concomitant medication, NSAID	57	21%
Concomitant medication, aspirin	66	24%
Concomitant medication, paracetamol (acetaminophen)	48	17%
Concomitant medication, sildenafil citrate	17	6%
Concomitant medication, quinolones	2	.1%
Concomitant medication, benzodiazepines except clonazepam	26	9%
Concomitant medication, amantadine HCl	52	19%
Concomitant medication, entacapone	93	34%
Concomitant medication, pergolide	44	16%
Concomitant medication, pramipexole	100	36%
Concomitant medication, ropinirole	38	14%
Concomitant medication, diphenhydramine	9	3%
Concomitant medication, lipid lowering drugs (statins)	16	6%
Concomitant medication, COX-2 inhibitors	18	7%
Concomitant medication, Angiotensin converting enzyme inhibitors and Angiotensin II blockers	30	11%
Concomitant medication, estrogens	34	12%

* calculated using Equation 4

Count is the number of subjects with their per cent of the population.

Were there any study design issues related to the drug-drug interaction studies?

The drug-drug interaction studies were designed in accordance with the actual clinical use of the interacting drug.

<u>Drug</u>	<u>Recommended Regimen</u>	<u>NDA Dosing</u>
Ciprofloxacin	500 mg dose/12 hr	500 mg dose/12 hr
Theophylline	400-600 mg/24 hr	60-500 mg/12 hr

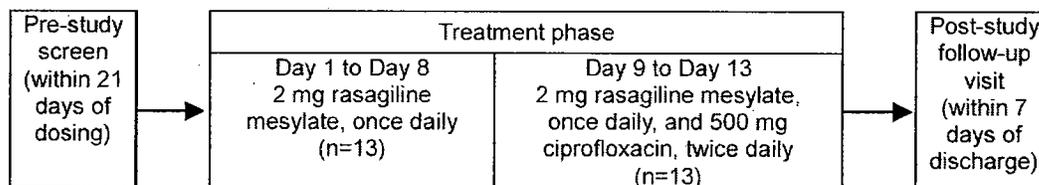
The design of the drug-drug interaction dense sampling studies were consistent with the dosage recommendations for ciprofloxacin but a little higher for theophylline. Drug-drug interaction studies Tempo and Presto were done during the course of therapy and there were no design issues.

Ciprofloxacin Study TVP-1012/426-

In vitro metabolism studies in human liver microsomes indicate that rasagiline is mainly metabolized by a single cytochrome P450 isoenzyme, CYP1A2. Since ciprofloxacin is a strong inhibitor of CYP1A2, and may be co-administered with rasagiline, they were studied as potential interacting drugs.

This was a single-centre, open-label, multiple-dose, phase I study, with 13 healthy male volunteers enrolled into the study to ensure that 12 completed. When resident in the Clinic, subjects were provided with standard, low tyramine, meals. Rasagiline 2 mg was administered to the subjects once daily from Day 1 for 13 days. For the final five days of rasagiline dosing, Days 9 to 13, twice-daily ciprofloxacin 500 mg was also administered. Blood samples were taken on these days up to 24 hours after the morning dose to evaluate the effect of concomitant administration of ciprofloxacin on the steady-state pharmacokinetics of rasagiline.

The study design is shown in the following Figure.



Was there a significant effect of ciprofloxacin on rasagiline as the substrate for CYP1A2?

Table 4. Mean \pm sd PK parameters of rasagiline following repeated doses of rasagiline mesylate alone on days 7 and 8 and co-administered with ciprofloxacin on days 9 to 13.

Parameter	units	Day 7	Day 8	Day 13
C_{max}	ng/mL	16.1 \pm 5.8	16.9 \pm 6.1	16.2 \pm 4.7
AUC ₀₋₂₄	ng.h/mL	17.1 \pm 5.6	20.6 \pm 6.1	40.1 \pm 10.9
AUC _{0-∞}	ng.h/mL	20.6 \pm 5.5	23.5 \pm 4.8	41.1 \pm 11.6
k_{el}	/h	0.2327 \pm 0.0979	0.2150 \pm 0.0377	0.2215 \pm 0.0686
$t_{1/2}$	h	3.31 \pm 0.95	3.30 \pm 0.49	3.55 \pm 1.70
t_{max}	h	0.42 \pm 0.15 [median 0.35]	0.58 \pm 0.47 [median 0.50]	0.87 \pm 0.60 [median 0.75]

Data are presented as mean \pm sd, with median also presented for t_{max}

Table 5. Mean PK parameters of 1-aminoindan following repeated doses of rasagiline mesylate alone and co-administered with ciprofloxacin on days 9 to 13.

Parameter	units	Day 7	Day 8	Day 13
C _{max}	ng/mL	5.8 ± 1.4	6.1 ± 1.5	4.3 ± 0.7
AUC ₀₋₂₄	ng.h/mL	80.3 ± 22.0	83.5 ± 21.5	65.9 ± 15.9
k _{el}	/h	0.0487 ± 0.0096	0.0435 ± 0.0090	0.0505 ± 0.0111
t _{1/2}	h	14.61 ± 2.23	16.44 ± 2.65	14.22 ± 2.55
t _{max}	h	1.30 ± 0.97 [median 1.00]	1.58 ± 1.12 [median 1.00]	2.52 ± 1.37 [median 2.02]

Data are presented as mean ± sd, with median also presented for t_{max}

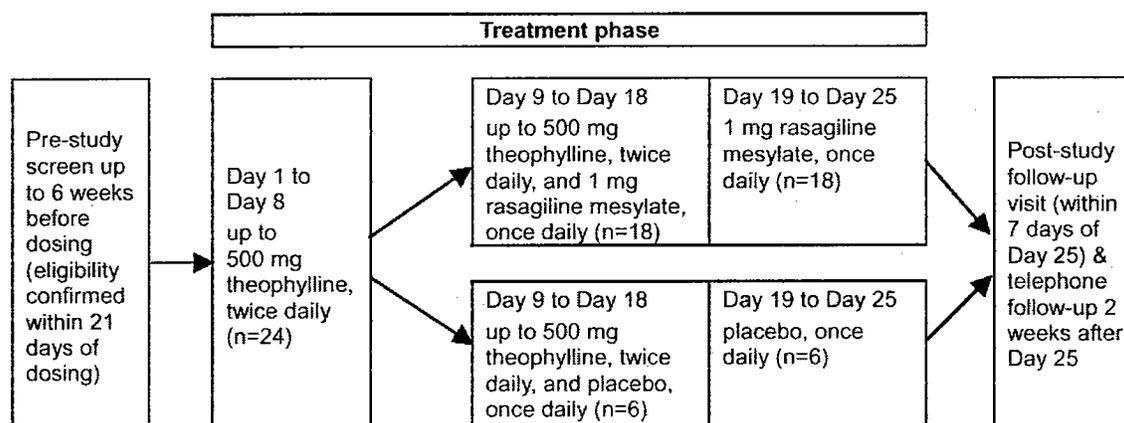
For rasagiline, the statistical analysis of the results from this study show that C_{max} was unaffected but occurred at a later t_{max} (by 18 min) when rasagiline mesylate was co-administered with ciprofloxacin compared to rasagiline mesylate alone. However the AUC of rasagiline increased by more than 80% in the presence of ciprofloxacin, although there was no change in the terminal elimination rate of rasagiline. The data for the metabolite, 1-aminoindan, showed almost a 30% reduction in C_{max} but at a considerably later t_{max}, almost 1 hr later, and at least a 20% reduction in AUC when the two drugs were co-administered.

The effect of rasagiline on ciprofloxacin was not studied.

Theophylline Study TVP-1012/430

Theophylline is known to be metabolized by CYP1A2 but has not been shown to either induce or inhibit this enzyme system. Since rasagiline is also a substrate for CYP1A2, also not known to induce or inhibit this enzyme system, a potential interaction between the two compounds might be of a substrate/substrate competition type. As theophylline has a narrow therapeutic window, even an interaction leading to a small increase in plasma levels of theophylline may cause side effects. This was a single-centre, double-blind, multiple-dose, phase I study, with 24 healthy male or female volunteers intended to complete the study. Subjects attended a screening visit within six weeks before dosing, with a re-evaluation within 21 days of dosing.

Figure 1 Study design



Subjects received theophylline alone for eight days, theophylline and rasagiline

mesylate for ten days and finally rasagiline mesylate alone for seven days. On Days 1 to 8 of the study, theophylline was administered twice daily, in the morning and evening, with each subject's dose titrated during this period to achieve steady-state pre-dose plasma levels of 8-12 mg/L. From Day 9 to Day 17, subjects received theophylline twice-daily at the same dose as Day 8, and on Day 18 the final theophylline dose was administered in the morning. During this period they also received, in the morning only, either rasagiline 1 mg once-daily (n=18) or placebo (n=6) once daily. From Day 19 to Day 25, subjects continued to take either rasagiline 1 mg once daily (n=18) or placebo (n=6) once daily. Fasting pharmacokinetic profiles on Days 8, 18 and 25 allowed evaluation of the effect of concomitant administration of theophylline and rasagiline mesylate on the steady-state pharmacokinetics of each drug.

Was there a significant effect of theophylline on rasagiline as the substrate for CYP1A2?

Table 6. Mean pharmacokinetic parameters of rasagiline following repeated doses of rasagiline mesylate alone and co-administered with theophylline.

Parameter	units	Day 18 (n=18)	Day 25 (n=18)
C _{max}	ng/mL	8.22±2.70	8.82±2.98
AUC _{0-t}	ng.h/mL	8.03±2.96	8.72±2.32
t _{max}	h	0.50	0.42

Data are presented as mean ± sd, except for t_{max}. For t_{max}, the median is presented.

Rasagiline pharmacokinetics were also unaffected by theophylline co-administration with no indication from the AUC and C_{max} data of an interaction with theophylline. There was an indication of about 15% lower AUC plasma levels of AI during co-administration of theophylline and rasagiline mesylate. C_{max} was almost the same. However there was also an increased elimination rate (shorter half-life) for this treatment. Hence this is the most likely cause of the reduced AUC, rather than an inhibitory effect of theophylline on rasagiline metabolism.

Was there a significant effect of rasagiline on theophylline as the substrate for CYP1A2?

Table 7. Mean pharmacokinetic parameters of theophylline following repeated doses of theophylline alone and co-administered with rasagiline mesylate.

Parameter	units	Day 8 (n=19)	Day 18 (n=18)
C _{max}	µg/mL	14.73±3.09	13.71±2.96
AUC ₀₋₁₂	µg.h/mL	143.95±27.61	134.19±28.78
t _{max}	h	4.00	4.00

Data are presented as mean ± sd, except for t_{max}. For t_{max}, the median is presented

For theophylline, the statistical analysis of the results from this study show that both Cmax and AUC were similar when theophylline and rasagiline mesylate were co-administered suggesting that there was no change in the systemic exposure of theophylline. Mean maximum steady-state plasma theophylline concentrations of 14.73±3.09 µg/mL on Day 8 and 13.71±2.96 µg/mL on Day 18 (rasagiline treatment group) indicate that the study was performed using relevant doses of theophylline since the therapeutic range of theophylline is 10-20 µg/mL.

ENTACAPONE

Did the population analysis indicate any noteworthy drug-drug interactions?

As a result of the population analysis only entacapone which blocks the peripheral metabolism of Levodopa caused an increase in rasagiline clearance from 64.7 L/h to 82.1 l/h (27%), however the effect was only marginally significant. (Δ OFV =12.2). Patients may experience less effect of rasagiline if on adjunct entacapone and switched to rasagiline.

TYRAMINE

Was there a significant effect of rasagiline on TYR₃₀ ratio (Dose of tyramine Δ 30 mmHg period I/ Dose of tyramine Δ 30 mmHg period II+Rasagiline)?

During period I subjects were dosed with placebo for days 1-10 then:

Day	Dose of tyramine
8	50 mg @ 0.5 hrs after placebo
9	100 mg @ 0.5 hrs after placebo
	200 mg @ 3.5 hrs after placebo
10	400 mg @ 0.5 hrs after placebo
	800 mg @ 3.5 hrs after placebo

During period II subjects were dosed with either 1 mg or 2 mg of rasagiline or 10 mg of selegiline or placebo.

Tyramine dosing was the same as period I.

Table 8. Mean \pm SD TYR30 ratio by treatment group

Treatment	TYR 30 Ratio
Placebo	1.0 \pm 0.5
1 mg TVP-1012	1.0 \pm 0.05
2 mg TVP-1012	2.7 \pm 1.0
10 mg selegiline	1.9 \pm 1.2

At the proposed marketed dose of 1 mg there was no effect of rasagiline on the TYR₃₀ ratio. However at the 2 mg dose the ratio was similar to the 10 mg dose of seligiline. This was further investigated by examining the individual systolic BP graphs versus time with the Medical Officer and it was determined that the individual changes were acceptable especially in the group with the TYR 30 ratio >2.

In moderately impaired hepatic patients the AUC at steady-state increases 7 fold while it increases 2 fold in mildly hepatically impairment patients relative to normal. Therefore several questions need to be addressed by the firm related to hepatic disease. The increase in the TY30 ratio may be dangerously high in the mildly impaired group and needs to be addressed by the firm due to the decrease in rasagiline clearance in hepatic disease.

SMOKING

What was the effect of smoking on the pharmacokinetics of rasagiline in Parkinson's Disease patients?

The issue of smoking was addressed in the population studies TEMPO which studied rasagiline under monotherapy conditions and PRESTO which studied it as adjunct therapy to Levodopa.

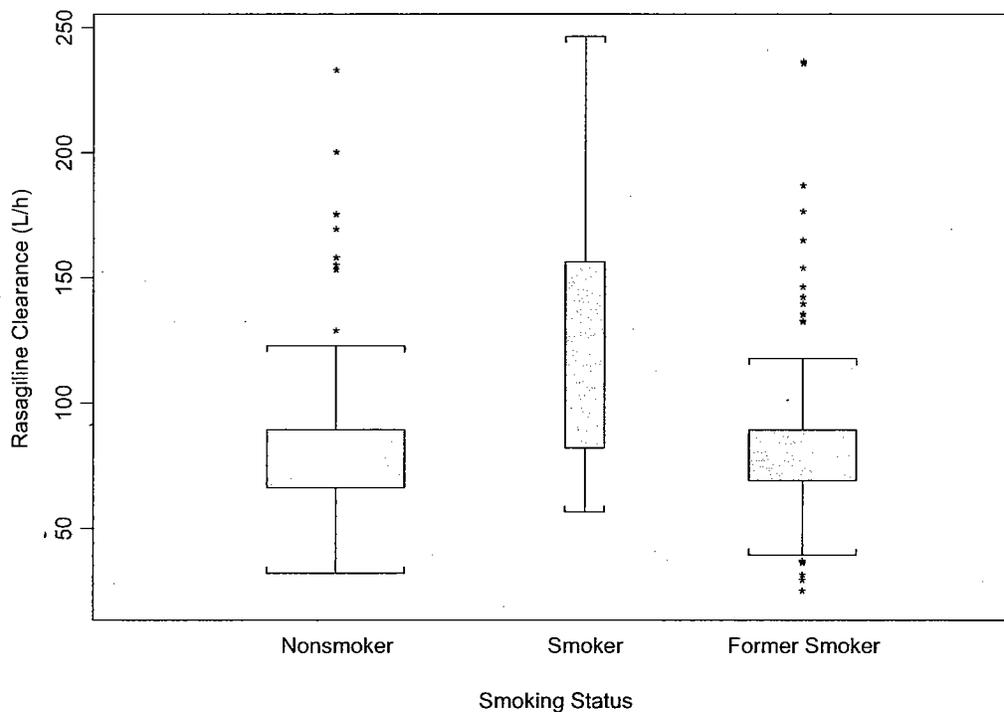


Figure 2. Box plot of rasagiline clearance by smoking status category, showing median (white line) and interquartile range (IQR, box). The whiskers span 1.5 times IQR. Outliers are shown by asterisks. Box width is proportional to the number of observations in each category. Data is from the Tempo monotherapy population study.

Table 9 presents the numbers of nonsmokers, smokers and former smokers in the TVP-1012/232 study population (TEMPO).

Table 9. Smoking status, summarized by category

	Nonsmokers	Smokers	Former Smokers
N (%)	209 (59.1%)	17 (4.8%)	128 (36.2%)

The results of the hypothesis testing showed that there was a significant effect of currently smoking tobacco on rasagiline clearance. In subjects who were currently smoking tobacco, there was an estimated increase in rasagiline clearance of 39.1% (95% confidence interval: 13.2%, 65.0%) relative to nonsmokers and former smokers.

In the PRESTO study (TVP-1012/133) done in PD patients taking Levodopa, there was a similar proportion of tobacco smokers (13 out of 276 subjects, 5% of the study population). In that study, there was no significant effect of tobacco smoking on rasagiline clearance. It appears that in the target population smoking had a different effect dependent upon whether the subjects were receiving monotherapy or adjunct therapy with Levodopa. It is unclear if this lack of an effect of smoking is directly attributable to the presence of Levodopa in the adjunct therapy PD patients.

LEVODOPA/CARBIDOPA

What was the effect of concomitant levodopa/carbidopa therapy on the pharmacokinetics of rasagiline in early stage Parkinson's Disease patients?

TEMPO STUDY

Study TVP-1012/232 was a multicenter, double-blind, placebo-controlled, parallel group, Phase III clinical trial of the efficacy, tolerability, and safety of two doses (1 mg and 2 mg/day) of rasagiline mesylate in early Parkinson's disease (PD) subjects not treated with levodopa. Some subjects (9%) received carbidopa/levodopa during the active-treatment phase but not during the placebo phase. Data from population study Tempo for those subjects that received concomitant carbidopa/levodopa exhibited a decrease in rasagiline CL/F of 31% (with an approximate 95% confidence interval of 23% to 39%). In the Tempo study rasagiline was the substrate however, due to the small N=31(8%) the data was never analyzed to determine if there was greater effectiveness when levodopa was added to rasagiline.

		CL/F (L/hr)					
		Weight ^a			Weight ^a		
		min	ref	max	min	ref	max
Age ^b	min	57.4	75.4	109.9	39.6	52.0	75.8
	ref	44.5	58.5	85.3	30.7	40.4	58.8
	max	39.9	52.4	76.3	27.5	36.1	52.7
		COM1 = 0			COM1 = 1		

PRESTO STUDY

Study TVP-1012/133 was a multicenter, randomized, double-blind, placebo-controlled, parallel group, phase III clinical trial of the efficacy, tolerability, and safety of two doses (0.5 mg or 1 mg/day) of rasagiline mesylate in Parkinson's disease (PD) subjects treated with levodopa and experiencing motor fluctuations. Subjects were randomized to one of two dosages of rasagiline or placebo. The effect was not significant. For the Presto study levodopa was the substrate and there was no effect of rasagiline on levodopa

FOOD EFFECTS- STUDY 1012/421

To determine the effect of a high fat meal on the pharmacokinetics of single doses of rasagiline a study was done in healthy adult volunteers.

The study drug was administered according to the following regimen :

- Treatment A : one TVP-1012 tablet dosed at 2 mg Rasagiline base (PAI)/tablet, 15 minutes after the beginning of a standard breakfast
- Treatment B : one TVP-1012 tablet dosed at 2 mg Rasagiline base (PAI)/tablet, fasting

Batch Number	K-21695
Date of Manufacture	December 1996
Manufacturer's Name & Site Address	Teva Pharmaceutical Industries Ltd. PO Box 353 Kfar Saba 44102 Israel
Expiry Date	December 1998

All study subjects were males.

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RASAGILINE N=18	C _{max} (ng.ml ⁻¹)	t _{max} (h)	AUC _{0-t} (ng.ml ⁻¹ .h)	AUC _{0-∞} (ng.ml ⁻¹ .h)	t _{1/2} (h)
Treatment A 2mg TVP-1012, in fed conditions					
Mean	10.01	0.80	10.02	10.52	0.82
s.d.	5.90	0.78	3.35	3.37	0.23
Median	8.97	0.50	9.37	9.71	0.79
Treatment B 2mg TVP-1012, in fasting conditions					
Mean	24.86	0.50	13.02	13.42	0.81
s.d.	10.83	0.27	3.85	3.96	0.34
Median	20.88	0.50	12.79	12.99	0.76
fed / fasting ratio					
Mean	0.49	-	0.80	0.81	-
s.d.	0.47	-	0.25	0.24	-
Median	0.30	-	0.73	0.77	-
Statistics	p < 0.001 (1)	NS (2)	p < 0.001 (1)	p < 0.001 (1)	NS (2)
90% confidence intervals	0.29-0.50	-	0.70-0.83	0.71-0.85	-

(1) : Analysis of variance (PROC GLM on SAS system) on log-transformed data

(2) : Wilcoxon signed rank test (PROC UNIVARIATE on SAS system) on natural data

The mean maximal plasma concentration decreases 60% after concomitant administration with food. The mean time to reach the maximal plasma concentration is delayed 18 minutes with food. Concomitant administration of 2 mg TVP-1012 with food also significantly decreases both mean AUC values (-23% and -22% for AUC_{0-t} and AUC_{inf}).

The relative bioavailability (F_{rel}) is 0.81 ± 0.24.

The label for rasagiline states that “Food does not affect the T_{max} of rasagiline, although C_{max} and exposure (AUC) are decreased by approximately 60% and 20%, respectively, when the drug is taken with a high fat meal.” Because AUC is not significantly affected, Agilect can be administered with or without food.

OCPB agrees with the firm’s label claim related to food.

INTRINSIC FACTORS

Gender Study 231

A multiple dosing study was conducted in PD patients who were not on levodopa/carbidopa. Patients were evaluated during a dose titration period of 3 weeks followed by a 7-week dosing period with daily doses of 1 mg, 2 mg or 4 mg of Rasagiline or placebo.

Single Dosing

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	DOSE (mg)	PAI		AI	
		AUC _{0-∞} ng.h/mL	C _{max} ng/mL	AUC _{0-∞} ng.h/mL	C _{max} ng/mL
Overall	1	11.83	5.91	7.87	2.40
	2	24.34	12.86	15.25	4.63
	4	46.71	21.67	33.30	10.17
Females	1	13.39	6.07	10.37	3.18
	2	28.79	17.91	17.83	5.35
	4	51.77	23.82	40.28	12.47
Males	1	11.05	5.83	6.62	2.01
	2	22.36	10.61	14.10	4.31
	4	42.37	20.05	28.06	8.44

Source: Appendix I7.1

*AUC_{0-∞} was calculated for PAI since regression analysis and previous studies suggested that a monoexponential decline in PAI concentrations was probable. AUC_{0-∞} was calculated for AI because no regression estimate of terminal slope was possible.

Study 112 Multiple Dosing for PD patients on Levodopa

Pharmacokinetic Parameter	Unit mg/day	Sex	Values ^a		
			0.5 mg/day (n=6♀, 3♂)	1.0 mg/day (n=2♀, 4♂)	2.0 mg/day (n=2♀, 6♂)
T _{max}	hours	Female	0.5	0.5	0.5
		Male	1.0 ± 0.9	0.5	0.8 ± 0.6
		F+M	0.7 ± 0.5	0.5	0.7 ± 0.6
C _{max}	ng/mL	Female	5.3 ± 2.7	9.4 ± 1.3	28.1 ± 11.2
		Male	2.9 ± 1.6	8.0 ± 2.6	10.6 ± 3.5
		F+M	4.5 ± 2.6	8.5 ± 2.2	14.9 ± 10.5
C _{max} adjusted to dose of 1 mg/Day	ng/mL	Female	10.5 ± 5.5	9.4 ± 1.3	14.0 ± 5.6
		Male	5.8 ± 3.2	8.0 ± 2.6	5.3 ± 1.8
		F+M	8.9 ± 5.2	8.5 ± 2.2	7.5 ± 5.3
AUC _{0-1h} (=AUC _{last})	ng x hr/mL	Female	7.7 ± 3.0	13.8 ± 2.1	36.1 ± 15.6
		Male	3.8 ± 1.1	11.7 ± 4.1	19.2 ± 4.5
		F+M	6.4 ± 3.1	12.4 ± 3.5	23.5 ± 10.5
AUC _∞	ng x hr/mL	Female	9.8 ± 4.8	14.7 ± 2.3	38.1 ± 14.6
		Male	23.51*	12.9 ± 5.0	25.6 ± 8.2
		F+M	NC	13.5 ± 4.1	28.7 ± 10.6
AUC _∞ adjusted to dose of 1mg/Day	ng x hr/mL	Female	19.6 ± 6.0	14.7 ± 2.3	19.1 ± 7.3
		Male	NC	12.9 ± 5.0	12.8 ± 4.1
		F+M	-	13.5 ± 4.1	14.4 ± 5.3

^a - Values are means ± SD for each PK parameter per dosage group

* - Blood sample of only one patient was available for the AUC_∞ calculation

Following multiple dosing with exposures up to 10 days females tended to have levels at day 10 that were 2.5 fold higher for C_{max} and 1.5 times higher for AUC at the 2 mg/day dose.

There were no apparent differences in gender following the 1 mg/day multiple dosing regimen.

Race

All studies were conducted in a population that was ~ 95% Caucasian.

Age and Weight

Table 10. Effect of covariates on Rasagiline/1-Aminoindan Pharmacokinetic Parameters

Expected values of rasagiline clearance (CL/F), central volume of distribution (V2/F) and 1-aminoindan clearance (CLM) are presented as a function of significant covariates in the final population PK model.

		CL/F (L/hr)			CL/F (L/hr)		
		Weight ^a			Weight ^a		
Age ^b	min	min	ref	max	min	ref	max
	ref	57.4	75.4	109.9	39.6	52.0 ^c	75.8
	max	44.5	58.5	85.3	30.7	40.4	58.8
		39.9	52.4	76.3	27.5	36.1	52.7
		COM1 = 0			COM1 = 1		

V2/F(L)		
Age ^b		
min	ref	max
205	125	101

		CLM(L/hr)		
		Weight ^a		
Age ^b	min	min	ref	max
	ref	23.8	34.4	57.4
	max	19.0	27.5	45.8
		17.2	24.9	41.5

^a Minimum = 42.3 kg, reference = 70 kg, maximum = 140.5 kg

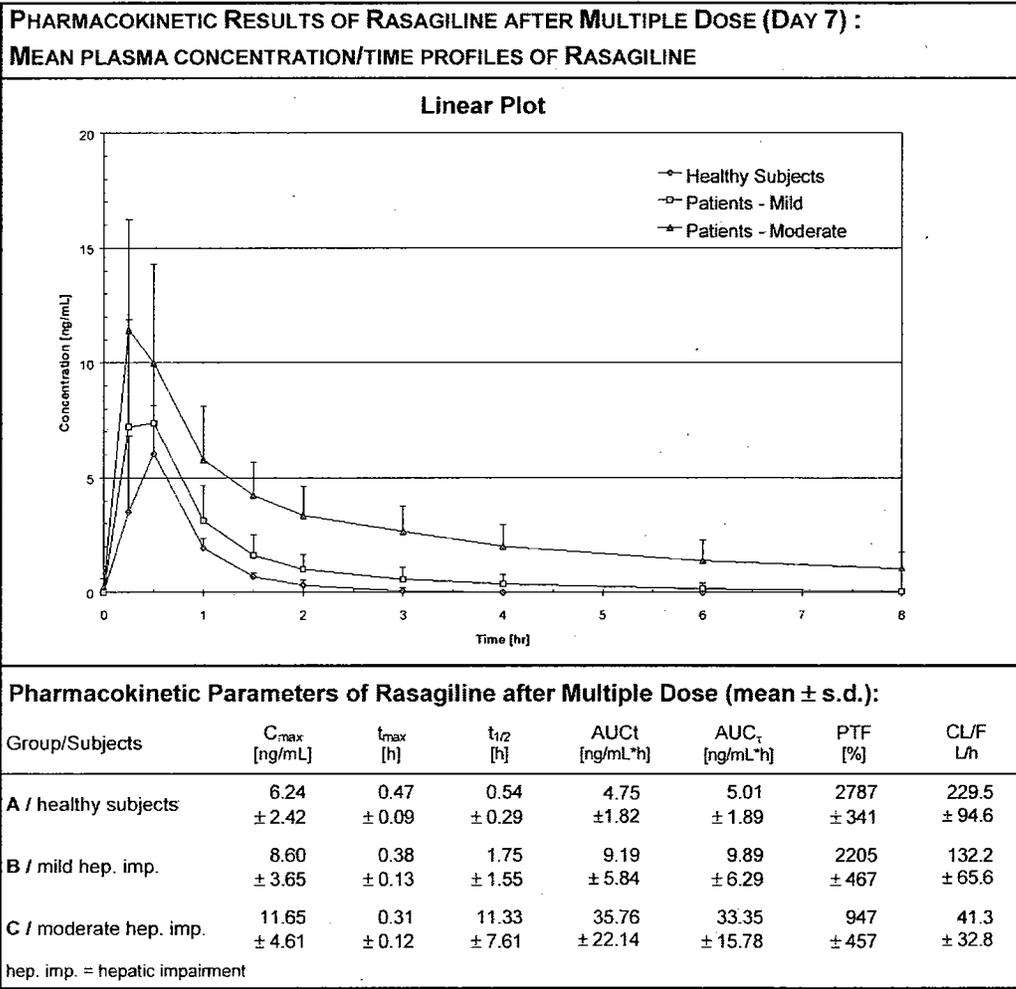
^b Minimum = 32 yr., reference = 60 yr., maximum = 79 yr.

The rasagiline CL/F estimate for a 70 kg, 60 year-old individual, with no concomitant medications, was 58.5 L/hr. Variability across the population in rasagiline CL/F was related to weight, age and concomitant levodopa/carbidopa therapy. A decrease in CL/F was associated with increasing age. For example, the expected CL/F for a typical 79 year-old individual would be about 11% less than a typical 60 year-old and approximately 30% less than a 32 year-old individual. Overall approximately 1% per year.

Weight affected CL/F in a positive manner. For an individual at the extreme upper end of weights for this population database (140.5 kg), the expected CL/F would be 85.3 L/hr (~ 45% greater than an individual with the reference weight of 70 kg who has a clearance of 58.5 L/hr).

LIVER DISEASE-Study 190-013

A single/multiple dose study (1 mg single dose, then 1mg/day for 7 days) was carried out in 24 subjects (8 per group). Subjects were stratified on the basis of their hepatic function to one of three groups: Group 1 with normal hepatic function, group 2 with mild hepatic impairment (Child class A), and group 3 with moderately impaired hepatic function (Child class B).



Results show an 8 fold increase in AUC_t and 7 fold increase for AUC _{τ} at steady-state between normal and moderately hepatic impaired subjects. For C_{max} there was only a two-fold increase between normal and moderately hepatic impaired subjects. Mildly impaired subjects had a 2 fold increase in AUC and a 1.4 fold increase in C_{max} compared to healthy subjects. Based upon these results the firm is recommending that Rasagiline should not be administered to subjects with moderate to severe hepatic impairment.

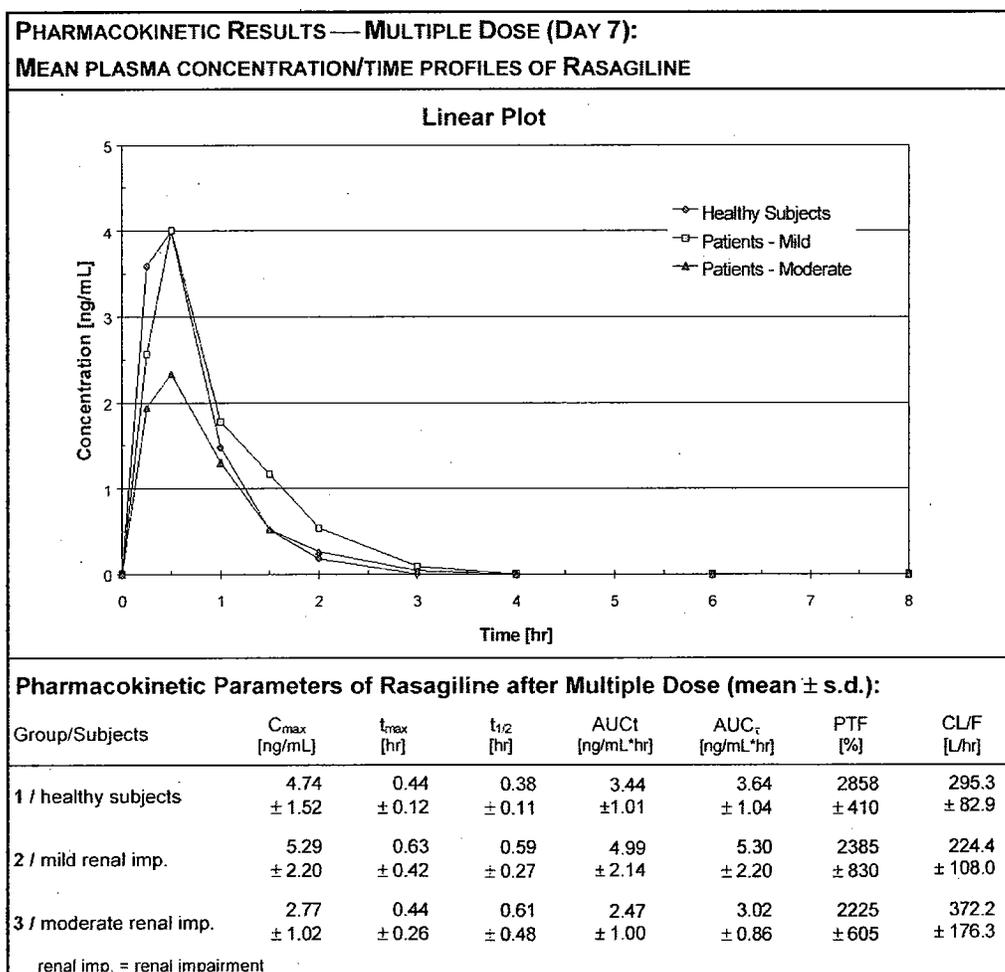
The firm supplied data related to the number of cigarettes smoked/subject in the study and it did not appear that smoking, up to 5 cigarettes/day, increased the clearance in the mildly impaired hepatic subjects.

Renal Disease Study TVP1012/425

The study was designed as a single-center, open, controlled, parallel multiple dose oral administration pharmacokinetic study, carried out in 24 completing subjects (8 per group). Subjects were stratified on the basis of their renal function to one of three groups: Group 1 with normal renal function, group 2 with mild renal impairment, and group 3 with moderately impaired renal function. The dose was 1 mg for single dose, followed by once daily dosing of 1 mg/day for 7 days).

Group Creatinine Clearance*	Renal function	N
1 > 80 mL/min	Normal	8
2 50-80 mL/min	Mildly	8
3 30-49 mL/min	Moderately impaired	8

* according to Cockcroft and Gault



For rasagiline, the profiles and pharmacokinetic characteristics for subjects with mild renal impairment (group 2) were all comparable to healthy subjects. In subjects with moderate renal impairment (group 3) a lower C_{max} (40%) and extent (AUC_t) (17%) of systemic exposure was observed compared to healthy subjects. However, the significance of this observation is confounded with the fact that for the moderate group they had only 2 smokers who had extremely low AUC_{tau} values of 0.66 and 1.19 which were 3 fold lower than the lowest value for AUC_{tau} in the mild renal impairment and normal subjects.

Rasagiline is extensively metabolized and renal elimination is not the primary route of elimination.

DOSING RECOMMENDATIONS

Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The recommended AGILECT dose for the treatment of Parkinson's disease patients is 1 mg administered once daily.

Change of levodopa dose in adjunct therapy: When AGILECT is used in combination with levodopa, _____ considered based upon individual response.

Patients with Hepatic Impairment: AGILECT plasma concentrations increase in patients with hepatic impairment. In patients with mild hepatic impairment _____
_____ AGILECT should not be used in patients with moderate to severe hepatic impairment.

The proposed dosage regimen of 1 mg in Caucasian patients and caution in dosing individuals with liver disease (i.e., due to their greater exposure) is supported by the Clinical Pharmacology data. However the question remains as to whether these special dosing concerns (including the possible effect of smoking) should be the same in other ethnic groups since the firm only studied Caucasians. _____

GENERAL BIOPHARMACEUTICS

BIOAVAILABILITY- Study TVP-1012/423

What is the bioavailability of the rasagiline tablet compared to a solution of rasagiline?

This was an open, randomized, single dose, two-way cross-over study in 14 healthy male volunteers. Each subject received a 2 mg dose of rasagiline, formulated as an oral formulation (Treatment A Test formulation) or an intravenous formulation (Treatment B Reference formulation) to evaluate the absolute bioavailability of rasagiline. There was at least a 21 day wash-out period between two treatment periods. The absolute bioavailability of rasagiline was 36%.

BIOEQUIVALENCE - Study TVP-1012/427

Was the to-be-marketed formulation BE to the clinical formulation?

This was an open-label, randomized, single-dose, two-period, two-treatment, two-sequence crossover study. Subjects were randomized to receive a single dose of two x 1mg rasagiline tablets on two separate occasions. Subjects received each of the following treatments according to a randomization code produced by Simbec Research Limited using the PROC PLAN procedure of SAS Version 8.2.

Admin 1 (A): 2 x 1mg Rasagiline tablet (To be Marketed Formulation; Test). Batch # MIN 063

Admin 2 (B): 2 x 1mg Rasagiline tablet (Clinical Trial Formulation; Reference). Batch #K-26703

There was a washout period of at least 21 days between doses.

The 1 mg to-be-marketed tablet was BE to the 1.0 mg of the clinically studied tablet.

The 90% CI were 86-104 for AUC and 87-119 for Cmax. Tmax for both formulations was 0.5 hr.

The batch formula for the commercial batches of 1 mg tablets is identical to the batch formula for the three primary stability batches. They are summarized in the following table. The intended batch size is tablets, which is also the batch size used for the manufacture of the three primary stability batches.

Table 11. Formulation

Components	Reference to Quality	Amount Per	Amount Per Batch
		Tablet [mg]	(tablets)
Rasagiline Mesylate	Standards Teva In-House		
Mannitol	USP, Ph. Eur.		
Colloidal Silicon Dioxide	NF, Ph. Eur.		
Starch ³	NF, Ph. Eur.		
Pregelatinized Starch	NF, Ph. Eur.		
Stearic Acid	NF, Ph. Eur.		
Talc	USP, Ph. Eur.		
Theoretical End Weight		210.0	210

1. Equivalent to 1 mg of rasagiline base (N-Propargyl-1-(R)-aminoindan base).

2. Also named Colloidal Anhydrous Silica (Ph. Eur.).

3. Also named Maize Starch (Ph. Eur.).

DISSOLUTION

Dissolution testing was performed on 12 tablets from the to-be marketed formulation, MIN063 (1mg pivotal biobatch (primary stability) tablets containing stearic acid) and K-26703 (1mg clinical biobatch tablets containing stearic acid) respectively.

Equipment USP, Apparatus 2 (Paddles),
Dissolution volume 500mL.
Medium 0.1N HCl (aq.)
Rotation speed 50rpm
Temperature 37°C
Sampling time 10, 15, 20 and 30 minutes
Method

Table 12.		Comparative Dissolution Results of MIN063 vs. K-26703							
		% RASAGILINE OF LABELED AMOUNT DISSOLVED IN 0.1N HCl							
		10 minutes		15 minutes		20 minutes		30 minutes	
Tab. #		MIN063	K-26703	MIN063	K-26703	MIN063	K-26703	MIN063	K-26703
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
Average		96	97	97	97	97	97	97	97
%RSD		1.7	1.9	1.3	1.5	1.4	1.3	1.0	1.2

In the additional dissolution study described in this report dissolution is compared between the batches that were used in the bioequivalence study TVP-1012/427 vs the 1 mg clinical batch produced with stearic acid., the dissolution profiles of the two batches were compared in three media: 0.1N HCl, buffer at pH 4.5 and buffer at pH 6.8

Table 13		Comparative Dissolution Results of MIN063 vs. K-26703 in 0.1N HCl							
		% RASAGILINE OF LABELED AMOUNT DISSOLVED IN BUFFER in 0.1N HCl							
		10 minutes		15 minutes		20 minutes		30 minutes	
Tab. #		MIN063	K-26703	MIN063	K-26703	MIN063	K-26703	MIN063	K-26703
1									
2									
3									

1 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

Average	88	91	89	94	90	94	90	95
%RSD	1.6	1.5	1.1	1.7	1.2	1.4	1.6	1.4

Based on the data provided, the firm's proposed dissolution method 0.1N HCL and specification (i.e., — in 15 min) are acceptable to OCPB. The data indicate that the two formulations MIN063 (1 mg manufactured with stearic acid from a —) and batch K-26703 (1mg clinical tablets containing stearic acid from an —) give the same dissolution results.

BCS Classification

Based upon the rapid dissolution of this product its BCS classification would be High Solubility-Low Permeability.

ANALYTICAL

What is the analytical methodology and is the method sufficiently robust to support the data presented?

Parameter	Rasagiline	AI
Method		
Freeze-thaw		
Benchtop Stability at RT		
Long term at -20° C		
Recovery		
Low		
Med		
High		

The analytical method can analyze — ng/ml of Rasagiline and is acceptable.

21 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

Andre Jackson _____

RD/FT Initialed by Raman Baweja, Ph.D. _____

Cc-NDA 21641, HFD-860 (Jackson, Baweja, Rahman, Gobburu, Mehta),
Central Documents Room (Biopharm-CDR)
OCPB Required Office Level Briefing May 10, 2004, List of Attendees (Atik Rahman, Allen Rudman, John Feeney, Peter Lee, Chandra Sahajwalla, Joga Gobburu, Atul Bhattaram, Robert Kumi, Pravin Jadhav, Lisa Jones, Robert Powell, Hank Malinowski, Mehul Mehta, Larry Lesko, Andre Jackson, Ray Baweja).

APPENDIX I

IN VITRO STUDIES

STUDY #—TVA 108/951876 PLASMA PROTEIN BINDING STUDY

NONCLINICAL ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION STUDIES OF RASAGILINE UTILIZING HUMAN BIOMATERIALS

MATERIALS

The compound ^{14}C -TVP101 as the hydrochloride salt (batch MR-TVA102-3, stated specific activity 31.5 mCi/mmol and radiochemical purity _____) was synthesised at _____. The certificate of analysis is shown in Appendix 2. The radiochemical purity of ^{14}C -TVP101 was determined during the course of the study and found to be _____ (Appendix 3).

Fresh control blood was obtained by cardiac puncture into EDTA tubes from 130 male mice (CD-1 strain, _____) and 21 male rats (Sprague-Dawley CD strain, _____). Fresh control blood was obtained by venepuncture into EDTA tubes from 9 male beagle dogs (stock animals maintained at _____) and from healthy volunteers among the staff of _____ who had taken no medication during the previous 7 days. The blood samples were centrifuged (ca 4000 rpm for 10 minutes, _____) with the minimum delay and the separated plasma transferred to plain tubes. Human plasma was not pooled. One pool of mouse, rat and dog plasma was prepared for the preliminary study and for the main part of the study 3 pools of mouse, rat and dog plasma were prepared from plasma obtained from at least 3 animals of each species. An aliquot of each pooled plasma sample was analysed for total protein and albumin in the Department of Clinical Pathology, _____.

PRELIMINARY EXPERIMENT

Binding of radioactivity to ultrafiltration membrane

Solutions of ^{14}C -TVP101 in isotonic phosphate buffered saline (pH 7.4) were prepared by spiking aliquots of phosphate buffered saline (4 ml) with aliquots (0.2 ml) of ^{14}C -TVP101 standard solutions in distilled water, to produce nominal concentrations of 10 ng/ml and 10 μg /ml. Duplicate aliquots (0.05 ml) of the resultant solutions were mixed with 7 ml scintillator _____ for liquid scintillation analysis. Three further aliquots of each solution (1 ml) were pipetted into _____ Units (_____ and centrifuged at 2000 g for 15 minutes. Duplicate aliquots (0.05 ml) of each filtrate sample were mixed with 7 ml scintillator _____ for liquid scintillation analysis.

For human plasma at a concentration of 1 ng ¹⁴C-TVP101/ml generally 10 ml of plasma was spiked with 0.5 ml of the appropriate standard solution of ¹⁴C-TVP101 in distilled water and the samples gently mixed for 10 minutes at about 37°C. Duplicate (0.1 ml) aliquots were taken for the determination of radioactivity and the pH of the plasma samples determined. Aliquots (1 ml) of plasma were loaded into the ultrafiltration tubes and centrifuged as described above. Aliquots (0.1 or 0.15 ml) from the ultrafiltrates were pooled for each subject and the radioactivity determined in the ultrafiltrate pool for each volunteer. The pH of the residual plasma was determined.

DATA PROCESSING

The extent of protein binding using the ultrafiltration method was calculated from the expression:

$$\% \text{ Bound} = 100 - \% \text{ free fraction}$$

$$\% \text{ Free fraction} = \frac{\text{concentration of radioactivity in ultrafiltrate}}{\text{concentration of radioactivity in unfiltered plasma}} \times 100$$

The extent of binding of ¹⁴C-TVP101 at 1, 10 and 100 ng/ml was determined in 4 male and 4 female subjects. In male subjects the extent of binding ranged from 90.4% to 93.7% and in female subjects from 88.7% to 92.8%. There were no notable changes in the extent of binding with increasing plasma concentrations of ¹⁴C-TVP101. The mean extent of binding of ¹⁴C-TVP101 to male human plasma proteins was 92.3% and to female human plasma proteins was 91.1%.

STUDY #-TVA 116/972994 –HUMAN ALBUMIN AND GLYCOPROTEIN BINDING

[¹⁴C]-RASAGILINE

THE IN VITRO BINDING OF [¹⁴C]-RASAGILINE TO HUMAN ALBUMIN AND HUMAN α-1-ACID GLYCOPROTEIN

APPEARS THIS WAY
ON ORIGINAL

EXPERIMENTAL

MATERIALS

The compound [¹⁴C]-rasagiline as the hydrochloride salt (batch MR-TVA 102-3, stated specific activity 31.5 mCi/mmol and radiochemical purity — was synthesised at —. The certificate of analysis is shown in Appendix 2. The radiochemical purity of this material was determined prior to the start of the study by TLC and was found to be —. Representative radiochromatograms are shown in Appendix 3.

Protein solutions were prepared using human albumin (fraction V; —) and human α -1-acid glycoprotein (—).

METHODS

Solutions of human albumin (0.58mM) and human α -1-acid glycoprotein (0.016mM) were prepared in isotonic phosphate buffered saline (pH 7.4). Aliquots of solutions of [¹⁴C]-rasagiline in isotonic phosphate buffered saline (pH 7.4) of nominal concentrations 30, 300 and 3000 ng/mL were spiked into the protein solutions to produce protein solutions of nominal concentrations 1, 10 and 100 ng [¹⁴C]-rasagiline/mL. The pH of the solutions was determined (—).

Concentrations of radioactivity were determined in duplicate aliquots by liquid scintillation analysis. Duplicate aliquots of each of the 10 and 100 ng/mL and nine aliquots of each of the 1 ng/mL protein solutions were pipetted into — Units (—) and centrifuged at 37°C for 15 minutes at 2000 rpm. Aliquots of each filtrate sample were mixed with 7 mL scintillator — for liquid scintillation analysis. A single aliquot (100 or 200 μ l) of each ultrafiltrate at the 10 and 100 ng/ml concentration was analysed and at the 1 ng/mL concentration an aliquot (140 or 200 μ l) was taken from each of the 9 ultrafiltrates, mixed together and the radioactivity in this pool measured.

DATA PROCESSING

The extent of protein binding using the ultrafiltration method was calculated from the expression:

$$\% \text{ Bound} = 100 - \% \text{ Free fraction}$$

$$\% \text{ Free fraction} = \frac{\text{concentration of radioactivity in ultrafiltrate as net value}}{\text{concentration of radioactivity in unfiltered solution as net value}} \times 100$$

Concentrations of [¹⁴C]-rasagiline in protein solutions and ultrafiltrates were expressed as ng rasagiline freebase/mL.

RESULTS AND DISCUSSION

Over the nominal concentration range of 1 to 100 ng/mL the extent of binding of [¹⁴C]-rasagiline to human albumin ranged from 61.3 to 66.2 % and this binding did not vary notably as a function of concentration. The mean extent of binding of [¹⁴C]-rasagiline to human albumin was 63.1%. The pH of the albumin solutions containing [¹⁴C]-rasagiline was between 7.2 and 7.3.

Over the nominal concentration range of 1 to 100 ng/mL the extent of binding of [¹⁴C]-rasagiline to human α -1-acid glycoprotein ranged from 33.8% (100ng/mL) to 64.1 % (1ng/mL). The extent of binding of [¹⁴C]-rasagiline decreased with increasing concentration of [¹⁴C]-rasagiline indicating a concentration dependent effect. The pH of the α -1-acid glycoprotein solutions containing [¹⁴C]-rasagiline was 7.7.

At the concentration range used [¹⁴C]-rasagiline was not extensively bound to human albumin or human α -1-acid glycoprotein.

STUDY # SB-2000-095-DRUG METABOLISM WITH MICROSOMES

CHARACTERIZATION OF TVP-1012 METABOLISM TESTED IN AN IN VITRO SYSTEM USING HUMAN, DOG AND MOUSE HEPATIC MICROSOMAL PREPARATIONS

OBJECTIVES

The objectives of the in vitro study were:

- to compare the metabolism of TVP-1012 in human, dog, rat and mouse hepatic microsomes
- to test the CYP 450 dependence of the metabolic pathways

METHODS

Under the provision of the original protocol the metabolic reaction was carried out in a human pooled microsomal preparation and in microsomes taken from one mouse, dog and rat.

These reactions were investigated at rasagiline substrate concentrations of 0.001 mM, 0.01 mM and 0.1 mM, at a fixed microsomal protein level of 1 mg/ml for 60 minutes in the presence of NADPH regenerating system, with the exception of rat.

Three reactions (mouse, dog and human) were also tested at the low concentration of the substrate (0.001 mM) without NADPH regenerating system in order to confirm the CYP 450 dependency.

Reactions were initiated by the addition of the substrate to the microsomal preparations. After the incubation period the reactions were terminated by denaturation with HCl. Each denaturated reaction was made basic with sodium hydroxide and extracted with ethyl acetate. The extracted material underwent TLC chromatography and was visualized using a phosphor imaging system.

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Table 1. Performed reactions in the experimental phase

Number of Sample	Target rasagiline *Concentration mM	Approximate Radioactive dose dpm / reaction	Microsome type
S1	0.001	21190	pooled human
S2	0.01	211900	pooled human
S3	0.1	211900	pooled human
S4	0.001	21190	naive mouse (M00501)
S5	0.01	211900	naive mouse (M00501)
S6	0.1	211900	naive mouse (M00501)
S7	0.001	21190	naive beagle dog (M00201)
S8	0.01	211900	naive beagle dog (M00201)
S9	0.1	21190	naive beagle dog (M00201)
S10	0.001	21190	pooled human No NADPH
S11	0.001	21190	naive mouse (M00501) No NADPH
S12	0.001	21190	naive beagle dog (M00201) No NADPH
S13	0.001	21190	naive rat (M00001)
S14	0.001	21190	pooled human Zero time control
S15	0.001	21190	naive mouse (M00501) Zero time control
S16	0.001	21190	naive beagle dog (M00201) Zero time control
S17	0.001	21190	Blank/no microsomes

*- At the low and middle concentrations, the test article was composed of the provided radioactive solution. At the concentration of 0.1 mM the radiolabelled test material was combined with a non-radioactive test article in order to generate the required concentration without increasing the radioactive dose.

RESULTS

Distribution of the metabolites at 0.01mM substrate concentration at 60 min.

Metabolites/ Species	3-OH AI Rf: 0.02	3-OH PAI cis-trans Rf: 0.05	unknown Rf: 0.08	1-AI Rf: 0.25	1-indanone Rf: 0.71	Unchanged rasagiline Rf: 0.60
human	0.6	1.8	5.2	23.5	ND*	53.9
mouse	2.7	3.2	9.4	38.4	1.4	29.4
rat	3.3	20.7	3.0	18.0	2.7	38.
dog	6.5	38.6	21.0	24.6	0.1	1.7

ND*: not detected

Depropargylation and hydroxylation were the two major metabolic elimination pathways in all species studied, leading to the production of aminoindan (1-AI) and 3-hydroxy propargylaminoindan (3-OH PAI). In addition, 3-hydroxy aminoindan (3-OH AI) and one unidentified metabolite were observed in all experimental systems. Other minor metabolites were identified at low levels, including 1-indanone, acetyl AI, 3-keto AI and 3-keto PAI. Additional low level metabolites were not yet identified. Possible metabolites that were tested but not found were hydroxylation products at position 6, 1-indanol, 3-hydroxy acetyl AI.

STUDY # WUJ00401-INHIBITORY EFFECT OF RASAGILINE ON P450

Investigation of the potential inhibitory effect of rasagiline mesylate (TVP-1012) on the metabolism of cytochrome P450 (CYP) model substrates

The objective of this study was to investigate the potential inhibitory effect of 1 µg/mL of the test substance, rasagiline mesylate, on a range of hepatic human cytochrome P450 (CYP) enzyme activities including the following: CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, 3A4 and 4A. These activities were measured using the following model substrates: ethoxyresorufin, coumarin, tolbutamide, S-mephenytoin, bufuralol, chlorzoxazone, testosterone and lauric acid respectively. The selected tests represent the major human P450 isoforms. Individual human liver microsomes from 4 individual livers were used for the investigation.

METHODS

Human liver microsomes from a pool of 4 individual livers (Lot # 0219) were supplied by the _____ and stored at -80°C prior to use and throughout the study. These microsomes were selected to express representative activities for all the major human cytochrome P450 isoforms.

The measurement methods for each substrate will not be presented but are presented in detail on pages 9-19 in \hypbio/hupharm/WUJ00401.pdf.

Time-dependent inhibition was assessed in order to account for any mechanism-based inhibition or the production of inhibitory metabolites following metabolism of rasagiline in the microsomal incubations.

In order to determine time-dependent inhibition, microsomes were preincubated in a shaking water bath in the presence of metabolic cofactors, 1 µg/mL of the test compound, potassium phosphate buffer and microsomal protein for 10 minutes. Reactions were then initiated by the addition of the CYP model substrate (approximately K_m). Triplicate incubations were conducted using the appropriate test compound vehicle controls. Model substrate activities were measured and reported for each replicate incubation. Inhibitory effects of the test substance were calculated as the percentage inhibition of CYP model substrate activity compared to the 'vehicle control'.

In comparison to 'vehicle incubations', rasagiline mesylate caused no significant inhibition (< 25% in all cases) of ethoxyresorufin *O*-deethylase, coumarin 7-hydroxylase, tolbutamide 4-hydroxylase, *S*-mephenytoin 4-hydroxylase, bufuralol 1'-hydroxylase, chlorzoxazone 6-hydroxylase, testosterone 6β-hydroxylase or lauric acid 12-hydroxylase activities in the presence of human liver microsomes. In addition, no significant inhibition (< 25% in all cases) was measured following a 10 minute pre-incubation in the presence of the metabolic cofactors.

In the present study, the potential inhibitory effect of 1 µg/mL rasagiline mesylate, on the *in vitro* metabolism of various CYP model substrates was examined using human liver

microsomes. The selected dose represents a concentration which is approximately 50-fold higher than the maximum human plasma concentration measured following treatment at the intended therapeutic doses of rasagiline.

Since rasagiline mesylate caused no inhibition of the model substrates, it was concluded that rasagiline mesylate at a final concentration of 1 µg/mL has no potential for interference with substrates of CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2C19, CYP2E1, CYP3A4 and CYP4A. Results from time-dependent experiments indicated that the compound did not cause mechanism-based inhibition of P450 isoforms.

STUDY # WUJ00401-P450 ISOFORM RESPONSIBLE FOR RASAGILINE METABOLISM

Evaluation of the Human Cytochrome P450 Isoforms Involved in the *In Vitro* Metabolism of Rasagiline Mesylate

Objectives

The aim of this study was to identify the human cytochrome P450 (CYP) enzyme(s) involved in the *in vitro* metabolism of Rasagiline mesylate (TVP-1012).

METHODS

[^{12/14}C] TVP-1012 (50 µM) was incubated with pooled human liver microsomes and microsomes prepared from baculovirus infected insect cells transfected with human CYP cDNA expressing CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, and 4A11 and control microsomes (no transfected CYP enzyme). The disappearance of TVP-1012 was assessed by HPLC with on-line radiochemical detection.

The effects of isoform-selective CYP inhibitors furafylline (CYP1A2), methoxsalen (CYP2A6), quercetin (CYP2C8), sulphaphenazole (CYP2C9), tranlycypromine (CYP2C19), S-mephenytoin (CYP2C19), quinidine (CYP2D6), diethyldithiocarbamate (DDC; CYP2E1) and ketoconazole (CYP3A4) on the disappearance of TVP1012 (50 µM) were determined using pooled human liver microsomes.

RESULTS

Initial investigative experiments were performed with a range of concentrations of parent compound (0.5, 1, 2, 5, 10, 15, 40 and 50 μM) in the presence of pooled human liver microsomes at 1 $\text{mg}\cdot\text{mL}^{-1}$ and a 30 minute incubation time. Under these conditions, the disappearance of parent compound ranged between 27.5% and 58.1%. A concentration of 50 μM of TVP-1012 was chosen for future experiments, as at this concentration, an adequate degree of disappearance was achieved (27.5%).

Under these conditions, one major and at least one other minor, more polar metabolite were detected. The main metabolite was tentatively identified as aminoindan by co-migration with an authentic standard provided by the Sponsor; the identity of the minor metabolite was not investigated further in this study.

Time and protein ranging studies were performed to identify optimum incubation conditions for pooled human liver microsomes. At a fixed incubation time of 30 minutes, disappearance of TVP-1012 (50 μM) appeared to be approximately linear up to a protein concentration of 1 $\text{mg}\cdot\text{mL}^{-1}$. At a fixed protein concentration of 1 $\text{mg}\cdot\text{mL}^{-1}$, disappearance of TVP-1012 (50 μM) appeared to be linear up to an incubation time of *ca.* 30 minutes.

Following a 60 minute incubation of [$^{12}/^{14}\text{C}$] TVP-1012 (50 μM) with — expressing various CYP isoforms, extensive disappearance (40.3%) of parent compound was observed only with — expressing CYP1A2, whilst the remaining — exhibited much lower activity. The degree of disappearance of parent compound was of a similar order to that of pooled human liver microsomes (45.6%). The major metabolite formed in the CYP1A2 — incubations co-eluted with the major metabolite formed in incubations with pooled human liver

microsomes. — expressing CYP1A1, 2C19, 2D6, 2E1 and 3A4 also catalysed the disappearance of TVP-1012 (10.6 – 15.5%).

Following incubation with isoform selective chemical inhibitors, furafylline (10µM; selective CYP1A2 inhibitor) and methoxsalen (10µM; selective CYP2A6 inhibitor) demonstrated notable inhibition of disappearance of parent compound compared to vehicle control activity (73.2 and 98.3% respectively). However, under these incubation conditions methoxsalen may not have exhibited CYP2A6-selective inhibition and, in addition, may have demonstrated inhibitory potential against CYP1A2. Thus, inhibition of TVP-1012 disappearance by methoxsalen was more likely to have been non-selective, rather than via inhibition of CYP2A6, which suggests that CYP2A6 is most likely not involved in the metabolism of TVP-1012.

Conclusions

- This study has indicated that in a human *in vitro* microsomal system, TVP-1012 undergoes a cytochrome P450-dependent metabolic elimination.
- The main metabolite was tentatively identified as aminoindan by co-migration with an authentic standard provided by the Sponsor.
- At least one additional minor metabolite was detected. This metabolite was more polar in nature than aminoindan, however, its identity was not further investigated.
- Experiments with supersomes expressing various CYP isoforms, and studies with various inhibitors have indicated that CYP1A2 is the predominant P450 isoform involved in the metabolic elimination of TVP-1012.

STUDY # TVP-1012/422 -¹⁴C-RASAGILINE MESYLATE ABSORPTION, METABOLISM AND EXCRETION IN HEALTHY MALE HUMAN SUBJECTS AFTER A SINGLE ORAL DOSE

OBJECTIVES

The objective of this study was to obtain information on the absorption, pharmacokinetics, plasma protein binding, metabolism and excretion of ¹⁴C-rasagiline

mesylate after a single oral administration of 3.12 mg (equivalent to 2 mg rasagiline free base) to healthy male human subjects.

MATERIALS

¹⁴C-Rasagiline mesylate was originally synthesised at ———. It was ——— on 24 April 2001 for the present study (as Batch No. NPE/TVA158/20) and subsequently stored in the dark at about -20°C in iso-propanol solution.

A total of eight healthy adult male human subjects were selected from volunteers using the criteria for exclusion defined in the Clinical Protocol (contained within the Clinical Report; Addendum A). Originally, six subjects (nos. 1 – 6) participated in this study, but due to the incomplete recovery of the administered radioactivity in their excreta they were recalled to the Clinic during the period Days 41 - 43 post-dose and an additional 24-hour excreta collection was performed to determine if detectable levels of radioactivity were being excreted. The study was then extended to include a further two subjects (nos. 7 and 8) and a longer sample collection period, since not all of the radioactivity administered to the original six subjects was recovered during 168 hours post-dose (Protocol Amendment no. 5: Appendix 2). Except for blood sampling (which was reduced), all procedures up to 168 hours post-dose were conducted according to the original protocol. Subjects remained resident in the Clinic and 24-hour urine and fecal collections were made until Day 15 (336 hours post-dose). Subjects returned to the Clinic on Days 18, 21, 24, 27 and 30 for daily residency periods when 24-hour urine and feces output were collected. As detectable levels of radioactivity were still being excreted in the Day 30 samples, the recovery period was further extended by including additional 24-hour urine and fecal collection periods on Days 34 and 38.

Doses were ingested by each volunteer directly from the glass beakers, the insides of which were then rinsed twice with 50 ml tap water and these washings also ingested.

SAMPLE COLLECTION

For subjects 1-6, blood samples were withdrawn by venepuncture or an indwelling cannula located in a suitable forearm vein before dosing and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, and 168 hours after dosing. Urine was collected from each subject before dosing (50 ml sample only retained) and during the following times after dosing (total sample voided): 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168 hours and Day 41-43 (*vide infra*). Faeces were collected during the 12-hour period before dosing (50 g sample only retained) and at 24-hour intervals after dosing for seven days (total sample voided) and Day 41-43 (*vide infra*). For subjects 7 and 8 only, urine and faeces samples were also collected at 24-hour intervals up to and including Day 14 post-dose, and at the following times: Day 18 (408-432 hours post-dose), Day 21 (480-504 hours post-dose), Day 24 (552-576 hours post-dose), Day 27 (624-648 hours post-dose), Day 30 (696-720 hours post-dose), Day 34 (792-816 hours post-dose) and Day 38 (888-912 hours post-dose).

DATA PROCESSING

Blood cells

Concentrations of radioactivity in blood cells (C_c) were calculated using the formula:

$$C_c = \frac{[C_B - C_P(1 - PCV)]}{PCV}$$

where C_B and C_P are the corresponding concentrations of radioactivity in whole-blood and plasma respectively, and PCV is the packed cell volume (haematocrit).

Association of radioactivity with blood cells (%) was calculated using the formula:

$$100[1 - R(1 - PCV)]$$

where R is the plasma : whole-blood radioactivity concentration ratio.

The extent (%) of binding to plasma proteins was calculated from the relationship:

$$100(D_i - D_u)/D_i$$

where D_i is the concentration of drug (represented by total radioactivity) in plasma before ultrafiltration and D_u is the unbound concentration in ultrafiltrate.

RESULTS

Radioactivity levels in whole-blood attained maximum values at the same time as plasma levels and declined subsequently at similar rates to those in plasma. For five of the six subjects, whole-blood concentrations of radioactivity were less than the corresponding plasma concentration at most sampling times. Calculated concentrations of radioactivity in blood cells for all subjects ranged from 10% to 120% of those in plasma, indicating that association of rasagiline and/or its metabolites with the erythrocytes was not extensive.

It was calculated that a mean total of 84.38% of the radioactive dose of ^{14}C -rasagiline mesylate to eight human subjects was excreted in urine and feces during 38 days after administration. Measured excretion data for the original six subjects are summarized in the following table:

Days after dosing	Urine	Feces	Total
1-7	60.15	7.06	67.21

Excretion was initially rapid, but a sizeable fraction of the dose was excreted relatively slowly, such that excretion was still continuing at a rate of about 2% dose per day at 7 days post-administration.

It was estimated from their excretion data and a semi-logarithmic plot of radioactivity remaining un-excreted in urine and feces vs. time that approximately 87% of the dose would have been excreted by Day 32. Support for this was obtained from measurement of the radioactivity in excreta samples collected for 24-hour periods at regular intervals after Day 14 until Day 38. When estimates of the percentage of the radioactive dose

excreted during the days when excreta were not collected are included, it could be calculated that 84% of the dose would have been excreted by Day 38.

Metabolite profiling of the excreta and plasma of the original six human subjects were determined by HPLC with radioactivity and UV detection. The results showed that biotransformation of the drug was very extensive and essentially complete prior to excretion, but at least 80% of the radioactivity in urine was associated with ten main radioactive components, each of which accounted for 2% of the dose or more. On the basis of their chromatographic retention properties, with mass spectroscopic confirmation in some cases, the more important of these components were tentatively identified as 3 OH-PAI and 3-keto-PAI, AI and 3-OH-AI, which were also present in urine as conjugates, together with an *N*-glucuronide (or possibly *N*-carbamoyl glucuronide) conjugate of rasagiline which was very abundant in urine shortly after dosing, but much less so afterwards.

Radioactivity levels in blood cells were calculated from the corresponding plasma and whole-blood values and the blood packed cell volumes. The results showed that cell concentrations of radioactivity were less than 10 ng equivalents/ml at all times, and varied rather erratically with time as well as between individuals. These data were reflected in the cells : plasma ratio, which ranged from a minimum of 0.1, to a maximum of 1.2 (Table) during the period when both concentrations were measurable. In general the mean blood cell : plasma ratio was *ca* 0.5 (range 0.21 – 0.66) indicating that association of radioactivity with the erythrocytes was not extensive.

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Blood cells : plasma radioactivity concentration ratios following a single oral administration of ¹⁴C-rasagiline mesylate to male human subjects 1 to 6

Collection time (hours)	Subject no./Sex						Mean	±	sd
	1M	2M	3M	4M	5M	6M			
0.25									ND
0.5							0.21	±	0.17
1							0.24	±	0.11
2							0.40	±	0.15
3							0.51	±	0.28
4							0.53	±	0.26
6							0.51	±	0.32
8							0.54	±	0.23
12							0.66	±	0.29
24							0.60	±	0.26
48									ND
72									ND
96									ND
120									ND
168									ND

SD Standard deviation

ND No radioactivity detected in plasma and/or blood cells; excluded from calculation of the mean. Mean values are given as ND when the results for three (*ie* 50%) or more of the subjects were ND

Note: Cell concentrations of radioactivity were calculated from the corresponding whole-blood and plasma levels and the packed cell volume (see Experimental Procedures: Data Processing)

STUDY RSLN_2 DETERMINATION OF ENANTIOMERIC CONVERSION

Objective

To determine if during the 10 days of study CD596 did Rasagiline mesylate which is the R-enantiomer of N-propargyl-1-aminoindan (R-PAI) bio-transform to the S-enantiomer of N-propargyl-1-aminoindan (S-PAI) in the plasma samples of healthy volunteers that were dosed with 5mg (group B) or 10mg (group C) of rasagiline mesylate per day.

Methodology

The methods employed in this additional bioanalytical study involved two analytical methods, the first one had enantio-selective capacity (HPLC normal phase with chiral column) and the second had high sensitivity capacity (LC/MS: MS technique). (study details can be found in EDR 21641/hpbio/humanpharm/rsln_2.pdf). In the first step, enantio-selective chromatography was employed in order to separate the R-PAI from the investigated S-PAI and collect the fractions that may have contained the S-PAI. In the second step, the collected fractions were injected to the LC/MS: MS in order to quantify the S-PAI, should it have been obtained *in-vivo* from biotransformation of the R-PAI. Spiking different amounts of S-PAI to naive human plasma and evaluating the linear concentration-response ratio established the validity of these two steps.

Table 1. List of plasma samples from study CD596

Patient No.	Patient Initials	Dose (mg/day)	Day	Time after Dosing (min.)
201	U	5	10	20
201		5	10	30
201		5	10	60
201		5	10	90
202		5	10	20
202		5	10	30
202		5	10	60
202		5	10	90
303	L	10	10	10
303		10	10	20
303		10	10	30
303		10	10	90

ANALYSIS OF THE PLASMA SAMPLES FROM STUDY CD596

The extracts from the 12 plasma of the three volunteers that were dosed with rasagiline were injected in into the LC/MS: MS. The response ratios ($^{12}\text{C}/^{13}\text{C}$) are presented in Table 2.

Table 2. Response ratios $^{12}\text{C}/^{13}\text{C}$ in the plasma samples.

Patient no.	201	202	303
Response ratio	0.257	0.298	0.369
	0.295	0.278	0.158
	0.208	0.235	0.221
	0.258	0.240	0.219
Mean*	0.254	0.263	0.242
% from noise (0.270)	-6%	-3%	-10%

* The mean was calculated for the responses even though came from different time points since they are all below the noise (below 0.270) level. The mean and the corresponding %RSD show that these are in fact noise responses detached from the R-PAI concentrations in the sample

4 CONCLUSION

Bioenantiomeric conversion did not occur *in-vivo* in volunteers dosed with 5 or 10 mg rasagiline per day. S-PAI was not detected (DL approximately 3.3ng/mL). All the values were below the upper noise level.

HEALTHY SUBJECT PHARMACOKINETIC STUDIES

STUDY CC547

TOLERANCE, PD AND PK OF TVP 101(PAI) AFTER ORAL ADMINISTRATION OF SINGLE RISING DOSES IN TWELVE NORMAL VOLUNTEERS

I. INTRODUCTION

This was the first study of PAI in humans. Its aim was to evaluate the tolerance, pharmacodynamic activity, and pharmacokinetics of PAI in healthy male volunteers who received single oral doses. PAI was administered as its hydrochloride salt, designated as TVP 101. The study employed a restrictively randomized, double-blind, placebo-controlled design with two parallel groups; subjects in one group received 0, 1, and 5 mg PAI, and subjects in the other group received 0, 2, and 10 mg PAI. Within each group, drug was administered in a rising dose, crossover fashion. After tolerance up to 10 mg PAI had been shown, half the subjects received a single 20 mg PAI dose.

The study was initiated based on encouraging nonclinical findings. A suitable battery of nonclinical toxicology and ADME studies in mice, rats, and dogs indicated that it was safe to proceed with this investigation in humans. In addition, the nonclinical pharmacology profile indicated that PAI was a potent, selective, irreversible, monoamine oxidase B (MAO-B) inhibitor with human therapeutic potential in a variety of neurologic diseases. The pharmacodynamic parameter in this study was inhibition of MAO-B activity in the human platelet.

Study Design

Twelve normal, healthy male subjects were divided into two groups of six subjects; each group received a placebo and two increasing doses of TVP 101 (1 and 5 mg doses or 2 and 10 mg doses). An additional dose, which was 20 mg TVP 101, was administered to six of these subjects without placebo control in accordance with an amendment to the protocol.

The duration of the study for each subject who completed the original three-way crossover was to be seven weeks, consisting of a two week run-in period, followed by three single oral administrations separated by wash-out periods of at least two weeks and a two week follow-up period after the last administration. For the six subjects who also received the 20 mg dose of TVP 101, an average of an additional 39 days was required. Fourteen days were required for the 20 mg dose follow-up.

The clinical study was performed from February 18, 1991 to June 11, 1991 in a clinical unit situated within

All subjects had to be non-smokers

Demographics: Age

	N	MEAN	SD	SEM	MIN	MAX	P(t)
Placebo, 1, 5 mg	6	24.8	6.6	2.7	20	38	> 0.05
Placebo, 2, 10 mg	6	21.5	1.2	0.5	20	23	> 0.05
All Subjects	12	23.2	4.9	1.4	20	38	--

Weight

	N	MEAN	SD	SEM	MIN	MAX	P(t)
Placebo, 1, 5 mg	6	71.9	9.8	4.0	60.5	89.0	> 0.05
Placebo, 2, 10 mg	6	68.4	8.2	3.4	56.6	80.6	> 0.05
All Subjects	12	70.2	8.8	2.5	56.6	89.0	--

Height

	N	MEAN	SD	SEM	MIN	MAX	P(t)
Placebo, 1, 5 mg	6	179.2	4.6	1.9	174.0	185.0	> 0.05
Placebo, 2, 10 mg	6	178.2	8.0	3.3	168.0	186.0	> 0.05
All Subjects	12	178.7	6.3	1.8	168.0	186.0	--

Treatments Administered:

Subjects were separated into two groups of 6 subjects, each group receiving a placebo and two increasing TVP 101 doses. The position of placebo in the sequence of the three dosing periods was randomly assigned within each dose group. A fourth treatment block was added later on the basis of early results to test yet a higher dose.

- Group A : 6 subjects received placebo and two rising single doses of 1 and 5 mg of TVP 101 (PAI)
- Group B : 6 subjects received placebo and two rising single doses of 2 and 10 mg of TVP 101 (PAI).
- 20 mg Two subjects from Group A and four subjects from Group GroupB received a single 20 mg dose of TVP 101. While all 12 subjects from the combined Groups A and B were invited to participate, only 6 accepted the invitation.

Subject Number	Subject Code	Period 1	Period 2	Period 3	Period 4
1		Placebo	1 mg	5 mg	20 mg
2		1 mg	Placebo	5 mg	--
3		1 mg	5 mg	Placebo	--
4		1 mg	5 mg	Placebo	--
5		1 mg	5 mg	Placebo	--
6		Placebo	1 mg	5 mg	--
7		2 mg	10 mg	Placebo	20 mg
108		2 mg	Placebo	10 mg	20 mg
9		Placebo	2 mg	10 mg	20 mg
10		Placebo	2 mg	10 mg	20 mg
11		2 mg	Placebo	10 mg	--
12		2 mg	10 mg	Placebo	--
14	(replaced #4)	1 mg	5 mg	Placebo	--
15	(replaced #5)	1 mg	Placebo	5 mg	20 mg

Sample Collection and Handling

F. PHARMACODYNAMIC EVALUATION

Pharmacodynamic activity was evaluated by determination of the platelet MAO-B activity. Platelet monoamine oxidase-B (MAO-B) activity was measured within the linear ranges for incubation time and enzyme concentration.

Pharmacokinetic evaluation

Blood samples for PAI and AI plasma level determinations were collected before dosing (T0h), then 0.5, 1, 2, 4, 8, and 24 hours after each administration. Each blood sample was drawn by direct veinipuncture using a 27-gauge needle. Each sample volume was 10 mL and was collected into two separate propylene tubes containing dry heparin. They were centrifuged at 4°C at 1100 G for ten minutes. Plasma was rapidly transferred to two propylene tubes, stoppered (airtight) and stored at minus 20 degrees Celsius (-20°C) until TVP 101 (PAI) and metabolite (AI) plasma level determinations were carried out.

Bioanalytical Methods-

Studies were conducted from February 1991 to June 1991. The analysis of the plasma samples for PAI&AI was conducted on: 18, 19, 22, 26, 27, 30-Jul-1991, 01-Aug-1991 and 05-Sep-1991. The analysis in human urine samples was conducted on: 21, 22, 28, 29, 30-Aug-1991 and 05, 10,11-Sep-1991 (data supplied by [redacted]). Therefore total storage time was 6 months.

Plasma

Parameter	PAI	AI
Method	GC/MS	GC/MS
Sensitivity/LOQ	0.25 ng/ml	0.5 ng/ml

Linearity (Standard curve samples)	0.25-10 ng/ml	0.5-10 ng/ml
Quality Control (QC) Samples	0.25, 1, 10 ng/ml	0.25, 1, 10 ng/ml
Precision of Standards (%CV)	8.6%@ 0.25 ng/ml 8.51%@ 10.2 ng/ml	7.4% @ 0.48 ng/ml 4.11%@ 9.5 ng/ml
Precision of QC Samples (%CV)	12%@ 0.25 ng/ml 6.51%@ 10.2 ng/ml	8.7%@0.5 ng/ml 8.44%@10.0 ng/ml
Accuracy of Standards (%)	99.2%@ 0.25 ng/ml 93%@ 10.2 ng/ml	112% @ 0.48 ng/ml 112% @ 10 ng/ml
Accuracy of QC Samples (%)	0%@ 0.25 ng/ml 95.2%@ 10.2 ng/ml	92% @ 0.5 ng/ml 102% @ 10 ng/ml

Statistical Analysis

A. SUBJECT SAMPLES

The subject sample for all the formal statistical analyses of demographic, pharmacodynamic, and pharmacokinetic data consisted of the twelve subjects who completed the original three-way crossover. The subject sample for the 20 mg dose phase of the study consisted of the six subjects who completed that phase of the study. All fourteen subjects administered study drug including the twelve subjects who completed the original three-way crossover and the two subjects who were withdrawn from the study after having received TVP 101 1 mg during Period 1 were considered in the safety assessments.

B. ANALYSES PERFORMED

Statistical analyses were performed by the Statistical Unit of the Innovative R& D Group of TEVA Pharmaceuticals using a Unix-based SAS package (SAS Institute, North Carolina).

1. Subject Information

Descriptive statistics (mean, standard deviation [s.d.], standard error [s.e.m.], minimum and maximum values) were determined for demographic values.

Student's t-test and the Wilcoxon 2 sample test were used to compare the baseline values of demographic and clinical examination parameters in the two groups of volunteers.

2. Pharmacodynamic (MAO-B) Data

The Shapiro-Wilk statistic was applied to check whether the data were normally distributed and a rank transformation was performed on data which were not normally distributed before applying parametric tests.

Analysis of Variance (ANOVA) was performed for assessing the significance of the effects of different components (such as dose or period) and their interaction on parameters such as MAO-P activity or % inhibition.

The Dunnett two tailed t-test was applied for pairwise comparisons between placebo (dose 0) and other doses.

The LSD (Least Significant Difference) pairwise comparison procedure was applied for the comparison of all doses to each other.

The Sign test was used in order to examine the significance of changes or differences within the different time periods.

All tests applied were two-tailed and a p-value of 5 % or less was considered statistically significant.

3. Pharmacokinetic Data

As PAI was detected only in a few plasma samples following administration of 1 mg of TVP 101, it was decided not to calculate AUC of PAI. After the 2 mg dose, only the AUC_{0-t} was calculated for PAI.

For the metabolite AI, although $AUC_{0-\infty}$ was calculated after the doses 1 mg and 2 mg, it was decided not to consider these values because of the too-high percentage of extrapolation between AUC_{0-t} and $AUC_{0-\infty}$.

Therefore, the AUC_{0-t} (normalized to the 1 mg dose), the $AUC_{0-\infty}$ (normalized to the 1 mg dose) and the $t_{1/2}$ were compared only between the three TVP 101 higher doses (5 mg, 10 mg and 20 mg) by a Student t-test for two groups comparison or by a Mann-Whitney test if the variances were not homogeneous.

Conversely, the C_{max} (normalized to the 1 mg dose) were compared between the 1 mg and 5 mg TVP 101 doses (group A) and between the 2 mg and 10 mg TVP 101 doses (group B) by an analysis of variance (2-way ANOVA) or by a Friedman test if the variances were not homogeneous. In addition, the C_{max} (normalized to the 1 mg dose) were compared between the TVP 101 doses administered to different groups of subjects (e.g. 1 mg versus 2 mg; 1 mg versus 10 mg) by a Student t-test for two groups comparison or by a Mann-Whitney test if the variances were not homogeneous.

RESULTS

Table 1. Mean calculated values, std. and N of % inhibition of MAOB by dose administered

	0 mg			1 mg			2 mg			5 mg			10 mg		
	AVE	STD	N	AVE	STD	N	AVE	STD	N	AVE	STD	N	AVE	STD	N
	%	%		%	%		%	%		%	%		%	%	
Hr 1	7.09	15.2	12	34.43	11.1	6	54.71	19.3	6	75.99	9.13	6	97.26	1.85	6
Hr 2	14.57	17.7	12	34.53	12.2	6	44.78	10.6	6	74.89	10.7	6	97.20	1.50	6
Hr 4	4.29	23.2	12	24.48	19.5	6	40.67	28.4	6	76.17	12.0	6	96.83	2.81	6
Hr 8	12.9	33.9	12	23.14	13.5	6	25.06	39.5	6	78.51	10.8	6	94.87	5.10	6
Hr 24	1.33	16.6	12	36.96	17.5	6	43.43	32.3	6	83.87	11.4	6	96.40	2.65	6
Hr 48	8.73	23.1	12	32.43	29.1	6	40.71	44.2	6	74.64	19.5	6	94.68	2.00	6
Hr 168	8.34	26.3	12	8.72	50.0	6	15.61	34.5	6	29.57	22.2	6	44.66	12.4	6
Hr 336	6.51	17.1	12	28.4	68.2	6	1.85	46.0	6	7.42	26.0	6	0.62	23.8	6

Cross reference data list: Appendix A, pages A.14, A.15

Table 2. Summary of PAI Pharmacokinetic Parameters

		Treatment				
		1 mg	2 mg	5 mg	10 mg	20 mg
C _{max} (ng/mL)	MEAN	2.50	4.89	14.36	30.33	71.18
	STD	0.92	1.96	8.23	4.80	20.63
t _{max} (h)	MEAN	0.50	0.50	0.50	0.50	0.58
	STD	0.00	0.00	0.00	0.00	0.20
AUC _{0-t} (ng/mL/h)	MEAN		3.55	11.50	37.66	117.03
	STD		1.51	5.88	12.06	35.34
AUC _{0-∞} (ng/mL/h)	MEAN			11.92	38.75	122.55
	STD			5.84	12.42	36.01
t _{1/2} (h)	MEAN			0.60	1.52	2.79
	STD			0.22	0.70	1.50
MRT (h)	MEAN			0.93	1.52	2.52
	STD			0.16	0.36	0.50
t _{lag} (h)	MEAN	0.00	0.00	0.00	0.00	0.00
	STD	0.00	0.00	0.00	0.00	0.00
C _{max} * (ng/mL)	MEAN	2.50	2.45	2.87	3.03	3.56
	STD	0.92	0.98	1.64	0.48	1.03
AUC _{0-t} * (ng/mL/h)	MEAN		1.78	2.30	3.77	5.85
	STD		0.75	1.17	1.21	1.77
AUC _{0-∞} * (ng/mL/h)	MEAN			2.39	3.88	6.13
	STD			1.17	1.24	1.80

* = Value Normalized to 1 mg Dose

Table 3. Summary of AI Pharmacokinetic Parameters

		Treatment				
		1 mg	2 mg	5 mg	10 mg	20 mg
C _{max} (ng/mL)	MEAN	1.08	2.37	8.48	22.79	41.58
	STD	0.36	0.45	4.14	9.28	7.46
t _{max} (h)	MEAN	1.00	1.00	1.00	1.33	1.17
	STD	0.55	0.55	0.55	1.33	0.68
AUC _{0-t} (ng/mL/h)	MEAN	4.26	12.89	77.94	188.34	412.62
	STD	2.33	1.91	17.09	32.96	65.06
AUC _{0-∞} (ng/mL/h)	MEAN	12.75	30.08	94.70	236.19	518.16
	STD	1.48	13.69	20.32	40.08	76.87
t _{1/2} (h)	MEAN	8.57	9.11	9.89	10.46	10.72
	STD	1.49	4.79	2.11	1.40	1.61
MRT (h)	MEAN	12.75	13.55	13.15	14.14	14.36
	STD	2.30	7.13	2.96	2.24	2.16
t _{lag} (h)	MEAN	0.00	0.00	0.00	0.00	0.00
	STD	0.00	0.00	0.00	0.00	0.00
C _{max} * (ng/mL)	MEAN	1.08	1.19	1.70	2.28	2.08
	STD	0.36	0.22	0.83	0.93	0.37
AUC _{0-t} * (ng/mL/h)	MEAN		6.45	15.59	18.84	20.63
	STD		0.95	3.42	3.29	3.26
AUC _{0-∞} * (ng/mL/h)	MEAN		15.04	18.94	23.62	25.91
	STD		6.84	4.07	4.01	3.85

* = Value Normalized to 1 mg Dose

As shown in Table 4 for the dose range tested (1-20mg), the results of the analyses demonstrate departure from dose proportionality in AUC for PAI and AI following a single dose

administration. For AUC 0-t the 95% CI values were of 1.35- 1.76 for PAI and 1.44-1.82 for AI, and for AUC0-inf the 95% CI values were slightly higher for PAI (1.60- 2.12) and lower for AI (1.16-1.35). This degree of non-proportionality is also demonstrated by quantifying the magnitude of the departure from proportionality (R), which for PAI were 1.56 and 1.45 for AUC0-t and AUC0-inf, respectively, and for AI 1.53 and 1.74 for AUC0-t and AUC0-Inf, respectively. Dose proportionality would result with R value of 2 within the CI.

Table 4. Study CC547- Summary Results of the Assessment of Dose Proportionality to AUC0-t Using the Power Model Analysis

PK Parameter	β Estimate (95% CI)*	R - Estimate of the Increase in Doses Required for Doubling the AUC (95% CI)**
AI	1.63 (1.44,1.82)	1.53 (1.46,1.62)
PAI	1.55 (1.35,1.76)	1.56 (1.48,1.67)

The results of the power model according to the method described by Gough et al. 1995, demonstrate departure from dose proportionality in AUC for PAI and AI following a single dose administration at the dose range of 1-20 mg.

Comment to the Medical Officer:

The firm has stated that the reason for not including other racial groups in the study population was due to the inclusion criteria in protocols CC547, as well as CD596, TVP-1012/421, TVP-1012/422, and TVP-1012/426 are reflecting the population pool available for the studies at the time and site of the study. The sponsor indicated that all the above protocols were finalized prior to the release of the FDA draft guidance "Collection of Race and Ethnicity Data in Clinical Trials" on Jan 2003.

STUDY CD596-MULTIPLE DOSING SUDY

TITLE : Study of tolerance, pharmacodynamic activity and pharmacokinetics of TVP-1012 (PAI) after repeated oral administrations of rising doses of 2, 5 and 10 mg/day (expressed as base) for ten days, in normal healthy volunteers.

This was the first repeated dose study of PAI (N-propargyl-1-R-aminoindan) in humans. Its aim was to evaluate the tolerance, pharmacodynamic activity, and pharmacokinetics of PAI in healthy male volunteers who received repeated oral doses. PAI was administered as its mesylate salt designed as TVP-1012. The study employed a randomized, double-blind, placebo-controlled design with three parallel groups; subjects in the first group received 2 mg/day PAI or placebo for 10 days, subjects in the second group received 5 mg/day PAI or placebo for 10 days and subjects in the third group received 10 mg/day PAI or placebo.

OBJECTIVES : The aims of the study were :

- to evaluate clinical and biological tolerance,
- to evaluate pharmacodynamic activity (on platelet MAO-B activity, catecholamines, their metabolites and 5-HT urine levels and psychometric tests),
- to evaluate pharmacokinetic parameters,

of TVP-1012 (PAI), after repeated oral administration of rising doses of 2, 5 and 10 mg/day (expressed as base) for 10 days, in normal healthy volunteers.

EXPERIMENTAL

DESIGN

: Double blind, placebo-controlled study, randomized with regard to placebo. Subjects were allocated to three parallel groups : in each group, six subjects received TVP-1012 (PAI) and two subjects received a placebo for 10 days (D1 to D10).

- Group A : 6 subjects received 2 mg TVP-1012 per day for 10 days and 2 subjects received placebo for 10 days
- Group B : 6 subjects received 5 mg TVP-1012 per day for 10 days and 2 subjects received placebo for 10 days
- Group C : 6 subjects received 10 mg TVP-1012 per day for 10 days and 2 subjects received placebo for 10 days

The day (D0) before the first day of the repeated administration, all subjects received a placebo and references for psychometric tests and catecholamines, their metabolites and 5-HT urine levels were determined.

All subjects were non smokers

Demographic Data

	MEAN	S.D	MIN.	MAX.
AGE (year)	24.5	3.4	18	30
WEIGHT (kg)	71.98	9.11	54.8	89.8
HEIGHT (cm)	178.4	6.4	165	190

Dose Selection

Doses of 2, 5 and 10 mg were chosen on the basis of animal pharmacology and toxicology data and on the basis of tolerance and pharmacodynamic data (platelet MAO-B activity inhibition) after single doses (1, 2, 5, 10 and 20 mg) in healthy volunteers.

Sample Collection and Handling

Blood samples for PAI and AI plasma determinations were collected at the following times on day 1 : 0 (before administration), 0.17, 0.33, 0.50, 0.75, 1.00, 1.50, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 16.00 and 24.00 hours after administration ; then on days 5, 6, 9 : just before daily morning administration and on day 10 : 0 (before administration), 0.17, 0.33, 0.50, 0.75, 1.00, 1.50, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after administration. Each blood sample was drawn by direct venipuncture. Each sample volume was 10 ml and was collected into two separate glass tubes, containing dry heparine —
 — . Samples were centrifuged at 4° C at 1 100 g for 10 minutes immediately after collection. Plasma was rapidly transferred to two glass tubes, stoppered (airtight) and stored at minus 20 degrees Celsius (-20°C) until PAI and AI plasma level determination.

Blood samples for platelet MAO-B activity evaluation was collected each day from Day 1 to Day 10, at the following times: T0 (before administration), and 2.0 hours after administration, on Day 11, 24 hours after the last administration and 3, 7, 10 and 14 days after the last administration (Day 13, Day 17, Day 20 and Day 24). Each blood sample was drawn by direct venipuncture without suction. Each sample volume was 7 ml and was collected into two 5 ml polypropylene tubes containing 0.5 ml 0.13 M sodium citrate each. Samples was centrifuged at 180 g for 10 minutes (room temperature) immediately after collection and the supernatant (platelet-rich plasma, PRP) was transferred to clean plastic tubes and centrifuged at 2000 g for 10 minutes (4°C). The platelets plugs obtained by centrifugation of the PRP was washed once by resuspension in 0.5 ml 0.3 M sucrose and recentrifuged at 2000 g for 10 minutes. The washed platelet plug was frozen at minus 20 degrees Celsius (-20°C) until determinations.

Urine samples for catecholamines (5-HT, 5-HIAA, dopamine, DOPAC, HVA) determination was collected on Day 0 and Day 1 during the following period : 0-24 hours after administration, on Day 10 during the following periods : 0-24, 24-48 and 48-72 hours after administration. Urinary volume and pH were measured for each sample ; 100 ml aliquots were collected and deep-frozen until determination of urinary levels.

Pharmacodynamic Evaluation

Pharmacodynamic activity was evaluated by determination of the platelet MAO-B activity, catecholamines urines levels and psychometric tests.

Analytical Methods

Bioanalytical Methods-

The study dates are as follows :

Initiation of clinical phase: 12/11/1992
 Completion of clinical phase: 4/02/1993
 Initiation of analytical phase: 1/03/1993
 Completion of analytical phase: 13/05/1993

Total sample storage time was 6 months.

Plasma

Parameter	PAI	AI
Method	GC/MS	GC/MS
Sensitivity/LOQ	0.25 ng/ml	0.5 ng/ml
Linearity (Standard curve samples)	0.25-10 ng/ml	0.5-10 ng/ml

Quality Control (QC) Samples	0.4, 2.5, 7.5 ng/ml	0.75, 2.5, 7.5 ng/ml
Precision of Standards (%CV)	7.8% @ 0.25 ng/ml 3.48% @ 10 ng/ml	5.8% @ 0.5 ng/ml 2.7% @ 10 ng/ml
Precision of QC Samples (%CV)	10% @ 0.4 ng/ml 7.7% @ 7.5 ng/ml	6.3% @ 0.75 ng/ml 4.11% @ 7.5 ng/ml
Accuracy of Standards (%)		
Accuracy of QC Samples (%)	100% @ 0.40 ng/ml 95.2% @ 7.5 ng/ml	105% @ 0.75 ng/ml 107% @ 7.5 ng/ml

Catecholamine measurement

Measurement of serotonin (5 HT), 5 HIAA, dopamine, DOPAC and HVA urinary concentrations was carried out using a high performance liquid chromatography with electrochemical detection in the oxidative mode.

Pharmacokinetic Evaluation

C_{max} is the maximal plasma concentration measured and t_{max} is the time to reach this concentration.

The experimental areas under the curves, AUC_{0-t} , were calculated according to the linear trapezoidal rule.

For PAI, the experimental area under the curves, AUC_{0-24h} , was calculated as follows :

$$AUC_{0-24h} = AUC_{0-t} + \Delta AUC$$

where :

$$\Delta AUC = C_1 \times \frac{(t_2 - t_1)}{2} \quad (2)$$

where C_1 is the last detectable concentration, t_1 the time on C_1 and t_2 the time immediately following t_1 (when $t_1 \neq 24$ h).

The terminal half-life, $t_{1/2}$, was evaluated according to the equation :

$$t_{1/2} = \frac{0.693}{k_e}$$

The renal clearance, Cl_r , was calculated for unchanged drug, after oral administration according to the following relation :

$$Cl_r = \frac{A_e}{AUC}$$

A_e is the total amount of drug excreted unchanged in the urine and the fraction of oral dose excreted unchanged, f_e , was calculated as follows :

$$f_e = \frac{A_e}{Dose} \times 100$$

RESULTS

Summary of PAI pharmacokinetic parameters mean \pm sd

	2 mg	5 mg	10 mg
C_{max} D1 (ng.ml ⁻¹)	9.55 (1.62)	26.43 (10.89)	56.13 (18.27)
C_{max} # D1 (ng.ml ⁻¹)	-	10.57 (4.36)	11.23 (3.65)
C_{max} D10 (ng.ml ⁻¹)	17.55 (3.51)	45.78 (19.26)	86.54 (27.47)
C_{max} # D10 (ng.ml ⁻¹)	-	18.31 (7.70)	17.31 (5.49)
t_{max} D1 (h)	0.36 (0.16)	0.51 (0.31)	0.54 (0.28)
t_{max} D10 (h)	0.40 (0.20)	0.49 (0.15)	0.51 (0.29)
AUC _{0-∞} D1 (ng.ml ⁻¹ .h)	5.85 (1.92)	18.61 (5.02)	53.53 (14.51)
AUC _{0-∞} # D1 (ng.ml ⁻¹ .h)	-	7.45 (2.01)	10.71 (2.90)
AUC ₀₋₂₄ D10 (ng.ml ⁻¹ .h)	20.02 (4.81)	55.25 (12.23)	116.27 (19.83)
AUC ₀₋₂₄ # D10 (ng.ml ⁻¹ .h)	-	22.10 (4.89)	23.25 (3.97)
$t_{1/2}$ D1 (h)	0.31 (0.10)	1.03 (0.79)	3.17 (1.51)
$t_{1/2}$ D10 (h)	2.06 (1.14)	3.04 (0.94)	3.50 (1.50)
Cl_r D1 (L.h ⁻¹)	1.11 (0.63)	0.35 (0.20)	0.50 (0.24)
Cl D10 (L.h ⁻¹)	0.56 (0.13)	0.15 (0.07)	0.32 (0.28)
Ae D1 (μg)	6.55 (3.98)	6.16 (3.00)	27.76 (16.85)
Ae D10 (μg)	11.46 (5.02)	8.16 (3.73)	35.73 (31.27)

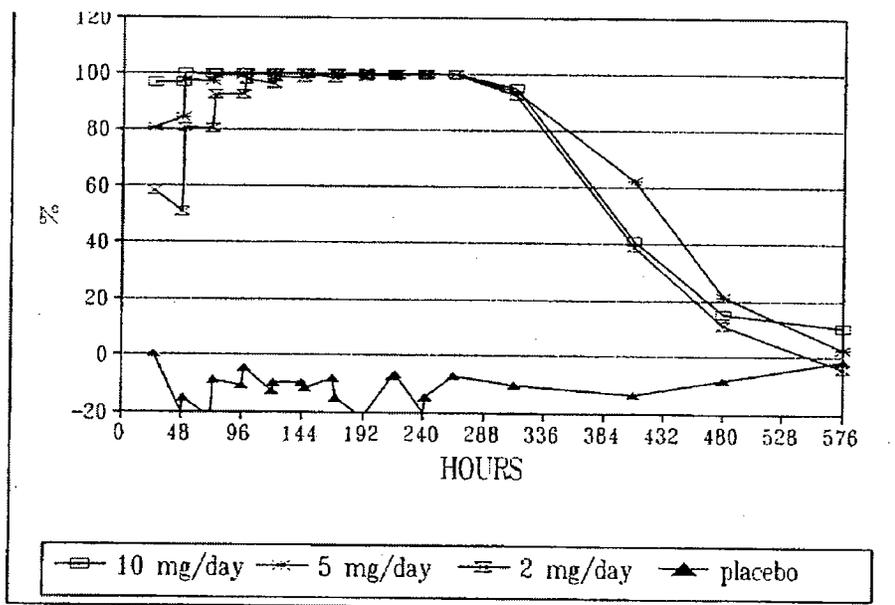
: Normalized to the 2 mg dose

Summary of AI pharmacokinetic parameters mean \pm sd

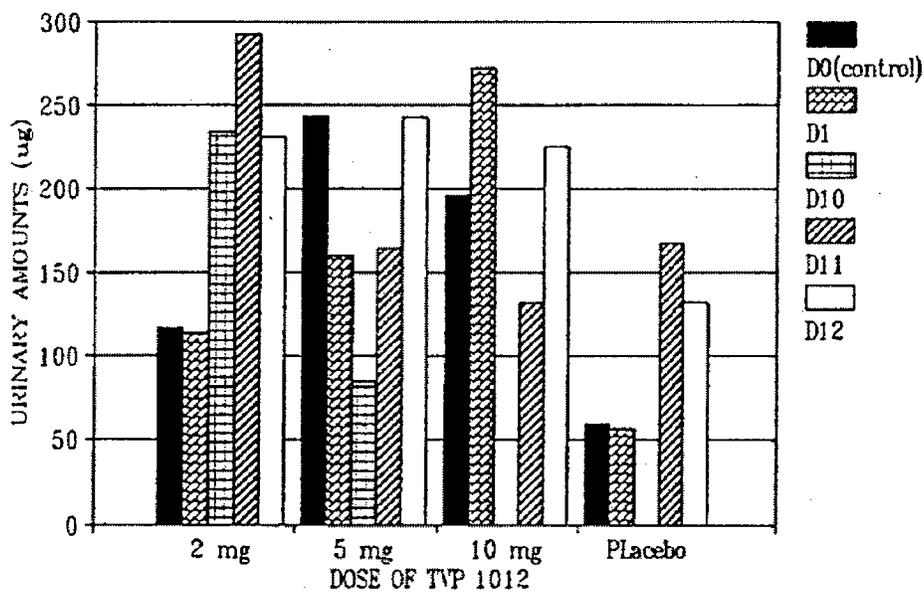
	2 mg	5 mg	10 mg
C_{max} D1 (ng.ml ⁻¹)	2.92 (0.40)	7.81 (1.02)	19.24 (2.91)
C_{max} # D1 (ng.ml ⁻¹)	-	3.12 (0.41)	3.85 (0.58)
C_{max} D10 (ng.ml ⁻¹)	5.12 (0.83)	14.86 (5.50)	27.00 (4.17)
C_{max} # D10 (ng.ml ⁻¹)	-	5.94 (2.20)	5.40 (0.83)
C_{min} D10 (ng.ml ⁻¹)	0.93 (0.51)	3.14 (1.38)	6.00 (1.06)
C_{min} # D10 (ng.ml ⁻¹)	-	1.26 (0.55)	1.20 (0.21)
t_{max} D1 (h)	1.00 (0.52)	2.04 (1.25)	1.75 (0.27)
t_{max} D10 (h)	1.42 (0.38)	2.25 (0.88)	1.67 (0.75)
AUC _{0-∞} D1 (ng.ml ⁻¹ .h)	46.39 (8.43)	137.90 (24.01)	333.44 (70.36)
AUC _{0-∞} # D1 (ng.ml ⁻¹ .h)	-	55.16 (9.60)	66.69 (14.07)
AUC ₀₋₂₄ D10 (ng.ml ⁻¹ .h)	65.62 (10.69)	181.06 (40.76)	370.62 (56.84)
AUC ₀₋₂₄ # D10 (ng.ml ⁻¹ .h)	-	72.42 (16.30)	74.12 (11.37)
t1/2 D1 (h)	11.61 (1.79)	11.92 (2.74)	11.28 (1.72)
t1/2 D10 (h)	11.57 (1.34)	11.48 (1.78)	10.41 (2.24)
Cl _r D1 (L.h ⁻¹)	2.93 (1.28)	1.31 (0.92)	2.89 (1.32)
Cl _r D10 (L.h ⁻¹)	4.38 (1.69)	1.36 (0.93)	3.85 (1.73)
Ae D1 (μg)	130.42 (54.11)	185.90 (139.71)	904.63 (374.46)
Ae D10 (μg)	281.56 (94.45)	226.34 (117.52)	1372.86 (439.30)

: Normalized to the 2 mg dose

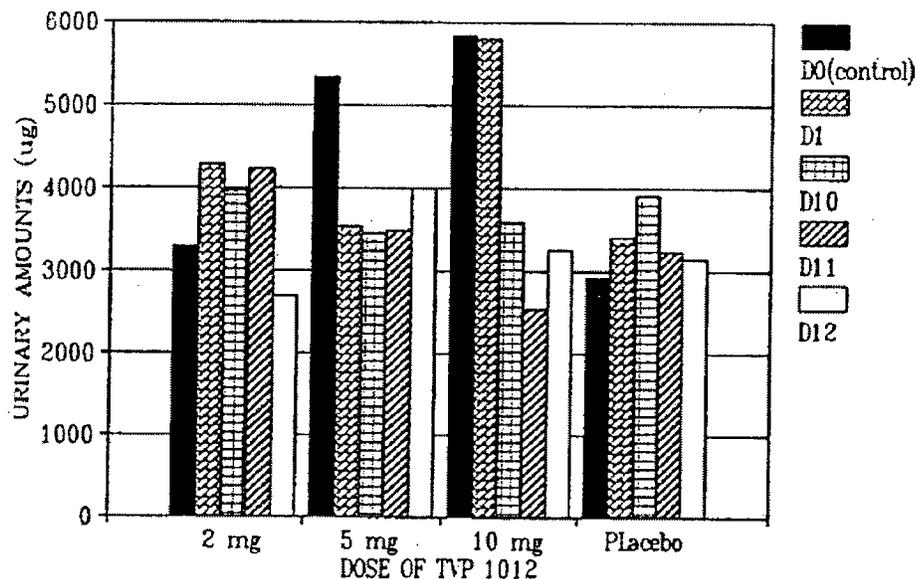
Inhibition of MAO-B activity in platelets by rasagiline as function of dose.



Mean urinary amounts of dopamine, 5-HIAA and HVA are presented in the figures below.



Mean Urinary Amounts of HVA



- QTc on day 2 (decrease with 0 mg, 2 mg, 5 mg, 10 mg). These variations were observed after placebo administration as well as after TVP-1012 administration. Values of QTc remained within normal range. These variations of QTc are considered by the investigator to be not clinically relevant.
- QTc on day 10 (decrease with 0 mg, 2 mg, 5 mg, 10 mg). These variations were observed after placebo administration as well as after TVP-1012 administration. Values of QTc remained within normal range. These variations of QTc are considered by the investigator to be not clinically relevant.

An inhibition of MAO-B platelet activity was observed at all PAI doses evaluated (2, 5 and 10 mg). This inhibition increased with the dose and was complete at the 5 mg and 10 mg PAI doses.

After administration of TVP-1012, the amounts of dopamine, 5-HIAA and HVA excreted in urine fluctuated depending on the day of collection. These fluctuations were not clearly correlated with the dose of TVP-1012 nor with the effect of the drug on the MAO-B activity. On the other hand environmental and physiological conditions probably influenced more markedly the overall excretion of these compounds than the inhibition of the MAO-B activity could do it.

This study has shown that after multiple dose administration of TVP-1012 (2, 5 and 10 mg per day), the maximum plasma concentrations of unchanged drug were almost doubled at steady state, whereas the AUC_{0-24} at steady state was twice or three times higher than after the first administration. Because the renal clearance of the unchanged drug is weak, its decrease at steady state is expected to moderately influence the bioavailability of the unchanged drug.

Subsequently one can postulate that the increase of the AUC at steady state might be due to an inhibition of the metabolic clearance of the unchanged drug after multiple dose administration. With regard to the main metabolite of PAI, it turns out that, with the 2 mg/day dose, the PAI to AI ratio increases from 0.13 on day 1 to 0.31 on day 10 (see Table 2.77). This suggests that the clearance of the metabolite might be increased at steady state, as exemplified by the increase of the renal clearance of AI observed on day 10 after 2 mg and 10 mg.

Trough values of PAI measured on day 5, 6 and 10

**APPEARS THIS WAY
ON ORIGINAL**

Relation Pharmacodynamic activity and pharmacokinetic:

A significant correlation between log C_{max} of PAI and percentage of inhibition of MAO-B was shown. The correlation was also found for log C_{max} of AI.

Study CD596 - Summary Results of the Assessment of Dose Proportionality Using the Power Model Analysis

PK Parameter	Day	AUC	β Estimate (95% CI)*	R- Estimate of the Increase in Doses Required for Doubling the AUC (95% CI)**
AI	1	AUC0-Inf	1.22 (1.07,1.37)	1.76 (1.66,1.91)
AI	10	AUC0-24	1.08 (0.94,1.21)	1.90 (1.77,2.09)
PAI	1	AUC0-Inf	1.38 (1.17,1.59)	1.65 (1.55,1.81)
PAI	10	AUC0-24	1.10 (0.95,1.26)	1.88 (1.74,2.08)

* ANOVA (SAS GLM Procedure) - SAS output is given in Attachment 1.

The results of the analysis demonstrate dose proportionality in AUC for PAI and AI on Day 10, with 95% CI values of 0.95-1.26 for PAI and 0.94-1.21 for AI. This proportionality is also demonstrated by the estimate of the increase in doses required for doubling the AUC (R) and its CI's which included 2 for both PAI and AI. The wide range of the CI indicates the high data variability and although the statistics support dose proportionality individual subjects could still show a greater than expected exposure at a given dose at steady-state and the CI for doubling just barely includes 2. The overall trend was for clearance to decrease with length of exposure.

STUDY TVP-1012/231-Tolerability of TVP-1012, a Novel MAO-B Inhibitor in PD patients

INTRODUCTION

TVP-1012 (Rasagiline Mesylate)

N-propargyl-1 (R)-aminoindan (PAI) is a potent, selective nonreversible inhibitor of MAO-B. In this document, the mesylate salt of PAI is referred to by using the code name "TVP-1012." The major metabolite of TVP-1012 is 1-(R)-aminoindan (AI), which is devoid of amphetamine-like properties but can synergize the dopaminergic action of TVP-1012.

OBJECTIVES

Primary Objective

The primary objective of this study was to evaluate the general safety and tolerability of TVP-1012 monotherapy in Parkinson's disease patients who were not on levodopa/carbidopa. Patients were evaluated during a dose titration period of 3 weeks, followed by a 7-week dosing period with a daily dose of 1 mg, 2 mg or 4 mg of TVP-1012 or placebo.

DEMOGRAPHIC CHARACTERISTICS

Parameter	TVP-1012			Placebo (n=13)
	1mg/day (n=15)	2mg/day (n=14)	4mg/day (n=14)	
Age (years)				
Mean(±SD)	59.3 (8.6)	60.3 (7.2)	62.0 (9.7)	64.8 (9.4)
Minimum-Maximum	47 - 73	46 - 69	42 - 75	44 - 75
Sex [n (%)]				
Male	10 (66.7)	10 (71.4)	8 (57.1)	10 (76.9)
Female	5 (33.3)	4 (28.6)	6 (42.9)	3 (23.1)
Race [n (%)]				
Caucasian	15 (100.0)	14 (100.0)	9 (64.3)	13 (100.0)
Black/Other	0	0	5 (35.7)	0
Weight (lbs)				
Mean(±SD)	170.8 (43.2)	178.0 (29.1)	160.4 (42.3)	198.7 (47.5)
Minimum-Maximum	113.0 - 236.0	125.0 - 224.0	98.5 - 259.5	126.0 - 308.0
Height (in.)				
Mean(±SD)	66.8 (3.5)	68.9 (3.1)	66.3 (4.2)	67.5 (3.3)
Minimum-Maximum	61.5 - 72.0	64.0 - 75.0	60.0 - 72.0	61.5 - 71.0

BASELINE DISEASE CHARACTERISTICS

Parameter	TVP-1012			Placebo (n=13)
	1mg/day (n=15)	2mg/day (n=14)	4mg/day (n=14)	
Duration of Disease (yrs)				
Mean(±SD)	1.3 (2.6)	0.4 (0.8)	0.3 (0.5)	0.8 (1.0)
Minimum-Maximum	0 - 10	0 - 3	0 - 1	0 - 3
Total UPDRS Score				
Mean(±SD)	18.2 (6.5)	21.0 (5.2)	20.2 (7.4)	17.7 (7.9)
Minimum-Maximum	9 - 29	12 - 31	10 - 33	6 - 31
Baseline CGIC Severity of Illness				
Mean(±SD)	2.9 (0.5)	2.7 (0.5)	2.7 (0.6)	2.9 (0.5)
Minimum-Maximum	2 - 4	2 - 4	1 - 3	2 - 4
Baseline Hoehn & Yahr Stage				
Mean(±SD)	1.5 (0.4)	1.6 (0.4)	1.6 (0.4)	1.5 (0.4)
Minimum-Maximum	1 - 2	1 - 2	1 - 2	1 - 2
Baseline Schwab & England AODL Score				
Mean(±SD)	90 (7.6)	89.3 (2.7)	88.6 (6.6)	89.2 (6.4)
Minimum-Maximum	70 - 100	80 - 90	70 - 100	80 - 100
Total Beck Inventory Score*				
Mean±SD	6.0 (3.3)	5.9 (4.8)	5.7 (3.6)	3.5 (2.6)
Minimum-Maximum	3 - 11	0 - 17	1 - 12	0 - 9

*Determined at Screening

Smokers were not excluded from the study. Case report form (CRF) smoking categories were 0, 1-10 and above 10 cigarettes per day. As demonstrated in Table 2, 2/15 (13.3%), 1/14 (7.1%) and 3/14 (21.4%) of the patients in the rasagiline 1, 2 and 4 mg groups, respectively smoked. Smokers were not included in the placebo group.

Table 1A. No. of Cigarettes/Day by Treatment Group

TVP-1012/231 No. of Cigarettes/Day	1 mg (N=15)	2 mg (N=14)	4 mg (N=14)	Placebo (N=13)				
0	13	86.7	13	92.9	11	78.6	13	100.0
1-10	0	0	0	0	1	7.1	0	0
>10	2	13.3	1	7.1	2	14.3	0	0

Cross Reference: Appendix 11.2 of the clinical study report (page 1528).

Analytical

The study was conducted from February 16, 1995-September 12, 1995.

Samples were analyzed from 12 December 1995 and ended on 16 December 1995.

Total sample storage time was 10 months.

Plasma

Parameter	PAI	AI
Method	GC/MS	GC/MS
Sensitivity/LOQ	0.25 ng/ml	0.25 ng/ml
Linearity (Standard curve samples)	0.25-25 ng/ml	0.5-25 ng/ml
Quality Control (QC) Samples	0.75, 2.5, 22 ng/ml	0.75, 2.5, 7.5 ng/ml
Precision of Standards (%CV)	4.5%@0.25 ng/ml 0.9%@25 ng/ml	1.7%@ 0.25 ng/ml 1.4%@ 25ng/ml
Precision of QC Samples (%CV)	3.7%@ 0.75 ng/ml 1.07%@ 22 ng/ml	4.5%@ 0.75 ng/ml 0.7%@ 22 ng/ml
Accuracy of Standards (%)	99.5%@ 0.25 ng/ml 99.7%@ 25 ng/ml	99.7%@ 0.25 ng/ml 99.1%@ 25 ng/ml
Accuracy of QC Samples (%)	97%@ 0.75 ng/ml 97%@ 22 ng/ml	99%@ 0.75 ng/ml 98%@ 22 ng/ml

The PAI and AI components were stable for 8 months when stored at -20 °C

Statistics

Because the primary objective of this study was to evaluate the general safety and

tolerability of TVP-1012, safety findings were based on the following sources:

- Physical Examination findings: descriptive statistics tables were supplied for mean, maximum, minimum, standard deviation and total sample size.
- Adverse Experiences: incidence rates were summarized into tables based on treatment, gender, causality, maximum severity and duration of treatment.
- Vital Signs: information recorded at each visit was tabulated. In addition, patient profile displays were generated for review of each patient's vital sign status from visit to visit, and the changes of values from baseline to end-point (last visit).
- Laboratory parameters: generated as patient profiles. Shift and grade change analyses were applied to examine potential treatment effects on each laboratory parameter.
- 24-hour ambulatory blood pressure monitoring and the home blood pressure diary: these were evaluated to show the relationship between treatment effects for baseline, first dose and Week 10 visits.

Platelet MAO-B inhibition was presented without summarization. The Unified Parkinson Disease Rating Scale (UPDRS) was summarized as the mean of the total UPDRS at each study visit for each treatment group as well as the difference between the mean total score at each visit and the mean at baseline.

In addition, the UPDRS was categorized into three components, as follows:

- I. Mentation, Behavior and Mood
- II. Activities of Daily Living
- III. Motor Examination

RESULTS

PK DATA

	DOSE (mg)	PAI		AI	
		AUC _{0-∞} ng.h/mL	C _{max} ng/mL	AUC _{0-t} ng.h/mL	C _{max} ng/mL
Overall	1	11.83	5.91	7.87	2.40
	2	24.34	12.86	15.25	4.63
	4	46.71	21.67	33.30	10.17
Females	1	13.39	6.07	10.37	3.18
	2	28.79	17.91	17.83	5.35
	4	51.77	23.82	40.28	12.47
Males	1	11.05	5.83	6.62	2.01
	2	22.36	10.61	14.10	4.31
	4	42.37	20.05	28.06	8.44

Source: Appendix 17.1

*AUC_{0-∞} was calculated for PAI since regression analysis and previous studies suggested that a monoexponential decline in PAI concentrations was probable. AUC_{0-t} was calculated for AI because no regression estimate of terminal slope was possible.

Patient No.	Dose	Visit	MAO-B Activity (nmoles/mg/h)
104	Placebo	1	1.37
		2	1.38
		4	ND
		10 Endpoint	43.98
		11 Post-Drug	11.25
		13 Post-Drug	5.02
109	1 mg	1	0.27
		2	0.05
		4	0.76
		10 Endpoint	0.11
		11 Post-Drug	0.59
		12 Post-Drug	1.78
110	2 mg	1	0.38
		2	0.05
		4	0.00
		10 Endpoint	0.02
		11 Post-Drug	0.78
		12 Post-Drug	1.49
111	4 mg	1	ND
		2	0.05
		4	0.30
		10 Endpoint	0.13
		11 Post-Drug	3.35
		12 Post-Drug	1.24
112	Placebo	1	0.97
		2	1.18
		4	1.68
		10 Endpoint	0.73
		11 Post-Drug	1.29
		12 Post-Drug	1.67

ND = Not Done
Source: Appendix 19.1

From the limited available data it can be seen that platelet MAO-B is inhibited by TVP-1012 and that the activity increases at the final evaluation 6 weeks after the last dose of study drug.

**APPEARS THIS WAY
ON ORIGINAL**

Treatment Group	1 mg/day	2 mg/day	4 mg/day	Placebo
	Mean ± (SD) Mean Diff. ^a ± (SE)	Mean ± (SD) Mean Diff. ± (SE)	Mean ± (SD) Mean Diff. ± (SE)	Mean ± (SD) Mean Diff. ± (SE)
N	15 ^b	14	14	13
Total				
Baseline	18.2 ± (6.5)	21.0 ± (5.2)	20.2 ± (7.4)	17.7 ± (7.9)
Endpoint	16.4 ± (7.0) -1.8 ± (1.3)	17.4 ± (9.0) -3.6 ± (1.7)	16.6 ± (8.7) -3.6 ± (1.2)	17.2 ± (8.5) -0.5 ± (0.8)
Post-Drug	17.6 ± (8.4) -0.9 ± (1.6)	20.2 ± (10.0) -0.8 ± (1.9)	19.4 ± (11.6) -0.9 ± (2.0)	18.8 ± (9.1) 1.1 ± (1.1)
Mental				
Baseline	1.1 ± (1.0)	1.3 ± (1.7)	1.4 ± (1.5)	0.2 ± (0.6)
Endpoint	0.7 ± (0.8) -0.4 ± (0.2)	1.2 ± (2.0) -0.1 ± (0.3)	0.8 ± (1.1) -0.6 ± (0.3)	0.3 ± (0.8) 0.1 ± (0.1)
Post-Drug	1.0 ± (0.9) -0.1 ± (0.4)	1.6 ± (2.2) 0.3 ± (0.3)	1.2 ± (2.2) -0.1 ± (0.4)	0.5 ± (0.9) 0.2 ± (0.2)
Motor				
Baseline	9.4 ± (3.9)	11.3 ± (3.0)	11.6 ± (3.8)	10.8 ± (4.8)
Endpoint	8.9 ± (3.7) -0.5 ± (0.7)	9.4 ± (4.9) -1.9 ± (1.1)	9.8 ± (4.6) -1.8 ± (0.6)	10.7 ± (4.9) -0.2 ± (0.6)
Post-Drug	9.5 ± (4.9) -0.1 ± (0.8)	10.9 ± (4.0) -0.4 ± (1.1)	11.6 ± (5.5) 0.1 ± (0.7)	11.5 ± (5.4) 0.6 ± (0.9)
ADL				
Baseline	7.7 ± (3.6)	8.4 ± (2.8)	7.3 ± (3.3)	6.6 ± (3.6)
Endpoint	6.9 ± (3.8) -0.9 ± (0.7)	6.7 ± (3.7) -1.7 ± (0.7)	6.0 ± (3.7) -1.3 ± (0.5)	6.2 ± (4.1) -0.4 ± (0.4)
Post-Drug	7.1 ± (3.6) -0.8 ± (0.7)	7.7 ± (4.9) -0.7 ± (0.8)	6.5 ± (5.0) -0.8 ± (1.1)	6.8 ± (3.8) 0.2 ± (0.5)

^a Mean difference between endpoint or post-drug and baseline

^b N = 14 for post-drug results

**APPEARS THIS WAY
ON ORIGINAL**

Time to peak PAI concentrations (C_{max}) was related linearly to dose and to dose corrected for body weight (dose/weight). Linear relationships were evident for male and female patients. Although PAI C_{max} values were slightly to moderately higher in female subjects than in males at each dose, the differences did not differ statistically. PAI plasma concentration AUC increased significantly with dose in the group as a whole and in female and male patient subgroups. PAI AUC divided by dose did not differ among doses (F=2.71, p=0.1085), confirming and supporting linear regression showing dose proportionality. PAI AUC increased linearly with dose overall and for female and male patients (r²=0.8727, p<0.0001 versus r²=0.8428, p<0.0001). PAI AUC tended to be higher in female patients than in male patients, but the differences were not significant. PAI half-life, volume of distribution and clearance were independent of administered dose and did not differ between female and male subjects. Overall, the mean half-life of PAI for the 4 mg dose was 1.34 hours. The mean volume of distribution was 182 L and the mean clearance value was 94.3 L/hour following the 4 mg dose. Mean half-lives were 1.51 ± 0.54 hour versus 1.19 ± 0.23 hour for females and males, respectively for the 4 mg dose; mean volume of distributions were 186 ± 107.4 versus 178.3 ± 70.2 L, respectively and did not differ for female and male subgroups; and mean clearance values were 82.3 ± 24.2 L/hour versus 104.6 ± 39.8 L/hour, respectively, and did not differ between female and male subgroups although the small sample of female patients (n=6) tended to have lower mean clearance values.

The total UPDRS scores at baseline were similar across all treatment groups (range 17.7 to 21). After 10 weeks of study drug administration, the mean difference from baseline for the 1 mg/day group was -1.8, -3.6 for the 2 mg/day group, -3.6 for the 4 mg/day group and -0.5 for those receiving placebo. The most consistent

improvement in total UPDRS across the 10-week treatment period occurred in the 2 mg/day group. Formal statistical analyses of efficacy results were not planned or done. Complete week-by-week results can be found in Appendix I3.1.

The apparent improvement in total UPDRS seen during the 10-week treatment period tended to be lost in the post-drug follow-up period. Six weeks after discontinuation of study drug, the mean difference from baseline for patients receiving 1 mg/day was -0.9; for those receiving 2 mg/day it was -0.8, it was -0.9 for those in the 4 mg/day group, and +1.1 for those receiving placebo.

The on-drug change seen during the 10-week dosing period was primarily attributable to decreases in the motor and ADL subcomponents of the UPDRS. The tendency for UPDRS scores to return to baseline values in the post-drug evaluation period primarily reflected an increase in motor subcomponent scores.

Comment:

1. The subjects were not delineated by smoking status for the data initially submitted for study 232 and were subsequently analyzed using population PK by the firm in study Tempo 232.

STUDY TVP-1012/112-Dose finding study in PD patients on Chronic Levodopa

A Multicenter Tolerability Dose Finding Study of TVP-1012 in Parkinsonian Patients on Chronic Levodopa Therapy

Objectives

To evaluate the safety and tolerability of rasagiline, following a 12-week dosing period with a daily dose of up to 2 mg, in Parkinson's disease patients on chronic levodopa/carbidopa or levodopa/benserazide therapy.

Secondary objectives included the evaluation of pharmacokinetic and pharmacodynamic activity and clinical effect of rasagiline.

Methods

Patients had to be diagnosed as having idiopathic Parkinson's disease and to be on chronic levodopa/carbidopa or levodopa/benserazide therapy for at least six months. The severity of the disease had to be determined according to Hoehn and Yahr staging. The patient population was made up of Parkinson's disease patients who were or were not fluctuating to levodopa therapy. Since it was an early Phase II study, the number of patients to be included in this study was not statistically determined.

Patients were randomized into four groups. Patients on 2 mg/day Rasagiline were brought gradually to the desired dose.

- ⊆ Group I was treated with 0.5 mg/day rasagiline for 12 weeks.
- ⊆ Group II was treated with 1 mg/day rasagiline for 12 weeks
- ⊆ Group III was treated with 1 mg/day rasagiline for one week and 2 mg/day rasagiline for 11 weeks.
- ⊆ Group IV was treated with placebo throughout the study period.

Patients were evaluated for vital signs, laboratory values, concomitant medications and adverse experiences at each visit and at follow-up visits.

Table 1: Dose and Dosage Schedule

Treatment Group/ Dosage	Placebo	0.5 mg/day	1 mg/day	2 mg/day
Week 1	-	0.5 mg	1 mg	1 mg
Weeks 2-12	-	0.5 mg	1 mg	2 mg

▷ Pharmacodynamics - Platelet MAO-B Inhibition

Blood for platelet MAO-B activity was collected at Visits 1 (baseline), 2 (Week 1), 3 (Week 2), at the termination visit and at the two follow-up visits in eight

patients at two study centers.

⊆ **Pharmacokinetics - Blood Levels of Rasagiline (PAI) and Aminoindan (AI)**

Blood samples for rasagiline and its metabolite (AI) level determinations were collected at Visits 2 (Week 1), 3 (Week 2), 5 (Week 6), at termination and at the first follow-up visit in 32 patients at five study centers. On visit days, patients were required to administer the study drug at the clinic. Blood was drawn before and half-an-hour after administration of the medication. At the termination visit, blood samples were also taken at 2 and 4 hours post drug administration. Samples were drawn by direct venipuncture, 10 ml each and were to be kept frozen until analysis was performed. The procedure of sample **handling was described by the firm.**

Clinical Assessment

▷ **Unified Parkinson's Disease Rating Scale (UPDRS)**

This rating scale was employed to assess the symptomatic severity of the disease. Quantitating the severity provides the means to determine the clinical status of the patient and the effect of the study drug.

Clinical assessment of this sort is divided into several categories:

- Measurements of mentation, behavior and mood (composed of 4 items).
- Activity of daily living when "on" and when "off" (composed of 13 items).
- Motor examination (composed of 27 items).
- Complications of therapy (dyskinesia, clinical fluctuations, other complications)
- Modified Hoehn and Yahr when "on" and when "off"
- Schwab and England Activities of daily living when "on" and when "off" (%).

▷ **Clinical Global Impression of Change (CGIC)**

This scale was used to determine whether the effect of the study drug was sufficient to allow its detection in an interview conducted by an experienced clinician familiar with the manifestations of Parkinson's disease. The assessment of this parameter was to reflect the change from the baseline interview rather than the change from any other reference point.

The rating scale used for this parameter is composed of three items: severity of illness (Score 0 to 6, from no symptoms to severe disease), global improvement (Score -3 to 3) and efficacy index (Score 1 to 16, from good to bad index). The rating is in order of increased severity. CGIC was assessed at each visit.

Table 2 A. Summary demographics for study subjects

TVP-1012/112		PLACEBO	TVP-1012 0.5MG	TVP-1012 1MG	TVP-1012 2MG
Gender					
Male	N	7	6	12	14
	%	53.8	28.6	66.7	77.8
Female	N	6	15	6	4
	%	46.2	71.4	33.3	22.2
Height (cm)	N	13	21	18	18
	MEAN	165.5	165.9	168.7	168.4
	STD	8.1	7.5	8.1	5.0
	MIN	154.0	156.0	151.0	159.0
	MAX	182.0	184.0	187.0	175.0
Weight (Kg)	N	13	21	18	18
	MEAN	70.2	67.4	71.2	70.9
	STD	8.7	10.5	9.4	12.1
	MIN	54.0	48.0	58.0	53.0
	MAX	88.0	90.0	89.0	92.0
Age (yrs)	N	13	21	18	18
	MEAN	57.0	57.4	56.7	56.6
	STD	4.9	4.9	6.4	7.5
	MIN	47.0	46.0	42.0	44.0
	MAX	64.0	64.0	64.0	65.0

Analytical

The study was conducted from January 29, 1996 August 10th, 1996.

Samples were analyzed on: 26-29-May-1997 and 30-Jun-1997.

The second set-up of the GC/MS method was conducted on: 09-10-Dec-1997 and 12-Dec-1997.

The second set of study samples was analyzed on: 15-19 and 22-24-Dec-1997. The total sample storage time was 2 years.

Plasma

Parameter	PAI	AI
Method	GC/MS	GC/MS
Sensitivity/LOQ	0.25 ng/ml	0.25 ng/ml

Linearity (Standard curve samples)	0.25-10 ng/ml	0.5-10 ng/ml
Quality Control (QC) Samples	0.4, 2.5, 7.5 ng/ml	0.75, 2.5, 7.5 ng/ml
Precision of Standards (%CV)	2.9% @ 0.25 ng/ml 1.2% @ 10 ng/ml	1.7% @ 0.5 ng/ml 1.1% @ 10 ng/ml
Precision of QC Samples (%CV)	6.8% @ 0.40 ng/ml 3.4% @ 7.5 ng/ml	4.8% @ 0.75 ng/ml 3.4% @ 7.5 ng/ml
Accuracy of Standards (%)	98.9% @ 0.25 ng/ml 99.7% @ 10 ng/ml	98.1% @ 0.25 ng/ml 95.5% @ 10 ng/ml
Accuracy of QC Samples (%)	92.2% @ 0.75 ng/ml 96.3% @ 22 ng/ml	96% @ 0.75 ng/ml 97% @ 22 ng/ml

The PAI and AI components were stable for 2 yrs when stored at -20 °C

RESULTS

Table 3A. Descriptive Statistics of Total UPDRS Score

TVP-1012/112	PLACEBO					TVP-1012 0.5MG					TVP-1012 1MG					TVP-1012 2MG					
	N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX	
Baseline																					
TOTAL UPDRS (ON)	13	34.7	19.3	11.0	81.0	21	39.3	21.1	13.0	99.0	18	30.3	16.0	6.0	70.0	18	34.8	20.7	9.0	95.0	
Change from Baseline TOTAL UPDRS (ON)	13	0.0	0.0	0.0	0.0	21	0.0	0.0	0.0	0.0	18	0.0	0.0	0.0	0.0	18	0.0	0.0	0.0	0.0	
Week 12																					
TOTAL UPDRS (ON)	13	29.3	18.1	5.0	86.0	21	31.6	21.8	7.0	95.0	18	26.3	18.1	4.0	84.0	18	27.8	24.2	7.0	101	
Change from Baseline TOTAL UPDRS (ON)	13	-5.4	9.0	-26	6.0	21	-7.7	10.8	-28	18.0	18	-4.0	8.1	-16	14.0	18	-7.1	11.3	-30	12.0	
Week 18 (FU2)																					
TOTAL UPDRS (ON)	12	34.3	22.8	4.0	81.0	21	32.9	22.3	4.0	97.0	18	27.3	15.9	1.0	65.0	18	32.6	25.1	4.0	101	
Change from Baseline TOTAL UPDRS (ON)	12	0.4	6.3	-11	11.0	21	-6.4	12.1	-29	18.0	18	-3.0	6.7	-16	7.0	18	-2.3	9.8	-17	22.0	

Blood samples were drawn from 32 patients, for determination of rasagiline and its major metabolite aminoindan, prior to drug administration and 30 minutes thereafter on the visit day of Weeks 1, 2, 6, 12 and 14 (first follow-up visit). In addition, at Week 12 (termination visit) blood samples were also taken at 2 and 4 hours post drug administration. Almost no detectable levels of rasagiline could be observed in the plasma of the patients prior to drug administration, irrespective of the dose consumed, throughout the course of the trial. This finding indicates that **no accumulation of the study drug occurs.**

Table 4A. Plasma Concentrations of Rasagiline before and 30 minutes after drug administration

TVP-1012/112		PLACEBO		TVP-1012 0.5MG		TVP-1012 1MG		TVP-1012 2MG	
		PAI Plasma Level at 0h (ng/ml)	PAI Plasma Level at 0.5h (ng/ml)	PAI Plasma Level at 0h (ng/ml)	PAI Plasma Level at 0.5h (ng/ml)	PAI Plasma Level at 0h (ng/ml)	PAI Plasma Level at 0.5h (ng/ml)	PAI Plasma Level at 0h (ng/ml)	PAI Plasma Level at 0.5h (ng/ml)
Visit No.									
Week 1	N	6	6	9	9	6	6	9	9
	MEAN	0.0	0.0	0.0	4.2	0.0	4.4	0.1	7.2
	STD	0.0	0.0	0.0	5.0	0.0	2.9	0.4	5.0
	MIN								
	MAX								
Week 2	N	6	6	8	8	6	6	9	9
	MEAN	0.0	0.0	0.1	2.9	0.0	6.1	0.0	17.1
	STD	0.0	0.0	0.2	1.2	0.0	2.8	0.1	5.8
	MIN								
	MAX								
Week 6	N	6	6	10	10	6	6	9	9
	MEAN	0.0	0.0	0.2	4.4	0.0	9.2	0.1	17.0
	STD	0.0	0.0	0.5	2.5	0.0	5.8	0.2	11.7
	MIN								
	MAX								
Week 12	N	6	6	10	10	8	7	9	9
	MEAN	0.0	0.0	0.0	4.1	1.0	8.6	0.0	14.8
	STD	0.0	0.0	0.0	2.7	2.6	2.0	0.0	10.1
	MIN								
	MAX								
Week 14 (FU1)	N	6	0	10	0	7	0	9	0
	MEAN	0.0	.	0.0	.	0.0	.	0.0	.
	STD	0.0	.	0.0	.	0.0	.	0.0	.
	MIN								
	MAX								

Table 5 A. Plasma Concentrations of Rasagiline two and four hours after drug administration

TVP-1012/112		PLACEBO		TVP-1012 0.5MG		TVP-1012 1MG		TVP-1012 2MG	
		PAI Plasma Level at 2h (ng/ml)	PAI Plasma Level at 4h (ng/ml)	PAI Plasma Level at 2h (ng/ml)	PAI Plasma Level at 4h (ng/ml)	PAI Plasma Level at 2h (ng/ml)	PAI Plasma Level at 4h (ng/ml)	PAI Plasma Level at 2h (ng/ml)	PAI Plasma Level at 4h (ng/ml)
Visit No.									
Week 12	N	6	6	9	10	6	6	8	8
	MEAN	0.0	0.0	0.9	0.5	1.6	0.7	4.0	1.8
	STD	0.0	0.0	0.3	0.7	0.9	0.4	1.4	0.6
	MIN								
	MAX								

Table 6 A. Mean calculated Rasagiline Pharmacokinetic Parameters

Pharmacokinetic Parameter	Unit mg/day	Sex	Values ^a		
			0.5 mg/day (n=6♀, 3♂)	1.0 mg/day (n=2♀, 4♂)	2.0 mg/day (n=2♀, 6♂)
T _{max}	hours	Female	0.5	0.5	0.5
		Male	1.0 ± 0.9	0.5	0.8 ± 0.6
		F+M	0.7 ± 0.5	0.5	0.7 ± 0.6
C _{max}	ng/mL	Female	5.3 ± 2.7	9.4 ± 1.3	28.1 ± 11.2
		Male	2.9 ± 1.6	8.0 ± 2.6	10.6 ± 3.5
		F+M	4.5 ± 2.6	8.5 ± 2.2	14.9 ± 10.5
C _{max} adjusted to dose of 1 mg/Day	ng/mL	Female	10.5 ± 5.5	9.4 ± 1.3	14.0 ± 5.6
		Male	5.8 ± 3.2	8.0 ± 2.6	5.3 ± 1.8
		F+M	8.9 ± 5.2	8.5 ± 2.2	7.5 ± 5.3
AUC _{0-4h} (=AUC _{last})	ng x hr/mL	Female	7.7 ± 3.0	13.8 ± 2.1	36.1 ± 15.6
		Male	3.8 ± 1.1	11.7 ± 4.1	19.2 ± 4.5
		F+M	6.4 ± 3.1	12.4 ± 3.5	23.5 ± 10.5
AUC _∞	ng x hr/mL	Female	9.8 ± 4.8	14.7 ± 2.3	38.1 ± 14.6
		Male	23.51*	12.9 ± 5.0	25.6 ± 8.2
		F+M	NC	13.5 ± 4.1	28.7 ± 10.6
AUC _∞ adjusted to dose of 1mg/Day	ng x hr/mL	Female	19.6 ± 6.0	14.7 ± 2.3	19.1 ± 7.3
		Male	NC	12.9 ± 5.0	12.8 ± 4.1
		F+M	-	13.5 ± 4.1	14.4 ± 5.3

^a - Values are means±SD for each PK parameter per dosage group

* - Blood sample of only one patient was available for the AUC_∞ calculation

Table 7A. Mean calculated Aminoindan Pharmacokinetic Parameters

Pharmacokinetic Parameter	Unit mg/day	Sex	Values ^a		
			0.5 mg/day (n=6♀, 3♂)	1.0 mg/day (n=2♀, 4♂)	2.0 mg/day (n=2♀, 5♂)
T _{max}	hours	Female	2.3 ± 0.8	3.0 ± 1.4	2.0
		Male	2.0	3.5 ± 1.0	2.4 ± 0.9
		F+M	2.2 ± 0.7	3.3 ± 1.0	2.3 ± 0.8
C _{max}	ng/mL	Female	1.9 ± 0.5	3.3 ± 1.2	7.1 ± 0.3
		Male	1.1 ± 0.5	2.6 ± 0.5	7.1 ± 3.1
		F+M	1.6 ± 0.6	2.6 ± 1.1	7.1 ± 2.5
C _{max} adjusted to dose of 1 mg/day	ng/mL	Female	3.7 ± 1.0	3.3 ± 1.2	3.6 ± 0.2
		Male	2.1 ± 0.9	2.6 ± 0.5	3.6 ± 1.5
		F+M	3.2 ± 1.2	2.6 ± 1.1	3.6 ± 1.3

^a - Values are means±SD for each PK parameter per dosage group.

It was found that patients treated with 0.5 mg or 2 mg rasagiline showed a greater reduction in their total UPDRS score at termination as compared with placebo patients or patients on 1 mg rasagiline. A more profound reduction was seen in patients who suffered from response fluctuations following chronic levodopa therapy (in 0.5 mg and 2 mg groups). This reduction was maintained in part for six weeks after cessation of dosing. The proportion of patients who achieved 30% or more reduction in the total UPDRS score after the completion of treatment was higher in the 0.5 mg and 2 mg groups. This was particularly noticeable in fluctuating patients of the 0.5 mg group (62.5% vs. 33% of placebo patients).

Comments:

1. Based upon the comparison of week 1 vs week 14 rasagiline and aminoindan levels at 30 min after dosing, there did not appear to be any accumulation for either the parent drug or metabolite. The firm's statements related to T_{max} and C_{max} are speculative since levels were collected at only 30 min, 2 and 4 hrs post-dose. Also any conclusions related to dose dependence is also speculative due to the sparse sampling scheme. In this study 50 patients were non-smokers, 12 had a history of smoking and 8 were current smokers. No statistical analysis was done by the firm to compare smokers to non-smokers due to the low numbers of patients. Although the number of smokers was small their presence could confound the interpretation of study results. The smoking issue for patients on adjunct therapy with Levodopa was addressed in the Presto clinical study 133.

INTRINSIC FACTOR STUDIES

STUDY TVP-1012/424-Hepatic Impairment

Rasagiline Pharmacokinetics after Single and Multiple Dose Oral Administration in Healthy Subjects and Patients with Mild and Moderate Hepatic Impairment

Rasagiline is mainly cleared by hepatic metabolism, with only a small percentage excreted unchanged in the urine following oral administration. Therefore, changes in hepatic function may have a direct effect on the plasma clearance of the drug. Other factors secondary to hepatic impairment, e.g. changes in protein binding, electrolyte composition, hepatic perfusion and lean body mass, may also affect plasma concentrations. Rasagiline might be prescribed to patients with impaired hepatic function, therefore the present study was designed to investigate the pharmacokinetics, safety and tolerability of single and multiple doses of rasagiline in subjects with varying degrees of hepatic function.

Primary Objectives

To compare the plasma pharmacokinetics of rasagiline and its metabolite aminoindan following a single dose of 1 mg rasagiline and once daily repeated dosing for 7 days of a 1 mg tablet of rasagiline in healthy subjects to subjects with mild and moderate hepatic impairment.

Secondary objectives

To investigate the safety and tolerability of rasagiline in subjects with mild and moderate hepatic impairment following once daily oral dosing for 7 days.

STUDY DESIGN

The present study was designed as a mono-centric, open, controlled, parallel multiple oral administration pharmacokinetic study, carried out in 24 completing subjects (8 per group). Subjects were stratified on the basis of their hepatic function to one of three groups: Group 1 with normal hepatic function, group 2 with mild hepatic impairment (Child class A), and group 3 with moderately impaired hepatic function (Child class B).

Inclusion Criteria

Subjects with stable hepatic impairment due to cirrhosis, as confirmed by previous biopsy specimen or liver/spleen scan consistent with cirrhosis with laboratory and clinical findings that support the diagnosis of cirrhosis. Subjects whose case record notes demonstrated stable hepatic function. Patients should, whenever possible, have exhibited stable biochemistry within the past 3 months prior to screening.

The classification was performed according to the moderate Child-Pugh classification by means of the parameters total bilirubin, serum albumin, ascites, hepatic encephalopathy, and of the parameters total bilirubin, serum albumin, ascites, hepatic encephalopathy, and prothrombin time. All subjects had to satisfy the criteria of either Class A (mild hepatic impairment, score 5 to 6 points) or B (moderate hepatic impairment, score 7 to 9 points) (see appendix 11.1 study protocol) The ages, weights and sexes of the subjects in all three groups were matched as closely as possible. As described in the study protocol, the healthy subjects were within 5 years of age and 10 kg for weight of the subjects with hepatic impairment.

The concurrent administration of all usual chronically administered drugs associated with hepatic failure was allowed. These include anti-hypertensive agents (beta blockers, alpha 1-blockers, calcium channel blockers, ACE inhibitors and angiotensin II), diuretics, cholesterol lowering drugs, xanthine oxidase inhibitors and H2 antagonists (not cimetidine). No Cyp1A2 inhibiting drugs were allowed. Concomitant use of any other drugs with MAO inhibiting effects, of antidepressants or anti-Parkinson medication was not allowed.

One tablet of the test preparation corresponding to a dose of 1 mg rasagiline was administered with 200 mL of tap water following an overnight fasting period. Light breakfast was served 0.5 hours after dosing. Throughout the whole hospitalisation period, the subjects received standardized meals with low tyramine.

Table 1 A. Demographic data for all enrolled subjects

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Subject No.	Initials	Status	Screening No.	Sex	Date of Birth	Age	Height	Weight	Ethnicity
1		moderate	1	Female		56	166	61	Caucasian
2	U	moderate	2	Male	U	52	183	81	Caucasian
3		moderate	6	Male		54	187	100	Caucasian
4		mild	4	Male		58	172	84	Caucasian
5		mild	7	Female		57	157	60.2	Caucasian
6		mild	5	Female		45	168	83.5	Caucasian
7		moderate	8	Male		50	177	69	Caucasian
8		moderate	9	Male		41	175	95	Caucasian
9		mild	13	Male		52	172	85	Caucasian
10		mild	14	Male		50	168	66	Caucasian
11		mild	10	Male		61	170	76	Caucasian
12		healthy	15	Male		54	176	78.5	Caucasian
13		moderate	12	Female		51	169	70	Caucasian
14		moderate	19	Male		53	178	88	Caucasian
15		healthy	17	Male		46	182	91.5	Caucasian
16		healthy	18	Female		53	166	59.4	Caucasian
17		moderate	22	Female		64	159	59	Caucasian
18		healthy	23	Male		60	181	104	Caucasian
19		healthy	20	Male		51	174	82.5	Caucasian
20		healthy	25	Male		44	178	84	Caucasian
21		mild	29	Female		54	164	86	Caucasian
22		healthy	32	Female		50	160	71	Caucasian
23		healthy	31	Female		61	170	76.5	Caucasian
24	U	mild	30	Male	U	52	169	70	Caucasian
25		moderate	26	Male		63	168	78	Caucasian

Subject 7 was withdrawn due to an unrelated adverse event and not included into descriptive statistics

Table 2 A. CRITERIA FOR CHILD-PUGH CLASSIFICATION

	Score		
	1	2	3
Total Bilirubin (mg/dl)	<2.0	2.0 - 3.0	>3.0
Serum Albumin (g/dl)	>3.5	2.8 - 3.5	<2.8
Ascites	Absent	Slight	Moderate
Hepatic Encephalopathy	None	Moderate	Severe
Prothrombin Time (%)	>70	40-70	<40

Appendix 5

Class A: Score 5-6

Class B: Score 7-9

Class C Score 10-15

Subjects were allowed in the study that smoked 5 cigarettes or less/day.

DETERMINATION OF ENCEPHALOPATHY FOR THE CALCULATION OF THE CHILD-PUGH SCORE

Encephalopathy Test – Number Connection Test

An encephalopathy test was to be performed on all patients with liver impairment at the screening visit. The number connection test will facilitate the diagnosis of hepatic encephalopathy. The test should be performed by the patient after the investigator's verbal instructions. The purpose is to correctly combine numbers with a pencil on a test chart as fast as possible. If the patient needs more than 40 seconds to perform the task, there is a strong indication of a latent hepatic encephalopathy. The classification for state of hepatic encephalopathy is shown in the table below:

Time in seconds	State of hepatic encephalopathy (HE)
< 40	No hepatic encephalopathy (HE)
41 – 60	< I Latent HE e.g mild to moderate symptomatic transitory psychotic syndrome
61 – 90	II Severe symptomatic transitory psychotic syndrome
91 – 120	III Clouding of consciousness/disorientation

Test not possible to IV Unconscious/coma
perform

Note: time >90 seconds exclusion criterion

BLOOD SAMPLING TIMES

Drug administration occurred during study periods 1 and 2 at approximately 08:00 hours central European time. After each dose, a light breakfast was served 0.5 hours after dosing. Pharmacokinetic blood samples were taken from each subject at the following time points:

Period 1 / Single Dose

Day 1: 0 h (pre-dose), 15 min, 30 min, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, and 18h after administration.

Period 2 / Multiple Dose

Day 2: 24 h after the first dosing, the last blood sample of period 1 was taken.

Day 3-6: Trough blood samples were taken pre-dose in the morning. **Day 7:** 0 h (pre-dose), 15 min, 30 min, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, and 18h. **Day 8:** Pharmacokinetic blood samples were taken 24h and 36h after dosing. **Day 9:** Pharmacokinetic blood samples were taken 48h after dosing.

Pharmacokinetic Analysis

The non-compartmental analysis was based on a model (Model 200) requiring an extravascular administration of the drug. For the maximal reached concentration (C_{max}), the observed values were reported. The AUC_t was calculated until the last quantifiable concentration (above LLOQ) different to 0 with the linear trapezoidal method; for AUC_{inf} the additional part was extrapolated to infinity. The terminal elimination half-life t_{1/2} was calculated using a log-linear regression of the concentration data including the last sampling time point with a measurable concentration of the respective analyte and if possible two further concentration/time pairs. Only those data points judged to describe the terminal log-linear decline were to be used in the regression.

Statistics

The two Child Pugh groups were both compared to the normal hepatic function group. Log transformed AUC_t and C_{max} and untransformed t_{max} values were analysed for single dose administration, whereas for multiple dose, the log transformed AUC_t, C_{max,ss} and peak:trough fluctuation and untransformed t_{max,ss} values were evaluated. Due to the low plasma concentrations observed for both compounds and the clearly differing terminal half-lives observed for the different treatment groups, the area under the curve AUC_t (up to the last measurable time point) was used for the bioequivalence assessment instead of the AUC₂₄. As an imbalanced extrapolation of the remaining part of the area under the curve had to be expected for the three different treatment groups, this parameter was selected in order to enable a more reliable evaluation. The differences between the means, standard errors associated with these differences and the 90% confidence intervals for these differences are presented in the present report. For AUC_t and C_{max} the ratio between the anti-logged treatment means and the corresponding anti-logged confidence interval are also presented.

Analytical

The study was conducted from August 13, 2001.

Sample analysis was completed on February 28, 2002. Total storage time was 6 months.

Plasma

Parameter	PAI	AI
Method	GC/MS	GC/MS
Sensitivity/LOQ	0.25 ng/ml	0.25 ng/ml
Linearity (Standard curve samples)	0.25-10 ng/ml	0.5-10 ng/ml
Quality Control (QC) Samples	0.4, 5, 9.0 ng/ml	0.75, 5, 9.0 ng/ml
Precision of Standards (%CV)	7.7% @ 0.25 ng/ml 0.9% @ 10 ng/ml	3.7% @ 0.5 ng/ml 1.7% @ 10 ng/ml
Precision of QC Samples (%CV)	9.1% @ 0.40 ng/ml 3.4% @ 7.5 ng/ml	6.9% @ 0.75 ng/ml 1.4% @ 7.5 ng/ml
Accuracy of Standards (%)	104% @ 0.25 ng/ml 101% @ 10 ng/ml	106% @ 0.25 ng/ml 102% @ 10 ng/ml
Accuracy of QC Samples (%)	110% @ 0.75 ng/ml 98% @ 22 ng/ml	96% @ 0.75 ng/ml 99% @ 22 ng/ml

RESULTS

Mean parameter values following single dose of rasagiline in normals subjects.

	Tmax h	Cmax ng/ml	T ½ h	AUCt ng/mlxh	AUCi ng/mlxh
Mean	0.44	4.29	0.29	2.68	3.59
SD	0.12	1.65	0.06	1.24	0.87
RSD	26.5	38.3	20.2	46.1	24.4
Max	0.50	6.48	0.36	4.47	4.60
Median	0.50	4.02	0.28	2.60	3.17
Min	0.25	2.40	0.23	1.25	2.80
Geomean	0.42	4.01	0.29	2.43	3.51
N	8	8	5	8	5

Mean parameter values following single dose of rasagiline in subjects with mild hepatic impairment.

	Tmax h	Cmax ng/ml	T ½ h	AUCt ng/mlxh	AUCi ng/mlxh
Mean	0.31	4.96	0.40	3.41	3.61
SD	0.12	2.16	0.15	1.10	1.11
RSD	37.0	43.5	36.7	32.1	30.8
Max	0.50	8.39	0.68	5.65	5.84
Median	0.25	4.08	0.40	3.13	3.28
Min	0.25	2.94	0.20	2.07	2.21
Geomean	0.30	4.61	0.38	3.28	3.48
N	8	8	8	8	8

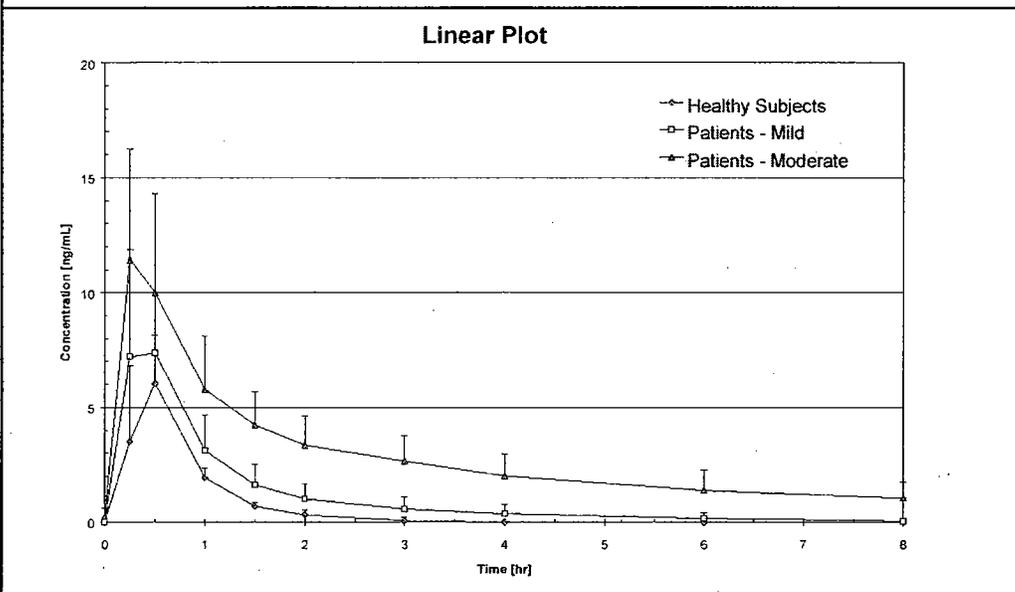
Mean parameter values following single dose of rasagiline in subjects with moderate hepatic impairment.

	Tmax h	Cmax ng/ml	T ½ h	AUCt ng/mlxh	AUCi ng/mlxh
Mean	0.75	1.00	11.1	4.57	14.42
SD	0.29	0.25	5.70	4.52	7.86
RSD	38.5	25.2	51.2	99.0	54.5
Max	1.00	1.3	17.1	9.14	20.30
Median	0.75	1.01	10.7	4.40	17.46
Min	0.50	0.69	5.69	0.33	5.49
Geomean	0.71	0.97	10.1	2.22	12.48
N	4	4	3	4	3

nc = not calculable

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**PHARMACOKINETIC RESULTS OF RASAGILINE AFTER MULTIPLE DOSE (DAY 7) :
MEAN PLASMA CONCENTRATION/TIME PROFILES OF RASAGILINE**



Pharmacokinetic Parameters of Rasagiline after Multiple Dose (mean \pm s.d.):

Group/Subjects	C_{max} [ng/mL]	t_{max} [h]	$t_{1/2}$ [h]	AUC _t [ng/mL*h]	AUC _{∞} [ng/mL*h]	PTF [%]	CL/F L/h
A / healthy subjects	6.24 \pm 2.42	0.47 \pm 0.09	0.54 \pm 0.29	4.75 \pm 1.82	5.01 \pm 1.89	2787 \pm 341	229.5 \pm 94.6
B / mild hep. imp.	8.60 \pm 3.65	0.38 \pm 0.13	1.75 \pm 1.55	9.19 \pm 5.84	9.89 \pm 6.29	2205 \pm 467	132.2 \pm 65.6
C / moderate hep. imp.	11.65 \pm 4.61	0.31 \pm 0.12	11.33 \pm 7.61	35.76 \pm 22.14	33.35 \pm 15.78	947 \pm 457	41.3 \pm 32.8

hep. imp. = hepatic impairment

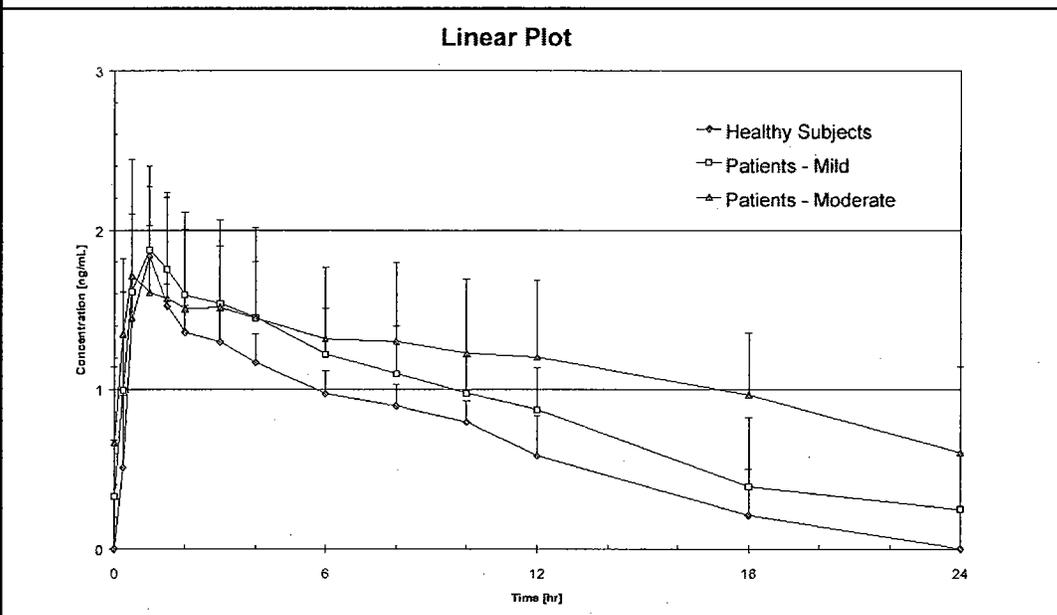
**Statistical Results of Rasagiline after Multiple Dose of 1 mg Rasagiline over 7 Days
Group 2 vs. Group 1**

AUCt:	90 % confidence interval (ANOVA / Log-transformed): ratio of geometric mean:	110.2 - 294.9 % 180.2 %
Cmax:	90 % confidence interval (ANOVA / Log-transformed): ratio of geometric mean:	96.3 - 198.2 % 138.1 %
PTF:	90 % confidence interval (ANOVA / Log-transformed): ratio of geometric mean:	57.7 - 105.7 % 78.1 %
tmax:	90 % confidence interval (ANOVA / Non-transformed): ratio of mean:	59.1 - 101.0 % 80.0 %

Group 3 vs. Group 1

AUCt:	90 % confidence interval (ANOVA / Log-transformed): ratio of geometric mean:	408.4 - 1093 % 668.2 %
Cmax:	90 % confidence interval (ANOVA / Log-transformed): ratio of geometric mean:	127.7 - 262.9 % 183.2 %
PTF:	90 % confidence interval (ANOVA / Log-transformed): ratio of geometric mean:	22.4 - 41.0 % 30.3 %
tmax:	90 % confidence interval (ANOVA / Non-transformed): ratio of mean:	45.7 - 87.6 % 66.7 %

**PHARMACOKINETIC RESULTS OF AMINOINDAN AFTER MULTIPLE DOSE (DAY 7):
MEAN PLASMA CONCENTRATION/TIME PROFILES OF AMINOINDAN**



Pharmacokinetic Parameters of Aminoindan after Multiple Dose (mean \pm s.d.):

Group/Subjects	C_{max} [ng/mL]	t_{max} [h]	$t_{1/2}$ [h]	AUC _t [ng/mL*h]	AUC _{∞} [ng/mL*h]	PTF [%]	CL/F L/h
A / healthy subjects	1.95 \pm 0.33	0.88 \pm 0.23	10.1 \pm 1.5	13.9 \pm 3.52	18.08 \pm 2.45	185 \pm 46.7	56.2 \pm 7.7
B / mild hep. imp.	1.97 \pm 0.51	1.00 \pm 0.38	17.8 \pm 10.1	20.54 \pm 10.33	23.06 \pm 6.14	141 \pm 37.1	46.2 \pm 12.4
C / moderate hep. imp.	1.89 \pm 0.72	1.13 \pm 1.22	36.2 \pm 30.9	37.97 \pm 21.85	28.07 \pm 10.42	95.4 \pm 45.3	40.5 \pm 15.1

hep. imp. = hepatic impairment

**Statistical Results of Aminoindan after Multiple Dose of 1 mg Rasagiline over 7 Days
Group 2 vs. Group 1**

AUC _t :	90 % confidence interval (ANOVA / Log-transformed): ratio of geometric mean:	90.9 - 208.7 % 137.8 %
C_{max} :	90 % confidence interval (ANOVA / Log-transformed): ratio of geometric mean:	76.5 - 128.7 % 99.3 %
PTF:	90 % confidence interval (ANOVA / Log-transformed) ratio of geometric mean:	56.0 - 103.1 % 76.0 %
t_{max} :	90 % confidence interval (ANOVA / Non-transformed) ratio of mean:	40.7 - 187.9 % 114.3 %

Group 3 vs. Group 1

AUC _t :	90 % confidence interval (ANOVA / Log-transformed): ratio of geometric mean:	156.9 - 359.9 % 237.6 %
C_{max} :	90 % confidence interval (ANOVA / Log-transformed) ratio of geometric mean:	70.2 - 118.1 % 91.0 %
PTF:	90 % confidence interval (ANOVA / Log-transformed): ratio of geometric mean:	35.1 - 64.7 % 47.6 %
t_{max} :	90 % confidence interval (ANOVA / Non-transformed): ratio of mean:	55.0 - 202.1 % 128.6 %

Figure 1 A. Individual plasma concentration/time curves of rasagiline in healthy subjects group 1 after multiple dosing

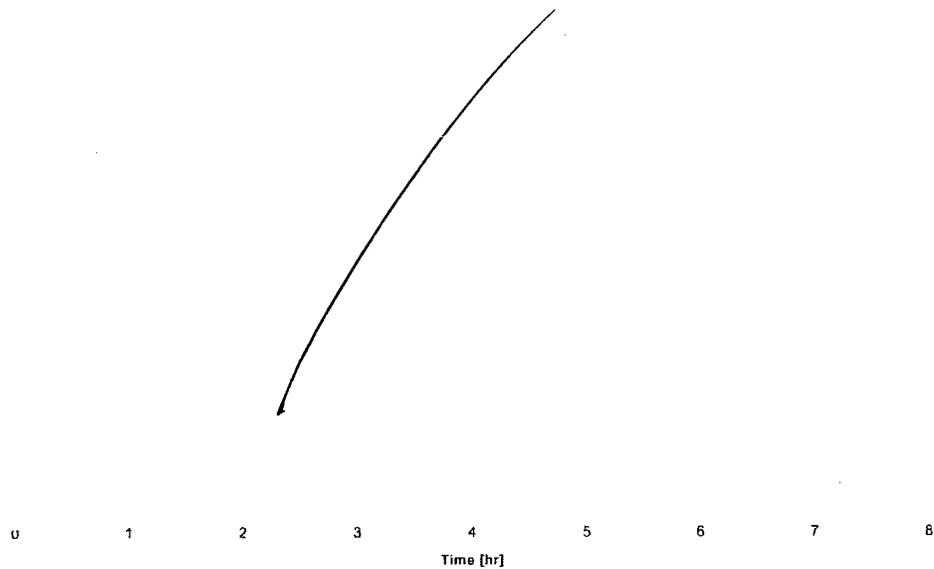


Figure 2 A. Individual plasma concentration/time curves of rasagiline in patients with mild hepatic impairment after multiple dosing

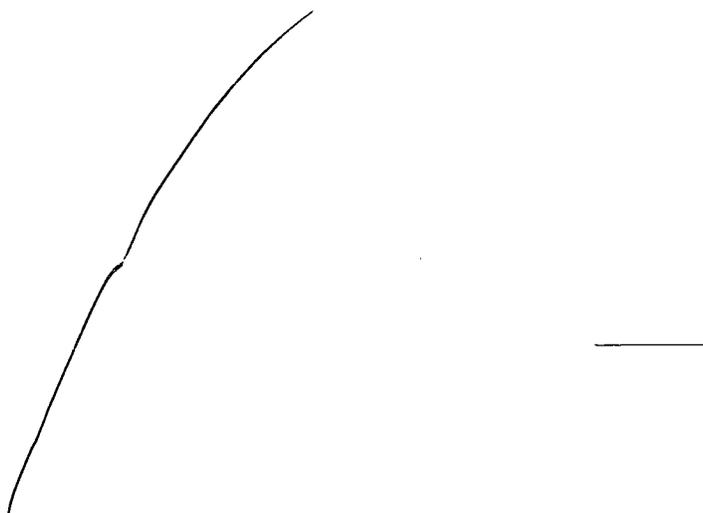
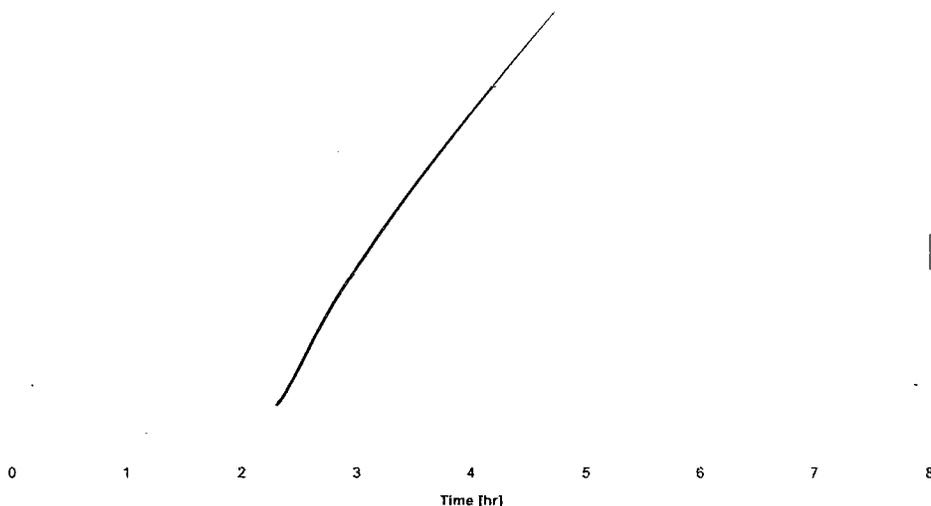


Figure 3 A. Individual plasma concentration/time curves of rasagiline in patients with moderate hepatic impairment after multiple dosing



Safety

SAFETY EVALUATION

From the results of the precautionary observations it was concluded that the safety and tolerability of the drugs administered remained within expected limits after multiple oral dose of 1 mg rasagiline. 25 patients were included into the study. One male patient was withdrawn due to an unrelated adverse event (alcohol withdrawal symptoms) so that 24 completed cases (8 for each group) were available. Among these 24 patients, adverse events were reported from 13 subjects: 5 subjects from Group 1 (healthy subjects), 5 from Group 2 (patients with mild hepatic impairment) and 3 from Group 3 (patients with moderate hepatic impairment). The severity of adverse events was mostly mild; three cases were qualified to be moderate. No serious adverse events were observed.

DISCUSSION AND CONCLUSIONS

In the present study 24 subjects (8 healthy, 8 with mild and 8 with moderate hepatic impairment) received one tablet 1 mg rasagiline per day over 7 days according to an open, parallel, multiple dose design.

For rasagiline, in both patient groups clearly higher concentration levels (C_{max}) and an increased extent (AUC) of exposure was observed after single dose, but particularly after multiple dose. In patients with moderate hepatic impairment the bioavailability (AUC_t) was enlarged after single dose by a factor of 2.4 and after multiple dose by a factor of 7.5. The half-life was clearly extended in the two treatment groups compared with healthy subjects. For aminoindan a lower effect was observed. The concentration levels C_{max} were almost comparable for all three groups after multiple dosing; however, as a result of the lower clearance the extent of exposure (AUC) was clearly increased for both patient groups compared to healthy subjects. Although the plasma levels were higher in patients with mild and moderate hepatic impairment, no increase of adverse events was observed. Therefore the higher rasagiline plasma concentration in patients with hepatic impairment seems to have no influence on the safety of the product under the conditions tested.

The firm believes that in view of the effects on AUC (7 x) and Cmax (2 x) in the moderate hepatic patients, the ethnic effect in this patient population if any, should be negligible in comparison to the effect of hepatic impairment.

Comments:

1. The firm's recommendation is that Rasagiline should not be administered to subjects with moderate to severe hepatic impairment.
2. The firm supplied data on the number of cigarettes smoked by the hepatically impaired subjects and it appears that there was no clear effect of smoking on the mildly impaired subjects.

STUDY TVP-1012/425-Renal Impairment

Rasagiline Pharmacokinetics after Single and Multiple Dose Oral Administration in Healthy Volunteers and Patients with Mild and Moderate Renal Impairment

STUDY OBJECTIVES

Primary Objectives

To compare the plasma pharmacokinetic parameters of rasagiline and its metabolite aminoin-dan (AI), following a single dose of 1mg rasagiline and following once daily repeated dosing of a 1 mg tablet of rasagiline for 7 days in healthy subjects and in subjects with mild and moderate renal impairment.

Secondary objectives

To investigate the safety and tolerability of rasagiline in subjects with mild and moderate renal impairment following once daily oral dosing for 7 days.

Rationale of the Clinical Trial

Rasagiline is mainly cleared by hepatic metabolism, with only a small percentage excreted unchanged in the urine following oral administration. However, rasagiline might be prescribed to a large extent to elderly patients with impaired renal function, therefore the present study is designed to investigate the pharmacokinetics, safety and tolerability of single and multiple doses of rasagiline in subjects with varying degrees of renal function.

Overall Study Design and Plan-Description

The present study was designed as a single-center, open, controlled, parallel multiple oral administration pharmacokinetic study, carried out in 24 completing subjects (8 per group). Subjects were stratified on the basis of their renal function to one of three groups: Group 1 with normal renal function, group 2 with mild renal impairment, and group 3 with moderately impaired renal function.

Group Creatinine Clearance*

- 1 > 80 mL/min
- 2 50-80 mL/min
- 3 30-49 mL/min

* according to Cockcroft and Gault

Renal function

- Normal
- Mildly
- Moderately impaired

N

- 8
- 8
- 8

Table 1 A. Demographic data of all enrolled subjects

Subject No.	Initials	Status	Screening No.	Sex	Date of Birth	Age	Height	Weight	BMI	Ethnicity
1		mild	3	Male		61	178	81	25.6	Caucasian
2	7	mild	2	Male	7	65	175	93	30.4	Caucasian
3	7	moderate	4	Male		59	179	77	24.0	Caucasian
4		mild	5	Male		50	168	62	22.0	Caucasian
5		moderate	6	Male		64	186	100	28.9	Caucasian
6		moderate	9	Male		63	176	69	22.3	Caucasian
7		healthy	8	Male		62	172	75	25.4	Caucasian
8		moderate	10	Male		40	182	70	21.1	Caucasian
9		mild	13	Male		52	180	90	27.8	Caucasian
10		moderate	11	Female		60	163	78	29.7	Caucasian
11		mild	19	Male		29	172	87	29.4	Caucasian
12		mild	17	Male		41	176	71	22.9	Caucasian
13		healthy	24	Male		54	185	95	27.8	Caucasian
14		healthy	16	Male		62	171	74	25.3	Caucasian
15		mild	20	Female		57	174	73	24.1	Caucasian
16		moderate	22	Male		61	177	73	23.3	Caucasian
17		healthy	26	Male		49	181	78.5	24.0	Caucasian
18		healthy	28	Male		49	174	78	25.8	Caucasian
19		healthy	27	Male		57	175	88.3	28.8	Caucasian
20		mild	29	Female		58	168	68	24.1	Caucasian
21		moderate	31	Female		58	172	96	32.4	Caucasian
22		healthy	33	Female		56	172	80	27.0	Caucasian
23		healthy	34	Female		61	171	87.5	29.9	Caucasian
24	U	moderate	35	Male	U	50	180	60.2	18.6	Caucasian

Creatinine clearance was calculated from screening serum creatinine levels using the equation below (Cockcroft and Gault equation) and the result entered into the CRF:

$$\text{Creatinine Clearance (ml/min)} = \frac{(140 - \text{age}) \times (\text{body wt in kg})}{72 \times \text{serum creatinine (mg 100ml}^{-1})} \quad (\times 0.85 \text{ for females})$$

Exclusion Criteria

Subjects who smoke more than 5 cigarettes/day or equivalent.

BLOOD SAMPLING TIMES

Drug administration occurred during study periods 1 and 2 at approximately 08:00 hours central European time. After each dose, a light breakfast was served 0.5 hours after dosing. Pharmacokinetic blood samples were taken from each subject at the following time points:

Period 1 / Single Dose

Day 1: 0 hr (pre-dose), 15 min, 30 min, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, and 18h after administration.

Period 2 / Multiple Dose

Day 2: 24 hr after the first dosing, the last blood sample of period 1 was taken.

Day 3-6: Trough blood samples were taken pre-dose in the morning. **Day 7:** 0 hr (pre-dose), 15 min, 30 min, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, and 18h. **Day 8:**

Pharmacokinetic blood samples were taken 24h and 36h after dosing. **Day 9:**
Pharmacokinetic blood samples were taken 48h after dosing.

Pharmacokinetic Evaluation

The pharmacokinetic parameters for rasagiline and aminoindan were determined by non-compartmental analysis (NCA) as described in section 3.5.7. For the maximal reached concentration (C_{max}), the observed values were reported. The AUC_t was calculated until the last quantifiable concentration (above LLOQ) different to 0 with the linear trapezoidal method; for AUC_{inf} the additional part was extrapolated to infinity.

The terminal elimination half-life t_{1/2} was calculated using a log-linear regression of the concentration data including the last sampling time point with a quantifiable concentration of the respective analyte and if possible two further concentration/time pairs. Only those data points judged to describe the terminal log-linear decline were to be used in the regression.

Data Analysis

The non-compartmental analysis was based on a model (Model 200) requiring an extravascular administration of the drug. For the maximal reached concentration (C_{max}), the observed values were reported. The AUC_t was calculated until the last quantifiable concentration (above LLOQ) different to 0 with the linear trapezoidal method; for AUC_{inf} the additional part was extrapolated to infinity.

The terminal elimination half-life t_{1/2} was calculated using a log-linear regression of the concentration data including the last sampling time point with a quantifiable concentration of the respective analyte and if possible two further concentration/time pairs. Only those data points judged to describe the terminal log-linear decline were to be used in the regression.

For both compounds rasagiline and aminoindan, log transformed AUC_t and C_{max} and untransformed t_{max} values following the single dose, were subjected to analysis of variance, fitting a term for subject group (different levels for the 2 groups with renal impairment and the normal renal function group). Log transformed AUC_t, C_{max,ss} and peak:trough fluctuation and untransformed t_{max,ss} values following the multiple dose were analyzed using the same methods. The two groups with a different degree of renal impairment were both compared to the normal renal function group with regard to rasagiline and aminoindan. The differences between the means, standard errors associated with these differences and the 90% confidence intervals for these differences are presented in the present report. For AUC_t and C_{max} the ratio between the anti-logged treatment means and the corresponding anti-logged confidence interval are also presented.

Analytical

The study was conducted from October 10, 2001-March 28, 2002

Analysis completed July 22, 2002

Total storage time 9 months

Plasma

Parameter	PAI	AI
Method	GC/MS	GC/MS
Sensitivity/LOQ	0.25 ng/ml	0.25 ng/ml

Linearity (Standard curve samples)	0.25-10 ng/ml	0.5-10 ng/ml
Quality Control (QC) Samples	0.4, 5, 9.0 ng/ml	0.75, 5, 9.0 ng/ml
Precision of Standards (%CV)	8.0% @ 0.25 ng/ml 1.3% @ 10 ng/ml	6.2% @ 0.5 ng/ml 2.2% @ 10 ng/ml
Precision of QC Samples (%CV)	15.4% @ 0.40 ng/ml 5.1% @ 7.5 ng/ml	10.5% @ 0.75 ng/ml 5.4% @ 7.5 ng/ml
Accuracy of Standards (%)	100% @ 0.25 ng/ml 100% @ 10 ng/ml	96% @ 0.25 ng/ml 99% @ 10 ng/ml
Accuracy of QC Samples (%)	97.5% @ 0.75 ng/ml 98.1% @ 22 ng/ml	101% @ 0.75 ng/ml 99% @ 22 ng/ml

RESULTS

Mean pharmacokinetic parameters for rasagiline after single oral dose of 1 mg rasagiline in healthy subjects (Group 1) / Part 1

	Tmax h	Cmax ng/ml	AUCt ng/mlxh
Descriptive Statistics			
Mean	0.34	4.11	2.46
SD	0.13	1.13	0.57
RSD	37.6	27.5	23.1
Max	0.50	5.96	3.20
Median	0.25	4.00	2.52
Min	0.25	2.44	1.63
Geomean	0.32	3.97	2.40
N	8	8	8

Mean pharmacokinetic parameters for rasagiline after single oral dose of 1 mg rasagiline in subjects with mild renal impairment (Group 2) / Part 1

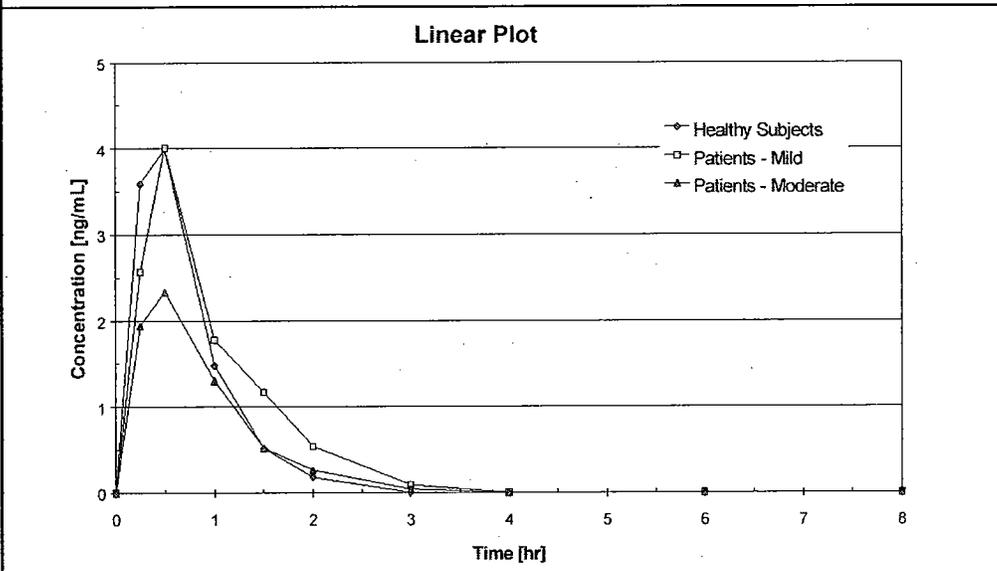
	Tmax h	Cmax ng/ml	AUCt ng/mlxh
Descriptive Statistics			
Mean	0.47	3.95	2.60
SD	0.25	1.85	0.73
RSD	52.9	46.7	28.0
Max	1.00	6.09	3.43
Median	0.50	4.13	2.65
Min	0.25	1.42	1.44
Geomean	0.42	3.51	2.50
N	8	8	8

Mean pharmacokinetic parameters for rasagiline after single oral dose of 1 mg rasagiline in subjects with moderate renal impairment (Group 3) / Part 1

	Tmax h	Cmax ng/ml	AUCt ng/mlxh
Descriptive Statistics			
Mean	0.44	2.31	1.51
SD	0.35	0.48	0.49
RSD	79.4	20.7	32.3
Max	1.00	3.3	2.38
Median	0.25	2.28	1.44
Min	0.25	1.54	0.93
Geomean	0.35	2.27	1.45
N	8	8	8

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**PHARMACOKINETIC RESULTS — MULTIPLE DOSE (DAY 7):
MEAN PLASMA CONCENTRATION/TIME PROFILES OF RASAGILINE**



Pharmacokinetic Parameters of Rasagiline after Multiple Dose (mean ± s.d.):

Group/Subjects	C _{max} [ng/mL]	t _{max} [hr]	t _{1/2} [hr]	AUC _t [ng/mL*hr]	AUC _∞ [ng/mL*hr]	PTF [%]	CL/F [L/hr]
1 / healthy subjects	4.74 ± 1.52	0.44 ± 0.12	0.38 ± 0.11	3.44 ± 1.01	3.64 ± 1.04	2858 ± 410	295.3 ± 82.9
2 / mild renal imp.	5.29 ± 2.20	0.63 ± 0.42	0.59 ± 0.27	4.99 ± 2.14	5.30 ± 2.20	2385 ± 830	224.4 ± 108.0
3 / moderate renal imp.	2.77 ± 1.02	0.44 ± 0.26	0.61 ± 0.48	2.47 ± 1.00	3.02 ± 0.86	2225 ± 605	372.2 ± 176.3

renal imp. = renal impairment

Statistical Results of Rasagiline after Multiple Dose of 1 mg Rasagiline over 7 Days

Group 2 vs. Group 1

AUC _t :	90 % confidence interval (ANOVA / log-transformed):	92.5 – 206.0 %
	Ratio of geometric mean:	138.1%
C _{max} :	90 % confidence interval (ANOVA / log-transformed):	74.1 – 154.3 %
	Ratio of geometric mean:	107.0%
PTF:	90 % confidence interval (ANOVA / log-transformed):	58.1 – 103.6%
	Ratio of geometric mean:	77.6%
t _{max} :	90 % confidence interval (ANOVA / non-transformed):	85.1 – 200.7%
	Ratio of mean:	142.9%

Group 3 vs. Group 1

AUC _t :	90 % confidence interval (ANOVA / log-transformed):	44.6 – 99.2%
	Ratio of geometric mean:	66.5%
C _{max} :	90 % confidence interval (ANOVA / log-transformed):	39.1 – 81.4%
	Ratio of geometric mean:	56.4%
PTF:	90 % confidence interval (ANOVA / log-transformed):	56.4 – 102.6%
	Ratio of geometric mean:	76.1%
t _{max} :	90 % confidence interval (ANOVA / non-transformed):	42.2 – 157.8%
	Ratio of mean:	100.0%

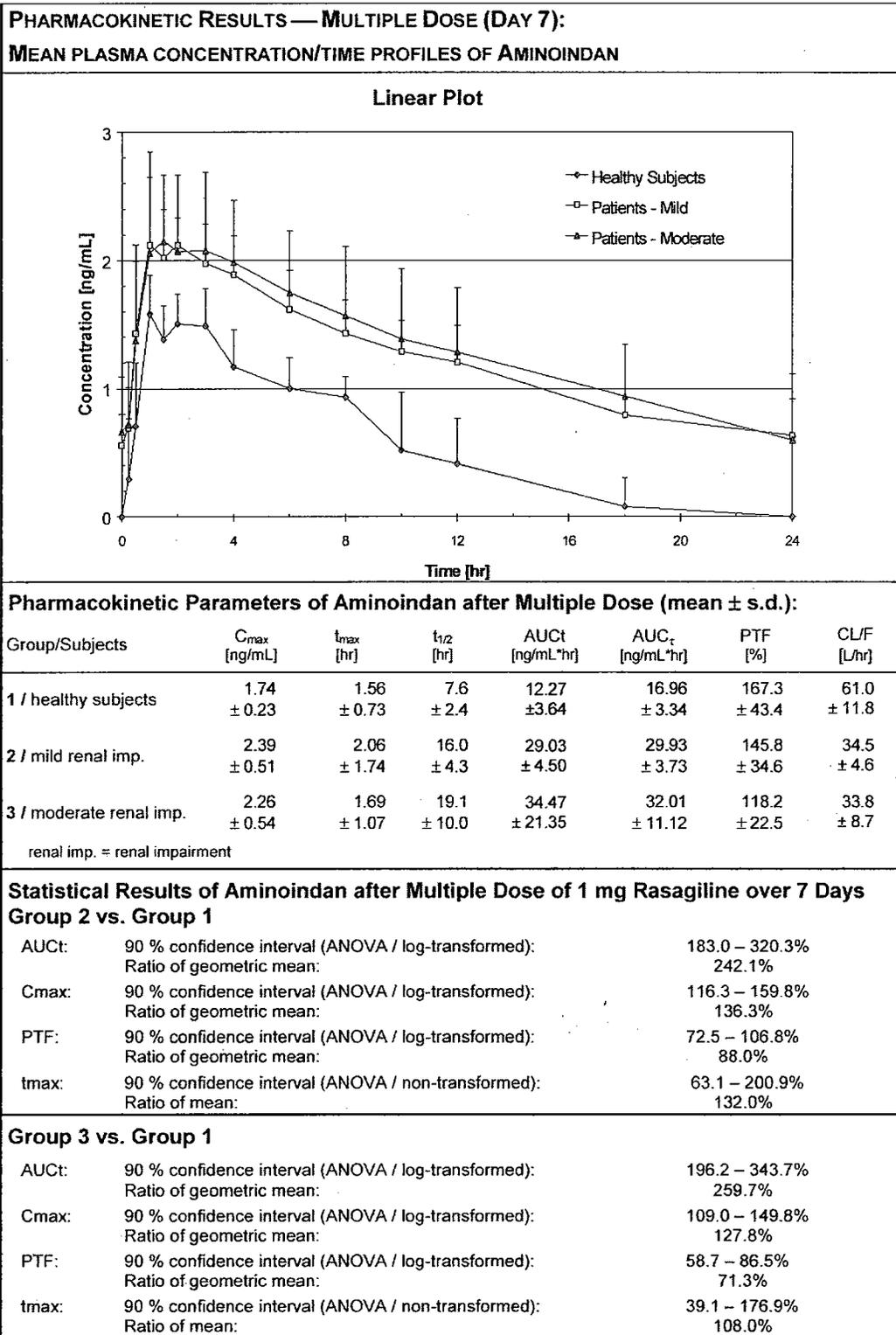


Fig. 1A. Mean plasma concentration/time curves (+SD) of rasagiline after multiple oral dose of rasagiline (linear plot 0 - 8 hr)

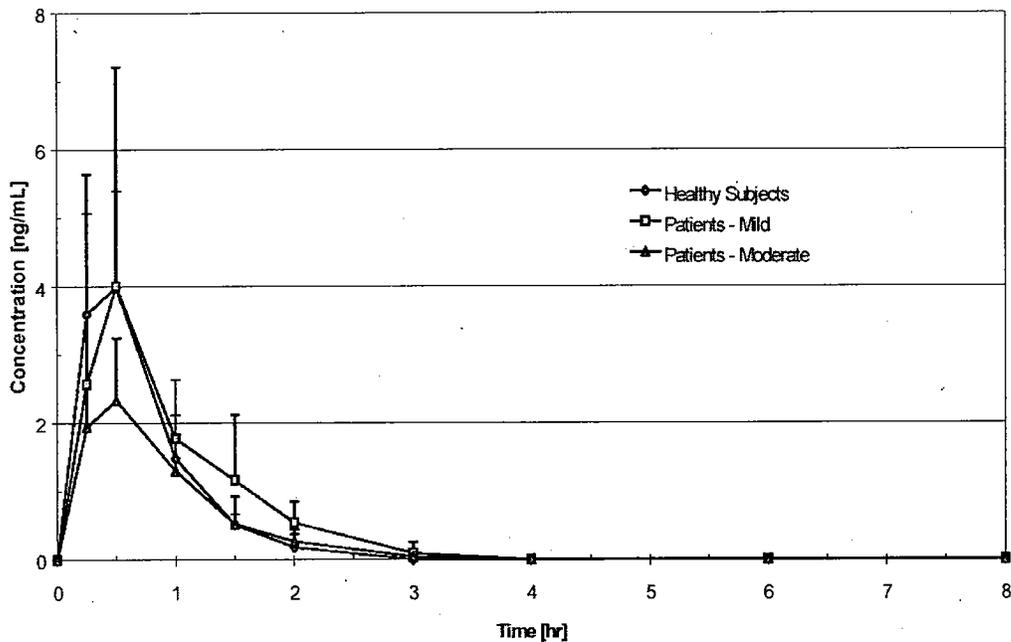
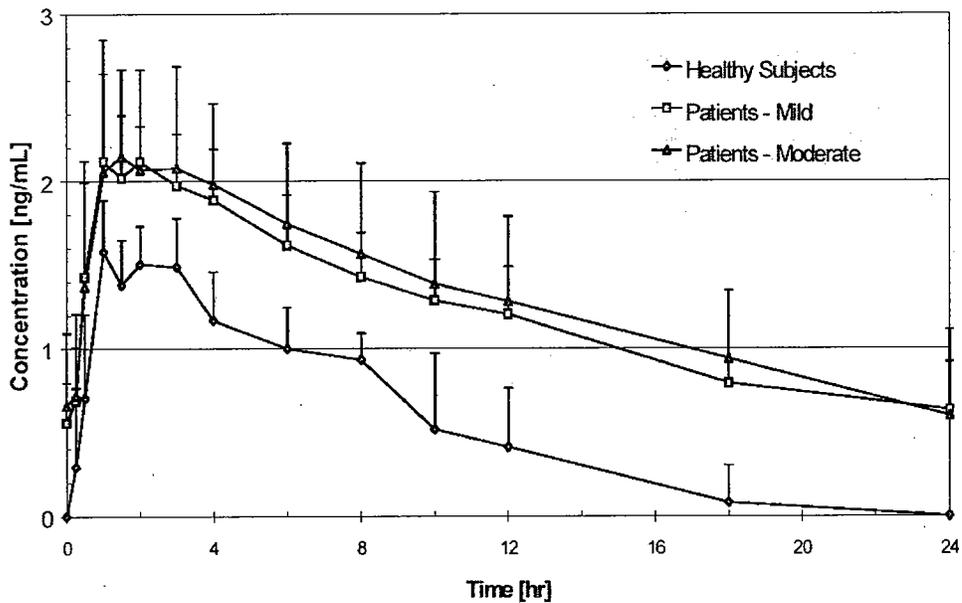


Fig. 2A. Mean plasma concentration/time curves (+SD) of aminoindan after multiple oral dose of rasagiline (linear plot 0 - 24 hr)



6. SAFETY EVALUATION

From the results of the precautionary observations it was concluded that the safety and tolerability of the drugs administered remained within expected limits after multiple oral dose of 1 mg Rasagiline. Adverse events were reported from 13 subjects, among those 4 subjects from Group 1 (healthy subjects), 4 from Group 2 (subjects with mild renal impairment) and 5 from Group 3 (subjects with moderate renal impairment). The severity of adverse events was mild in 14 cases; also 14 cases were rated to be moderate. No serious adverse events were observed. All adverse events recovered without sequelae. Six adverse events (7 cases, 4

subjects) soft stools, myalgia, diarrhoea, anthralgia, meteo-rism and calf cramps were judged to be probably related. 14 adverse events (19 cases, 10 subjects) were presumed to have a possibly relation; the other AEs had an unlikely or unrelated causal relation to the study drug.

Discussion

For rasagiline, the profiles and pharmacokinetic characteristics for healthy subjects and those with mild renal impairment (group 2) were all comparable after single and after multiple dose. In subjects with moderate renal impairment (group 3) a lower C_{max} and extent (AUC_t) of systemic exposure was observed after single and multiple dose compared to healthy subjects and subjects with mild renal impairment.

For aminoindan, significant differences were observed between subjects in the renal impairment groups (group 2 and 3) and healthy subjects (group 1). The absorption rate (C_{max} and t_{max}) was almost comparable for all three groups; however, as a result of the lower clearance the extent of systemic exposure (AUC_t) was increased for both subject groups with renal impairment compared to healthy subjects. It is possible that the decreased renal function in the moderate results in an increase in hepatic function?

Exposure for the metabolite seemed to follow the pattern for higher exposure with decreased renal function since the metabolite is excreted via the urine although the firm speculates that “ Regarding aminoindan, in Group 1 the plasma clearance is equivalent to 1600 mL/min for single dose and 1000 mL/min for multiple dose. In either case, plasma clearance is higher than combined GFR and tubular secretion. However, in groups 2 and 3, plasma clearance is as half as the plasma clearance in Group 1, strongly suggesting that clearance of AI is predominantly renal. This is because the creatinine clearance in Group 2 is about half that in Group 1, and that in Group 3 is about one-third of that in Group 1. However, Groups 3 and 2 seem to be similar in the context of aminoindan clearance, although one could expect AI clearance in Group 3 to be slower than in Group 2. A possible reason for that could be a further metabolism of aminoindan. “

Comment:

1. Dose adjustments based upon classification of renal function is not warranted based upon these study results.

STUDY TVP-1012/426-Ciprofloxacin Drug-Drug Interaction

ASSESSMENT OF METABOLIC INHIBITION BY CIPROFLOXACIN ON THE PHARMACOKINETIC PROFILE OF RASAGILINE MESYLATE, FOLLOWING MULTIPLE-DOSE CO-ADMINISTRATION TO HEALTHY VOLUNTEERS.

Study Introduction and Objectives

In vitro metabolism studies³ in human liver microsomes indicate that rasagiline is mainly metabolized by a single cytochrome P450 isoenzyme, CYP1A2. Since ciprofloxacin is a strong inhibitor of CYP1A2, and may be co-administered with rasagiline, it is appropriate to investigate the effect on rasagiline pharmacokinetics of concomitant administration of ciprofloxacin and rasagiline.

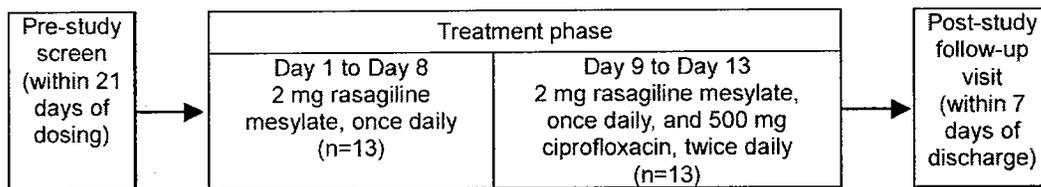
OBJECTIVES

To evaluate the pharmacokinetic profile of rasagiline mesylate after concomitant administration of ciprofloxacin.

Study Design

Subjects were admitted to the Clinic on the evening before dosing. Rasagiline 2 mg was administered to the subjects once daily from Day 1 for 13 days. For the final five days of rasagiline dosing, Days 9 to 13, twice-daily ciprofloxacin 500 mg was also administered. Blood samples were taken on these days up to 24 hours after the morning dose to evaluate the effect of concomitant administration of ciprofloxacin on the steady-state pharmacokinetics of rasagiline. Blood samples were also taken pre-dose on Days 10 to 12.

The study design is shown in Figure 1 A.



Exclusion Criteria:

Smokers, or ex-smokers who had smoked in the six months prior to dose administration or who used another form of nicotine containing product

Table 1A: Demographic and Baseline Characteristics

Statistic	Gender	Race	Age years	Height cm	Weight kg	BMI kg/m ²
Mean ± sd	Male (n=13)	Caucasian (n=13)	28.6 ± 6.75	176.5 ± 7.49	73.10 ± 7.12	23.55 ± 2.71
Range (min – max)			(20- 41)	(162 – 187)	(62.8 – 91.3)	(19.8 – 29.3)

Treatment Administered:

All subjects received two 1-mg rasagiline tablets daily as a single oral dose, administered in the morning, for 13 days (Days 1 to 13). On Days 9 to 13, all subjects also received oral doses of 500 mg ciprofloxacin at the same time as rasagiline and 12 hours later. All doses were administered with the subject sitting upright with 180 mL water.

Sample Collection and Handling

Blood samples (approximately 10 mL) were withdrawn, by venepuncture or indwelling cannula, from a suitable forearm vein into lithium heparin tubes at the following times on Day 7, Day 8 and Day 13: 0 hours (pre-dose), 5, 10, 20, 30, 45 minutes and 1, 1.5, 2, 3, 4, 8, 12 and 24 hours post-dose. Pre-dose blood samples were also taken on Days 10 to 12.

Bioanalytical Methods-

Studied Period (years):

Clinical March 2002-April 2002

Parameter	RASAGILINE	AMINOINDAN
Method	GC/MS/MS	GC/MS/MS
Sensitivity/LOQ	0.25 ng/ml	0.5 ng/ml
Linearity (Standard curve samples)	0.25-10 ng/ml	0.5-10 ng/ml
Quality Control (QC) Samples	0.4, 5.0, 9.0 ng/ml	0.75, 5.0, 9.0 ng/ml
Precision of Standards (%CV)	4% @0.25 ng/ml 1.2% @ 10 ng/ml	6% @0.5 ng/ml 1.2% @ 10 ng/ml
Precision of QC Samples (%CV)	12.2%@ 0.4 ng/ml 5.17% @ 9.0 ng/ml	7.6%@ 0.75ng/ml 4.8% @ 9.0 ng/ml
Accuracy of Standards (%)	100% @ 0.25 ng/ml 100.4% @ 10 ng/ml	100% @ 0.25 ng/ml 99.2% @ 10 ng/ml
Accuracy of QC Samples (%)	102% @ 0.4 g/ml 105% @ 9.0 ng/ml	104% @ 0.4 g/ml 107% @ 9.0 ng/ml

Statistical Analysis

The following non-compartmental pharmacokinetic parameters were estimated for each subject from the plasma concentration profiles of rasagiline and 1-aminoindan. Actual sampling times were used for the calculation of pharmacokinetic parameters.

C_{max} maximum plasma concentration over the sampling phase for each study day, directly obtained from the experimental data of plasma concentration versus time curves, without interpolation

AUC_{0-24} area under the plasma concentration-time curve (time 0 hours to time 24 hours) calculated by the linear trapezoidal rule

t_{max} time to C_{max} for each study day

Where there were sufficient data points (at least three) on the terminal portion of the elimination phase of the plasma profile, and where it was appropriate to do so, the following additional parameters were calculated:

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time of dosing to infinity, calculated by the linear trapezoidal rule to the last quantifiable concentration (C_t) with the residual area to infinity calculated from C_t/k_{el} . Hence $AUC_{0-\infty} = AUC_{0-t} + C_t/k_{el}$

k_{el} apparent elimination rate constant determined from the slope of the semi-log plot of plasma concentration against time for the terminal portion of the plasma profile

$t_{1/2}$ apparent elimination half-life calculated as $\ln 2/k_{el}$

RESULTS

Figure 2A. Mean plasma concentrations of rasagiline in healthy volunteers following repeated once daily 2 mg doses of rasagiline mesylate alone and co-administered with repeated twice daily 500 mg doses of ciprofloxacin

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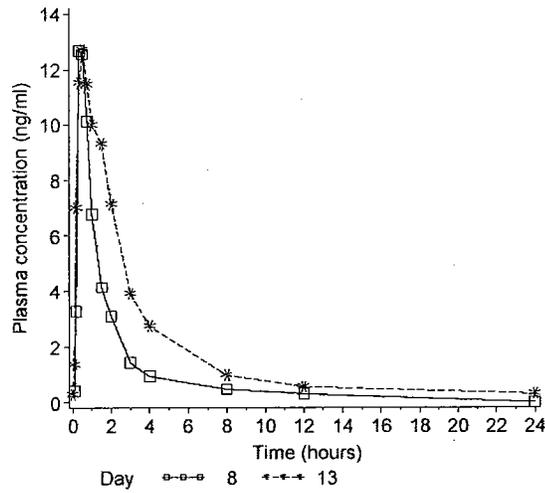


Figure 3A. Mean plasma concentrations of 1-aminoindan in healthy volunteers following repeated once daily 2 mg doses of rasagiline mesylate alone and co-administered with repeated twice daily 500 mg doses of ciprofloxacin

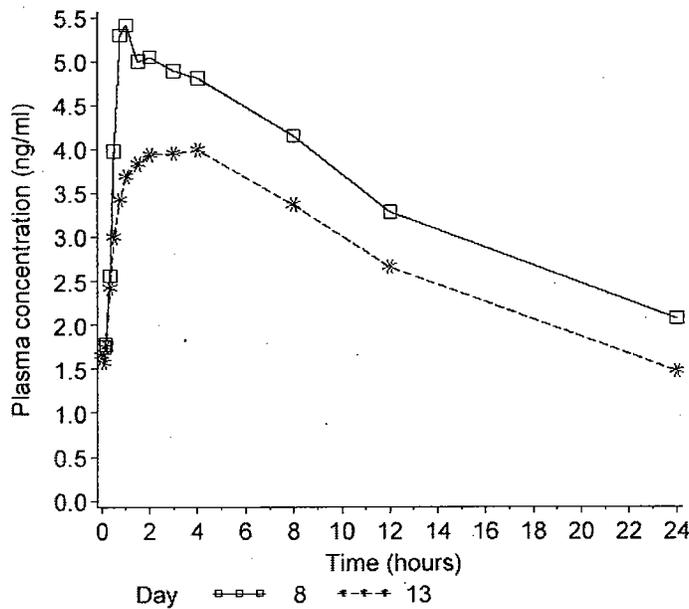


Table 2A. Analysis of pharmacokinetic parameters of rasagiline following repeated doses of rasagiline mesylate alone and co-administered with ciprofloxacin

Parameter	Units	N	Day 13 mean	Day 8 mean	Mean ratio ^a	Lower 90% CI for ratio	Upper 90% CI for ratio
C _{max} ^b	ng/mL	13	15.5	15.8	98.2%	79.2%	121.9%
AUC _{0-24h} ^b	ng.h/mL	13	38.8	19.6	197.5%	176.8%	220.6%
AUC _{0-∞} ^b	ng.h/mL	9	39.7	21.7	183.4%	166.2%	202.4%
kel	/h	9	0.2215	0.2150	92.7%	76.0%	109.5%
T _{max} ^c	h	13	0.75	0.50	166.7%	83.3%	258.3%

a Ratio (Day 13/Day 8) of treatment regimens, expressed as a percentage

b Means and 90% CI based on logarithmically transformed data; back-transformed results are presented

c Mean replaced by median. Hodges-Lehmann estimator for the median ratio is presented along with the corresponding 90% CI (large sample approx.)

Table 3A. Analysis of pharmacokinetic parameters of 1-aminoindan following repeated doses of rasagiline mesylate alone and co-administered with ciprofloxacin

Parameter	Units	N	Day 13 mean	Day 8 mean	Mean ratio ^a	Lower 90% CI for ratio	Upper 90% CI for ratio
C _{max} ^b	ng/mL	13	4.2	5.9	71.1%	66.7%	75.9%
AUC _{0-24h} ^b	ng.h/mL	13	64.3	81.1	79.3%	76.8%	81.9%
kel	/h	13	0.0505	0.0435	117.9%	106.1%	129.6%
T _{max} ^c	h	13	2.00	1.00	225.0%	116.7%	316.7%

A Ratio (Day 13/Day 8) of treatment regimens, expressed as a percentage

b Means and 90% CI based on logarithmically transformed data; back-transformed results are presented

c Mean replaced by median. Hodges-Lehmann estimator for the median ratio is presented along with the corresponding 90% CI (large sample approx.)

Comments:

1. In vitro metabolism studies in human liver microsomes had indicated that rasagiline is mainly metabolised by a single cytochrome P450 isoenzyme, CYP1A2. Since ciprofloxacin is a strong inhibitor of CYP1A2, and may be co-administered with rasagiline, it was appropriate to investigate the effect on rasagiline pharmacokinetics of concomitant administration of ciprofloxacin and rasagiline.

2. Rasagiline pharmacokinetics exhibited biphasic elimination. There was a rapid decline in plasma levels up to about eight hours post dose and then a slower terminal elimination phase. 1-aminoindan appeared rapidly in the systemic circulation following rasagiline administration and tended to show a single elimination phase within four hours after dosing. In the presence of ciprofloxacin, the rapid formation of 1-aminoindan by the metabolism of rasagiline was inhibited, resulting in prolonged plasma levels of rasagiline (AUC increased by more than 80%) and a delayed formation of 1-aminoindan (later t_{max}). This inhibitory effect ultimately reduced the amounts of 1-aminoindan formed (29% lower C_{max} and 21% lower AUC). Despite the increased rasagiline AUC of at least 80%, the C_{max} results were not consistent across all subjects, with some subjects showing increased C_{max} but others showing reduced C_{max}. From the plasma profiles of rasagiline, it is evident that most of the effect of this inhibition occurred between two and eight hours post dose. Thereafter the usual slower decline from plasma was evident, and hence the terminal elimination rate remained unchanged despite the inhibitory effects of ciprofloxacin. Furthermore, there was no evidence of increased accumulation of rasagiline on repeated dosing when co-

administered with ciprofloxacin, i.e. the pre-dose levels of rasagiline were similar on Days 8 and 13.

3. There was no indication of an increase in the frequency of adverse events nor of any increase in the severity of adverse events when rasagiline was co-administered with ciprofloxacin, compared to rasagiline alone.

4. The effect of rasagiline on ciprofloxacin was not studied.

STUDY NUMBER: TVP-1012/430-Theophylline Drug-Drug Interaction

ASSESSMENT OF PHARMACOKINETIC INTERACTION OF RASAGILINE MESYLATE AND THEOPHYLLINE FOLLOWING MULTIPLE DOSE CO-ADMINISTRATION TO HEALTHY SUBJECTS.

STUDY OBJECTIVES

Primary

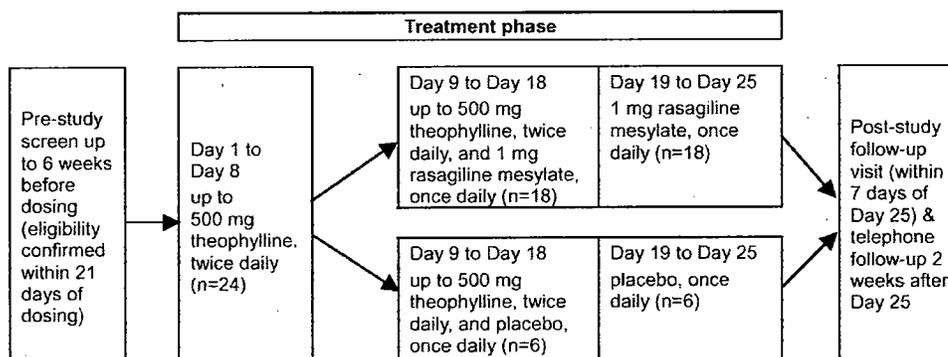
- To evaluate the pharmacokinetic profiles of rasagiline and theophylline after concomitant administration.

Secondary

- To monitor the safety and tolerability of multiple dose co-administration of theophylline and rasagiline.

Study Design

Figure 1A. Study design.



Exclusion Criteria

- smokers, or ex-smokers who had smoked in the six months prior to dose administration or who used another form of nicotine containing product
- known allergy or intolerance to any compound in the test product or any other closely related compound (e.g. selegiline)

Table 2A: Demographic and Baseline Characteristics

Treatment group	Gender	Race	Age	Height	Weight	BMI
			years	cm	kg	kg/m ²
Placebo	Male (n=4)	Caucasian (n=6)	29.0 ± 7.8	175.3 ± 7.6	76.78 ± 11.03	24.88 ± 2.25
	Female (n=2)		(20-43)	(166-183)	(62.1-90.8)	(22.5-27.4)
Rasagiline	Male (n=7)	Caucasian (n=18)	38.4 ± 11.7	168.9 ± 10.0	70.65 ± 10.22	24.73 ± 2.45
	Female (n=12)	Asian (n=1)	(21-55)	(156-187)	(54.8-95.2)	(20.7-28.8)
Overall	Male (n=11)	Caucasian (n=24)	36.1 ± 11.5	170.4 ± 9.8	72.12 ± 10.53	24.76 ± 2.36
	Female (n=14)	Asian (n=1)	(20-55)	(156-187)	(54.8-95.2)	(20.7-28.8)

Mean ± sd and range (min – max)

Treatment Administered:

The following batches of trial medication were supplied:

- Rasagiline mesylate tablets, 1 mg, batch number K-26332, expiry date June 2003
- Placebo for rasagiline mesylate tablets, 1 mg, batch number K-26428, expiry date August 2003
- Theophylline capsules, theophylline 60 mg, batch number 3604X2 (), expiry date January 2004
- Theophylline capsules, theophylline 125 mg, batch number 2001 (), expiry date June 2005
- Theophylline capsules, theophylline 250 mg, batch number 3008 (), expiry date July 2005

Sample Collection and Handling

Day 8 (theophylline only):

0 hours (pre-dose), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 12 hours post-dose

Day 18 (theophylline and rasagiline):

0 hours (pre-dose), 10, 20, 30, 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12 and 24 hours post-dose

Day 25 (rasagiline only):

0 hours (pre-dose), 10, 20, 30, 45 minutes and 1, 1.5, 2, 3, 4, 8, 12 and 24 hours post-dose

Bioanalytical Methods-

Studied Period (years):

Clinical –December 9, 2002-March 13, 2003

Analytical January 24-March 13, 2003

Total storage =93 days

The samples were assayed at

Parameter	Theophylline	Rasagiline	Aminoindan
Method	HPLC\UV detection	GCMS	GCMS

Sensitivity/LOQ	50 ng/ml	0.25 ng/ml	0.5 ng/ml
Linearity (Standard curve samples)	50-20000 ng/ml	0.25-10 ng/ml	0.5-10 ng/ml
Quality Control (QC) Samples	100 ng/ml 10000 ng/ml 16000 ng/ml	0.4 ng/ml 5.0 ng/ml 7.5 ng/ml	0.75 ng/ml 5.0 ng/ml 7.5 ng/ml
Precision of Standards (%CV)	3.35% @ 50 ng/ml 0.79% @ 20000 ng/ml	6.17% @ 0.25 ng/ml 1.05% @ 10.0 ng/ml	5.5% @ 0.5 ng/ml 2.6% @ 10 ng/ml
Precision of QC Samples (%CV)	4.27% @ 100 ng/ml 1.98% @ 16000 ng/ml	8.4% @ 0.4 ng/ml 2.5% @ 7.5 ng/ml	5.3% @ 0.75 ng/ml 3.0% @ 7.5 ng/ml
Accuracy of Standards (%)	103% @ 50 ng/ml 100% @ 20000 ng/ml	106% @ 0.25 ng/ml 100% @ 10.0 ng/ml	106% @ 0.5 ng/ml 102% @ 10 ng/ml
Accuracy of QC Samples (%)	103% @ 100 ng/ml 105% @ 16000 ng/ml	96% @ 0.4 ng/ml 106% @ 7.5 ng/ml	105% @ 0.75 ng/ml 1040% @ 7.5 ng/ml

Assay validation for theophylline was presented in vol 51, pg 982 of 1062 and is acceptable and will not be presented since it is a standard HPLC assay.

Statistical Analysis

The following non-compartmental pharmacokinetic parameters were estimated for each subject from the plasma concentration profiles of rasagiline and 1-aminoindan. Actual sampling times were used for the calculation of pharmacokinetic parameters.

C_{max} maximum plasma concentration over the sampling phase for each study day, directly obtained from the experimental data of plasma concentration versus time curves, without interpolation

AUC_{0-24} area under the plasma concentration-time curve (time 0 hours to time 24 hours) calculated by the linear trapezoidal rule

t_{max} time to C_{max} for each study day

Where there were sufficient data points (at least three) on the terminal portion of the elimination phase of the plasma profile, and where it was appropriate to do so, the following additional parameters were calculated:

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time of dosing to infinity, calculated by the linear trapezoidal rule to the last quantifiable concentration (C_t) with the residual area to infinity calculated from C_t/k_{cl} . Hence $AUC_{0-\infty} = AUC_{0-t} + C_t/k_{cl}$

RESULTS

Table 3A. Mean pharmacokinetic parameters of theophylline following repeated doses of theophylline alone and co-administered with placebo

Parameter	units	Day 8 (n=6)	Day 18 (n=6)
C _{max}	µg/mL	14.82±1.81	14.58±2.80
AUC ₀₋₁₂	µg.h/mL	148.59±21.53	146.28±29.96
t _{max}	h	5.00	4.51

Data are presented as mean ± sd, except for t_{max}. For t_{max}, the median is presented.

Table 4A. Mean pharmacokinetic parameters of theophylline following repeated doses of theophylline alone and co-administered with rasagiline mesylate

Parameter	units	Day 8 (n=19)	Day 18 (n=18)
C _{max}	µg/mL	14.73±3.09	13.71±2.96
AUC ₀₋₁₂	µg.h/mL	143.95±27.61	134.19±28.78
t _{max}	h	4.00	4.00

Data are presented as mean ± sd, except for t_{max}. For t_{max}, the median is presented

Table 5A. Mean pharmacokinetic parameters of rasagiline following repeated doses of rasagiline mesylate alone and co-administered with theophylline

Parameter	units	Day 18 (n=18)	Day 25 (n=18)
C _{max}	ng/mL	8.22±2.70	8.82±2.98
AUC _{0-t}	ng.h/mL	8.03±2.96	8.72±2.32
t _{max}	h	0.50	0.42

Data are presented as mean ± sd, except for t_{max}. For t_{max}, the median is presented.

Table 6A. Mean pharmacokinetic parameters of AI following repeated doses of rasagiline mesylate alone and co-administered with theophylline

Parameter	units	Day 18 (n=18)	Day 25 (n=18)
C _{max}	ng/mL	2.70±0.72	2.84±0.87
AUC _{0-t}	ng.h/mL	31.21±10.58	40.48±14.38
AUC ₀₋₂₄	ng.h/mL	35.08±10.79	41.67±12.57
kel	/h	0.0574±0.0107	0.0434±0.0068
t _{1/2}	h	12.46±2.23	16.37±2.67
t _{max}	h	1.25	2.00

Data are presented as mean ± sd, except for t_{max}. For t_{max}, the median is presented.

Conclusions:

For theophylline, the statistical analysis of the results from this study show that both C_{max} and AUC were similar when theophylline and rasagiline mesylate were co-administered, suggesting that there was no change in the systemic exposure of theophylline. Mean maximum steady-state plasma theophylline concentrations of 14.73±3.09 µg/mL on Day 8 and 13.71±2.96 µg/mL on Day 18 (rasagiline treatment

group) indicate that the study was performed using relevant doses of theophylline since the therapeutic range of theophylline is 10-20 µg/mL.

Rasagiline pharmacokinetics were also unaffected by theophylline co-administration with no indication from the AUC data of an interaction with theophylline. There was an indication of lower plasma levels of AI during co-administration of theophylline and rasagiline mesylate. However there was also an increased elimination rate (shorter half-life) for this treatment. Hence this is the most likely cause of the reduced AUC, rather than an inhibitory effect of theophylline on rasagiline metabolism.

STUDY P94159-Tyramine Study-Normals

PHARMACODYNAMIC INTERACTION STUDY BETWEEN TVP-1012 AND ORAL TYRAMINE AFTER REPEATED ORAL ADMINISTRATION OF 1, 2 MG/DAY TVP-1012 OR 10 MG/DAY SELEGILINE FOR TEN DAYS IN THREE GROUPS OF NINE NORMAL HEALTHY VOLUNTEERS

Study Introduction

TVP-1012 (N-propargyl-1-R-aminoindan mesylate, PAI) is a potent, selective, non reversible monoamine oxidase type B (MAO-B) inhibitor. It is presently developed as a treatment of Parkinson's disease. TVP-1012 has been previously investigated in healthy subjects at daily doses up to 10 mg given once daily for ten days. The drug showed a good clinical safety and tolerability.

Although TVP-1012 is a selective MAO-B inhibitor in all experimental animals, its selectivity in human was not assessed. Partial inhibition of MAO-A may lead to tyramine potentiation, i.e. increased sensitivity to tyramine resulting in blood pressure elevation. Therefore, the present study was performed to investigate a possible interaction with tyramine to evaluate the potential risk for patients receiving the drug together with a normal diet, which may contain tyramine.

Objectives

The main objective of the study was to determine the effect of 50, 100, 200, 400 and 800 mg tyramine given orally on systolic blood pressure in healthy male subjects after repeated oral administrations of daily doses of 1 and 2 mg/day of TVP-1012 or 10 mg/day selegiline administered once daily for ten days.

The end-point was to determine the dose of tyramine which induced an increase in the systolic blood pressure of at least 30 mmHg in comparison to the blood pressure measured prior to the respective tyramine administration.

The study protocol was amended (amendment 2) : an extra group of 9 subjects was added to study the effect of the same doses of tyramine on systolic blood pressure after pre-treatment with 10 mg Selegiline (Deprenyl®, a selective irreversible MAO-B inhibitor, marketed without dietary limitations with respect to tyramine), another potent MAO-B inhibitor. The main objective of this amendment is to compare the results of the interaction between TVP-1012 and tyramine with the results of the interaction between a reference MAO-B inhibitor : selegiline and tyramine.

Design

Twenty-seven (27) healthy male subjects were divided into three parallel groups of nine subjects each. All subjects underwent two subsequent treatment schedules of 10 days each, separated by a wash-out period of seven days.

Period 1:

During Period 1, all subjects received single-blind, under fasting conditions, placebo from Day 1 to Day 10. On Day 8, Day 9 and Day 10 tyramine was administered, also under fasted conditions, as follows:

on Day 8: 50 mg tyramine given 0.5 hours after placebo administration,

on Day 9: 100 mg tyramine given 0.5 hours after placebo administration and 200 mg tyramine given 3.5 hours after placebo administration,

on Day 10: 400 mg tyramine given 0.5 hours after placebo administration and 800 mg tyramine given 3.5 hours after placebo administration.

Period 2:

During Period 2, all subjects received, under fasting conditions, a double blind treatment (TVP-1012, 1 mg/day or 2 mg / day selegiline or placebo from Day 1 to Day 10.

Group 1: Six subjects received 1 mg TVP-1012 per day and three subjects received placebo,

Group 2: Six subjects received 2 mg TVP-1012 per day and three subjects received placebo,

Group 3: Six subjects received 10 mg selegiline per day and three subjects received placebo.

On Day 8, Day 9 and Day 10 tyramine was administered, also under fasting conditions, as described for period 1:

on Day 8: 50 mg tyramine given 0.5 hours after TVP-1012, selegiline or placebo administration,

on Day 9: 100 mg tyramine given 0.5 hours after TVP-1012, selegiline, or placebo administration and 200 mg tyramine given 3.5 hours after TVP-1012, selegiline or placebo administration,

on Day 10: 400 mg tyramine given 0.5 hours after TVP-1012, selegiline or placebo administration and 800 mg tyramine given 3.5 hours after TVP-1012, selegiline or placebo administration.

The three groups were studied sequentially, starting with the 1 mg TVP-1012 group (Group 1).

Demographics

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 ± 3.0 (24.0-31.0)	23.0 ± 2.4 (20.0-26.0)	24.1 ± 2.6 (21.0-27.0)	25.5 ± 4.2 (19.0-32.0)
Weight (kg)	74.4 ± 7.4 (64.2-81.6)	69.4 ± 10.2 (61.4-88.0)	75.6 ± 9.2 (66.0-89.0)	75.7 ± 8.5 (59.6-89.2)
Height (cm)	179 ± 4.7 (174-187)	175 ± 10.2 (165-190)	180 ± 6.5 (172-189)	178 ± 7.0 (168-188)

Smokers were excluded from the study population.

Sample Collection and Handling

Day 8: Blood pressure was measured in 5-minute intervals in the supine position from 0.5 hours to 3.0 hours after TVP-1012, selegiline, or placebo administration (corresponding to the time period from immediately after tyramine administration up to 2.5 hours thereafter).

Day 9 and Day 10: Blood pressure was measured in 5-minute intervals in the supine position from 0.5 hours to 6.0 hours after TVP-1012, selegiline or placebo administration (corresponding to the time period from immediately after the first tyramine administration up to 2.5 hours after the second one).

Tyramine sampling times

Day 8 of each period: 0.5 h (pre-dose for tyramine), 1.5h, 3.5h, 4.5h and 6.0h after TVP-1012, selegiline, or placebo administrations

Day 9 and Day 10 of each period: 0.5h (pre-dose for the first daily tyramine administration), 1.5h, 3.5h (pre-dose for the second daily tyramine administration), 4.5h and 6.0h after TVP-1012, selegiline, or placebo administrations

MAO-B activity

Day 7 of each period: 1h after TVP-1012, selegiline, or placebo administrations.

Plasma samples for rasagiline and aminoindan.

Day 1 of period 2: 0h (pre-dose), 0.5h, 1.0h, 2.0h, 4.0h, 8.0h and 12h after TVP-1012 or placebo administrations.

Day 2 of period 2: 0h (pre-dose) and 1.0h after TVP-1012 or placebo administrations.

Day 8 of period 2: 0h (pre-dose for TVP-1012 or placebo administrations).

Day 9 and Day 10 of period 2: 0h (pre-dose), 0.5h, 1.0h, 2.0h, 4.0h and 8.0h after TVP-1012 or placebo administrations.

Bioanalytical Methods-

Studied Period (years):

The study was done by _____

Clinical study dates were not supplied.

Analyses of study samples were performed from 08/08/1995 to 30/11/1995 for tyramine, from 17/07/1995 to 17/11/1995 for PAI and AI and from 21/12/1995 to 28/01/1996 for DOPEG.

All subjects were Caucasian.

Since stability has been exhibited for > 1 year for PAI and AI the absence of actual clinical dates is not important.

Parameter	Rasagiline	Aminoindan
Method	GC\MS	GC\MS
Sensitivity/LOQ	0.25 ng/ml	0.5 ng/ml
Linearity (Standard curve samples)	0.25-10 ng/ml	0.5-10 ng/ml
Quality Control (QC) Samples	0.4 ng/ml 2.50 ng/ml 7.5 ng/ml	0.75 ng/ml 2.50 ng/ml 7.5 ng/ml
Precision of Standards (%CV)	7.37% @ 0.25ng/ml 2.50% @ 10.0 ng/ml	6.14% @ 0.5 ng/ml 2.67% @ 10 ng/ml
Precision of QC Samples (%CV)	9.8 @ 0.4 ng/ml 7.52 @ 7.5 ng/ml	8.05% @ 0.75 ng/ml 4.56% @ 7.5 ng/ml
Accuracy of Standards (%)	93% @ 0.25ng/ml 99.3% @ 10ng/ml	99.3% @ 0.5 ng/ml 99.0% @ 10 ng/ml
Accuracy of QC Samples (%)	99% @ 0.4 ng/ml 99% @ 7.5 ng/ml	99% @ 0.75 ng/ml 103% @ 7.5 ng/ml

Statistical Analysis

Primary variables

The pharmacodynamic endpoint was the dose of tyramine which induced an increase in systolic blood pressure by 30 mmHg or more (TYR₃₀). The change in systolic blood pressure was computed as the difference between the actual systolic blood pressure value after tyramine administration and the systolic blood pressure value obtained immediately before tyramine administration (baseline measurements at Day 8, Day 9 and Day 10). To obtain this value, minute by minute blood pressure recordings were recorded when the subjects was close to reach the endpoint (these values were documented on separate paper sheets which are added to the individual Case Record Forms as comment sheets). The highest values for systolic and diastolic blood pressure as well as of pulse rate on the days of tyramine administrations were selected and put into the database.

Two cohorts were considered for endpoint assessment, the ITT cohort and the Completed cohort.

The ITT cohort consisted of all subjects who have been randomised.

The completed cohort consisted of all subjects who completed the study according to protocol.

In the present report, only the evaluation with the completing subjects is presented.

Two approaches were used to define the main endpoint:

- The dose of tyramine which induced an increase in systolic blood pressure by 30 mmHg or more (strict protocol criteria).
- The dose of tyramine which induced an increase in systolic blood pressure by 30 mmHg or more and/or the following clinical criteria:

Drug effect assessment

The distribution of the subjects having reached the pharmacodynamic endpoint as defined above is tabulated according to treatment groups and dose of tyramine administered. Also a TYR₃₀ - ratio was calculated as the ratio of the tyramine dose with which the clinical endpoint was reached at Period 1 divided by the tyramine dose with which the clinical endpoint was reached at Period 2. However, the following assumptions were made:

- For subjects who never reached TYR₃₀, it was assumed that with a much higher dose of tyramine the TYR₃₀ could have been reached.
- For those subjects who never reached TYR₃₀ and who received tyramine doses up to 400 mg and 800 mg, respectively, the highest dose to reach TYR₃₀ was assumed to be 450 mg and 850 mg, respectively. Calculations were done using these figures.

Secondary variables

Pharmacokinetics

Descriptive statistics are presented for t_{max} , C_{max} and AUC of PAI and AI for Period 2.

Plasma Tyramine

Descriptive statistics are presented for t_{max} , C_{max} and AUC of tyramine for Period 1 and Period 2 MAO-B activity.

Descriptive statistics are presented for MAO-B activity for Period 1 and Period 2.

Pharmacokinetic Analysis

Before the analysis of variance the normality of the distribution and the homogeneity of variance were verified, when these conditions were not proved a correspondent non-parametric test was used. The between day analysis of C_{max} and AUC was carried out by analysis of variance using PROC GLM on the logarithmically transformed data. The 90% standard confidence interval limits for relative treatment differences were calculated by geometric means based on logarithmic transformation of the intraindividual ratios of C_{max} and AUC. The between day analysis of t_{max} was based on the non-parametric Wilcoxon signed rank test and was carried out using PROC UNIVARIATE.

RESULTS

Table 1A. Mean \pm SD TYR30 ratio by treatment group

Treatment	TYR 30 Ratio
Placebo	1.0 \pm 0.5
1 mg TVP-1012	1.0 \pm 0.05
2 mg TVP-1012	2.7 \pm 1.0
10 mg selegiline	1.9 \pm 1.2

Source: individual data for period 1 and 2 are presented in Table 2A.

Table 2A. Mean \pm SD values of the plasma concentrations of tyramine and their Period2/Period 1 ratios assessed 1 hour after 50 mg and 100 mg tyramine administrations during multiple oral administrations 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 3A. Mean \pm SD values of the pharmacokinetic parameters of Rasagiline after multiple oral administrations at Day 9 of the study.

Parameter	1 mg TVP-1012	2 mg TVP-1012
t_{max} (h)	0.58 \pm 0.20	0.58 \pm 0.20
C_{max} (ng/ml)	7.49 \pm 2.19	12.09 \pm 3.88
AUC (ng/ml·h)	5.84 \pm 0.98	24.68 \pm 6.15

Similar results were seen for Day 10

Table 4A. Mean \pm SD values of the pharmacokinetic parameters of the metabolite AI after multiple oral administrations at Day 9 of the study.

Parameter	1 mg TVP-1012	2 mg TVP-1012
t_{max} (h)	1.67 \pm 1.33	5.08 \pm 3.38
C_{max} (ng/ml)	2.51 \pm 0.72	5.35 \pm 0.87
AUC (ng/ml•h)	14.81 \pm 4.85	37.90 \pm 6.54

Summary:

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.

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 AI, AUC values also increased more than dose-proportionally. Based on previous PK studies it is known that the t_{max} of 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.

Comments:

1. The Medical Officer reviewed the individual systolic BP graphs and found individual changes to be acceptable especially in the group with the TYR 30 ratio=2. However there was some concern for subjects with hepatic disease which needs to be addressed by the firm.
2. Study 132, was conducted in PD patients taking levodopa. Extreme challenge of tyramine (fasting conditions and very high tyramine doses) is not considered medically safe and therefore, the original intention of this design was to challenge the patients with tyramine doses exceeding those that might be consumed in real life and under fed conditions. The main consideration in this study was to allow the evaluation of the tyramine pressor effect in PD patients without jeopardizing the patients safety.

STUDY TVP-1012/132A-Oral Rasagiline in PD Patients using Levodopa/Carbidopa

PHARMACODYNAMIC INTERACTION BETWEEN ORAL RASAGILINE MESYLATE (TVP-1012) AND ORAL TYRAMINE IN PARKINSONIAN PATIENTS USING LEVODOPA/CARBIDOPA

Background

To evaluate the interaction between tyramine and MAO-inhibitors. Following a 1000-kcal meal the bioavailability of tyramine is reduced by a factor of about 2.8 compared to ingestion of tyramine alone. Therefore, tyramine is usually given with food to avoid over-estimation of the pressor effect of a given amount of dietary tyramine. Sensitivity to tyramine is assessed by measuring the pressor response following the administration of a standard tyramine dose (or several escalating doses) combined with food. The pressor response with and without the MAO-I is assessed and the proportion of subjects exhibiting a rise of ≥ 30 mm Hg in systolic BP post-tyramine dosing is calculated.

STUDY OBJECTIVES

PRIMARY OBJECTIVES

The primary objective of this study was to assess the safety and tolerability of 1 and 2 mg/day rasagiline concomitantly administered with oral tyramine, wherein the tyramine is mixed with food, in PD subjects on chronic LD/CD therapy.

SECONDARY OBJECTIVES

The secondary objectives were to evaluate:

Pharmacokinetics of rasagiline (PAI) and its major metabolite (AI) during a 70-day treatment period at a daily dose of 1 or 2 mg in subjects on chronic LD/CD.

Pharmacodynamics of rasagiline as measured by platelet MAO-B inhibition.

Pharmacokinetics of LD in rasagiline treated subjects in comparison to the pharmacokinetics before initiation of rasagiline therapy.

The changes in Unified Parkinson Disease Rating Scale (UPDRS), Quality of Life Scale and ON/OFF Fluctuation Diary.

Study Design

The study duration was 14 weeks (98 days), during which subjects participated in 13 visits (Table 1A).

Table 1A.

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

This was a double blind, placebo controlled, randomized, single center, Phase II, clinical pharmacology study. Twenty-nine (29) subjects were screened, of whom twenty (20) were

found eligible for the study. Subjects were assigned to two sequential groups (1 mg and 2 mg rasagiline). In each group, three subjects were randomly assigned to receive placebo while the remaining subjects were administered rasagiline at the assigned dose. Only upon successful and safe completion of the first study phase by the subjects receiving 1 mg rasagiline, was the second group (2mg rasagiline or placebo) allowed initiating treatment.

During the first three weeks of the study, subjects received the assigned rasagiline dose (1 or 2 mg/day) or placebo and maintained a tyramine-restricted diet. On Day 22, the subjects were admitted to the hospital for a three-day monitoring period to evaluate their response to tyramine challenge. During the first 24 days, maintenance of the low tyramine diet was mandatory. A week prior to the initiation of the study (Day -7), subjects were challenged with 75 mg tyramine, subject response to which served as baseline. A controlled escalating dose of tyramine was to be given with the morning meal on Days 22, 23 and 24 (25 mg, 50 mg and 75 mg, respectively). Additionally, 75 mg tyramine was to be added to the morning meal on Day 70 (Termination). On Days 22, 23, 24 and 70, prior to tyramine intake, subjects ingested their regular LD/CD tablets and their assigned rasagiline or placebo dose. **Misinterpretation** of the protocol led to a consistent deviation from its instruction to provide tyramine **with** the morning meal. As a result of a protocol misinterpretation, the controlled escalating dose of tyramine was mixed with applesauce and administered prior to subjects breakfast. Administering tyramine in applesauce to subjects in a fasting condition represents a deviation from protocol (Section 6.1) and led to rapid absorption and increased bioavailability of tyramine.

Subjects were not screened for smoking.

Table 2A. Descriptive Statistics of Demographic Characteristics

**APPEARS THIS WAY
ON ORIGINAL**

TVP1012/132		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

Sample Collection and Handling Rasagiline/Tyramine Interaction

Vital signs monitoring was performed on Day -7 (every 15 minutes for the initial 2 hours and every 30 minutes for the next 2 hours) following the consumption of 75 mg of tyramine. On Days 22, 23, 24 and 70, in the presence of study drug telemetry was performed (every 5 minutes for the first 2 hrs and every 15 min for the next 2 hrs) following the consumption of 25 mg, 50 mg, 75 mg and 75 mg of tyramine, respectively,. On each of these days and for each subject, the maximal increase of supine systolic BP from the measurement taken prior to tyramine administration at the same day (Δp) and the time to that increase (Δt) was calculated. The ratio $\Delta p/\Delta t$ was also calculated reflecting the systolic BP increase per unit of time. The change in Δp , Δt and $\Delta p/\Delta t$ ratio of Day 23, 24 and 70 to that of Day -7 and 22 was calculated and compared by treatment group. The area under the curve (AUC) for change in individual systolic BP over time was calculated. In addition, potassium levels were measured.

PHARMACODYNAMICS AND PHARMACOKINETICS

Rasagiline and Aminoindan

Blood samples for the determination of rasagiline and its metabolite (AI) levels were collected on Days 1, 23 and 70, prior to study drug administration and 0.5, 1, 2 and 4 hours thereafter.

Levodopa and Carbidopa

Blood samples for determining LD and CD levels were taken on Days -7, 1, 23 and 70 before the morning LD/CD dose and 0.5, 1, 2 and 4 hours thereafter. On Day -7, baseline levels were determined for each subject. Blood samples were taken prior to LD/CD tablet administration and 0.5, 1, 2 and 4 hours thereafter. These measurements constituted the baseline values and served as the reference against which LD and CD levels measured on Days 23 and 70 (termination) were compared. This permitted investigators to assess whether any change in plasma LD levels had occurred following the co-administration of rasagiline.

Platelet MAO-B Inhibition

Blood samples for platelet MAO-B activity were collected on Days 1 (baseline), 22, 70, 84 and 98, in each subject, prior to the LD/CD treatment.

Descriptions for the other measures such as UPDRS score, Quality of life Score, ON/OFF diaries are presented in the Appendix 15.1 by the sponsor.

Statistical Analysis

Pharmacokinetics and Pharmacodynamics

Descriptive statistics including mean, standard deviation, minimum and maximum values were used to summarize the data which is presented by treatment group. The following analyses were made:

Blood samples for PAI and AI were taken at Days 1, 23 and 70. C_{max}, t_{max}, and AUC were calculated for each of the subjects at each of these days.

LD PK

Blood samples for LD were taken at Days -7, 1, 23 and 70. C_{max}, t_{max}, and AUC were calculated for each of the subjects on each of these days. The ratio between these PK parameters calculated for Days 23 and 70, to those measured at day 1, was calculated and is presented in a summary tables.

MAO-B Activity

The inhibition of the MAO-B activity was calculated for Days 22, 70, 84 and 98 as the percent reduction from the actual measurement taken at day 1 prior to study-drug administration.

Assessment of Clinical Effect

The following analyses were performed:

UPDRS (Total, Mentation, ADL, Motor and Therapy Complications), Hoehn & Yahr and Schwab & England scales. An assessment of these parameters was performed during screening and at Days 1, 42, 70 and 98. Changes from day 1 (baseline) were calculated for Days 42, 70 and 98. Descriptive statistics including mean, standard deviation, minimum and maximum are presented by treatment group.

Quality of Life Assessment (QOL)

QOL questionnaires were distributed at days 1, 21, 70 and 98. The eight dimensions of the QOL questionnaire: Mobility, ADL, Emotional well being, Stigma, Social support, Cognition, Communication and Bodily discomfort, were scored. Additionally, a total QOL score was calculated as the mean of the eight dimension scores. Results are presented in the same way as the UPDRS score.

RESULTS

Table 3A. Descriptive Statistics of Sitting Systolic Blood Pressure by Treatment Group and Time Interval from Tyramine Challenge, Day 70

PROTOCOL TVP1012/132	TREATMENT GROUP														
	1mg					Placebo					2mg				
	MEAN	STD	N	MIN	MAX	MEAN	STD	N	MIN	MAX	MEAN	STD	N	MIN	MAX
TIME INTERVAL (HOURS)															
0	140.7	14.0	3	126	154	151.3	11.0	3	144	164	132.7	23.0	6	104	161
2	120.5	10.3	6	106	131	134.8	22.0	6	114	174	107.8	21.7	6	79	145
4	133.3	16.1	6	121	159	144.5	19.1	6	123	176	134.8	20.7	6	114	170

Comments:

1. The results show that there does not appear to be an effect of Tyramine in PD subjects taking Sinemet. Subjects receiving placebo exhibited BP changes similar to those treated with Rasagiline at 1 mg (Post text tables, Table 3A in the review, 19-65 pages 157 of 296 to 203 of 296 vol 58). The 2 subjects #206 and # 207 that received the 2 mg dose and had a tyramine/rasagiline interaction had Cmax values of 27.7 ng/ml and 6.18 ng/ml at the times of their events on days 23 and day 70 respectively. This did not appear to be related to plasma level since other subjects at the 1 mg dose(#1105) with Cmax values of 8.6 ng/ml and subject (# 2206) at the 2 mg dose with a 13.5 ng/ml Cmax did not have a clinical manifestation of a tyramine/rasagiline interaction although their levels exceeded those (6.18 ng/ml) for #207.

STUDY NO: TVP-1012/423 –Absolute Bioavailability

ASSESSMENT OF ABSOLUTE BIOAVAILABILITY OF RASAGILINE IN HEALTHY SUBJECTS – COMPARISON OF SYSTEMIC EXPOSURE AFTER A

**SINGLE ORAL ADMINISTRATION VERSUS A SINGLE INTRAVENOUS
ADMINISTRATION**

STUDY OBJECTIVES

The objectives of the study were to determine the absolute bioavailability of rasagiline (PAI, TVP-1012) after a single oral administration (2 mg) in healthy subjects in comparison to a single intravenous administration (2 mg), - to assess the safety and tolerability of IV Rasagiline, in fourteen (14) healthy male volunteers, with at least 12 completers.

STUDY DESIGN

This was an open, randomised, single dose, two-way cross-over study in 14 healthy male volunteers. The study was divided into study periods 1 and 2, each with a duration of 1 day. Each subject received on day 1 of each study period a 2 mg dose of rasagiline, formulated as an oral formulation (Treatment A Test formulation) or as an intravenous formulation (Treatment B Reference formulation) to evaluate the absolute bioavailability of rasagiline. Each subject received the treatments in a randomised order prescribed by the Department of Biostatistics. Serial blood samples were collected immediately pre-dose and up to 24 hours after each dose. There was at least a 21 day wash-out period between two treatment periods. Smokers were not excluded from the study.

Demographics

Age - Weight - Height - BMI

Parameters	Sequence	N	Mean	SD	SEM	Min.	Max.
Age (years)	AB	7	32.4	10.2	3.9	19	45
	BA	7	28.6	5.6	2.1	20	37
	Total	14	30.5	8.1	2.2	19	45
Weight (kg)	AB	7	72.47	12.29	4.64	56.0	88.2
	BA	7	74.81	8.68	3.28	59.5	86.0
	Total	14	73.64	10.29	2.75	56.0	88.2
Height (cm)	AB	7	172.1	8.7	3.3	160	183
	BA	7	180.7	6.0	2.3	173	189
	Total	14	176.4	8.5	2.3	160	189
Body Mass Index (kg/m ²)	AB	7	24.39	3.20	1.21	20.9	29.8
	BA	7	22.97	3.05	1.15	18.0	26.5
	Total	14	23.68	3.09	0.83	18.0	29.8

Gender - Ethnic group

Parameters	Sequence		N	%
Gender	AB	Male	7	100.0
	BA	Male	7	100.0
	Total	Male	14	100.0
Ethnic group	AB	Black	2	28.6
		Caucasian	4	57.1
		Other	1	14.3
	BA	Black	2	28.6
		Caucasian	5	71.4
	Total	Black	4	28.6
		Caucasian	9	64.3
		Other	1	7.1

Analytical

STUDY DATES :

First subject in (screening):	October 1 st , 2002
First study-drug administration :	October 7 th , 2002
Last study-drug administration :	November 14 th , 2002
Last subject out (completion) :	November 21 st , 2002

The analytical was conducted by

Parameter	Rasagiline	Aminoindan
Method	GC\MS	GC\MS
Sensitivity/LOQ	0.25 ng/ml	0.5 ng/ml
Linearity (Standard curve samples)	0.25-10 ng/ml	0.5-10 ng/ml
Quality Control (QC) Samples	0.4 ng/ml 5.0 ng/ml 9.0 ng/ml	0.75 ng/ml 5.0 ng/ml 9.0 ng/ml
Precision of Standards (%CV)	4.35% @ 0.25 ng/ml 0.91% @ 10 ng/ml	8.0% @ 0.5 ng/ml 2.3% @ 10 ng/ml
Precision of QC Samples (%CV)	11.43% @ 0.4 ng/ml 4.10% @ 9.0 ng/ml	8.7% @ 0.75 ng/ml 4.0% @ 9.0 ng/ml
Accuracy of Standards (%)	92% @ 0.25ng/ml 98.5% @ 10ng/ml	100% @ 0.5 ng/ml 99.0% @ 10 ng/ml
Accuracy of QC Samples (%)	87.5% @ 0.4 ng/ml 95% @ 9.0 ng/ml	92% @ 0.75 ng/ml 99% @ 9.0 ng/ml

Pharmacokinetics

Blood samples were collected at:

I.V. : 0 (pre-dosing), 5 min, 10 min, 15 min, 20 min, 30 min, 45 min, 60 min, 90 min, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h and 24 hours after commencing dosing. Oral : 0 (pre-dosing), 10 min, 20 min, 30 min, 45 min, 60 min, 90 min, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h and 24 hours after commencing dosing.

DATA ANALYSIS

From plasma concentration versus time profiles, the following pharmacokinetic parameters were calculated: C_{max} , AUC, t_{max} , $t_{1/2}$, for PAI and AI, and F_{abs} , CL, Vd ($Vd\beta$ and Vd_{ss}) for rasagiline.

RESULTS

Figure 1A. Mean and SD of plasma concentration-time profiles of rasagiline obtained after single oral and intravenous administration of 2 mg of rasagiline (Logarithmic scale)

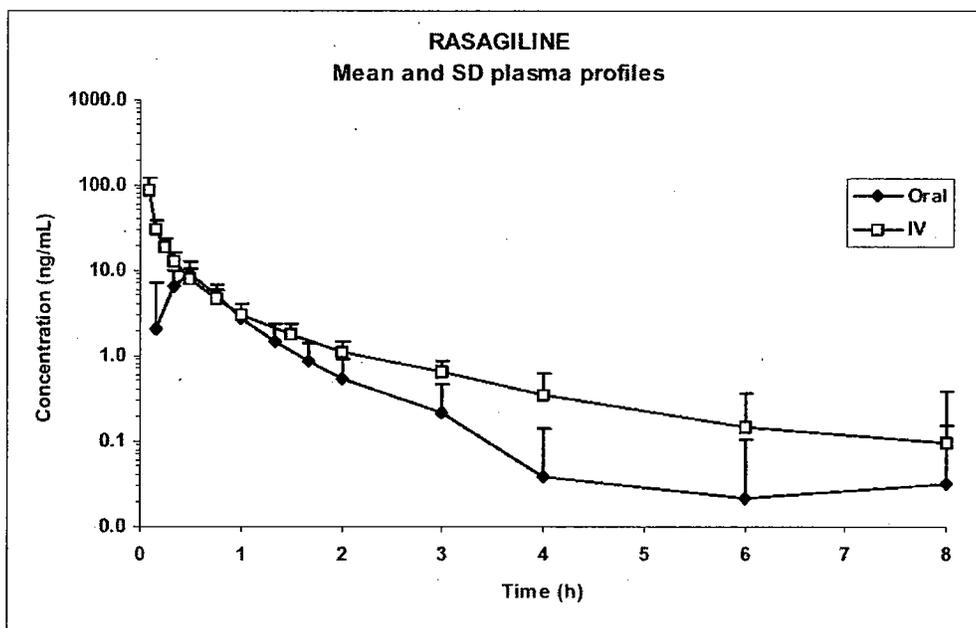


Table 1A. Mean and SD of pharmacokinetic parameters of rasagiline after single oral and intravenous administration of 2 mg of rasagiline

RASAGILINE	C_{max} (ng/ml)	$t_{max}^{\#}$ (h)	AUC_{0-1} (h*ng/ml)	$AUC_{0-\infty}$ (h*ng/ml)	$t_{1/2}$ (h)	MRT (h)	$Vd\beta$ (L)	Vd_{ss} (L)	CL_{tot} (ml/min)	Fabs
Oral										
Geometric Mean	9.53		6.47	6.84*			-	-	-	
Mean	10.34	0.50	6.66	7.06*	0.92*	1.08*	-	-	-	
SD	4.35	0.17- 0.75	1.63	1.86*	0.75*	0.52*	-	-	-	
CV (%)	42	-	24	26*	82*	49*	-	-	-	
IV										
Geometric Mean	82.09		19.30	20.73*						
Mean	87.51	0.08	20.04	21.54*	1.88*	0.94*	243*	87	1668*	0.36**
SD	32.45	0.08- 0.08	5.86	6.41*	1.50*	0.53*	162*	39	467*	0.16**
CV (%)	37	-	29	30*	80*	57*	67*	45	28*	44**
Statistics										
ANOVA	p<0.0001		p<0.0001	p<0.0001**						
90%CI			0.31-0.37	0.32-0.39**						
Point Estimate			0.34	0.35**						

#: Median (min-max) value of the maximal plasma concentration (Oral) or the first measured plasma concentration (IV)
*: N=13 subjects **: N=12 subjects

CONCLUSION

Based on the $AUC_{0-\infty}$ of the 12 available subjects for both treatments, the mean absolute bioavailability was 0.36 (90% CI 0.32-0.39) after administration of 2 mg rasagiline as two 1 mg tablets compared with the same dose administered intravenously through an i.v. bolus. As $AUC_{0-\infty}$ could not be computed for subjects 7 and 8, the absolute bioavailability was also calculated using the AUC_{0-1} . Based on this parameter (estimated for the 14 subjects), the mean absolute bioavailability was also 0.36 (90% CI 0.31-0.37) thus confirming that the evaluation of the absolute bioavailability based on the 12 subjects was not biased.

Rasagiline is cleared rapidly from the circulation as exemplified by the total body clearance of 100 L/H (1668 ml/min) after intravenous administration.

STUDY NO: TVP-1012/427-Bioequivalence Study

A SINGLE DOSE TWO-WAY CROSSOVER BIOEQUIVALENCE STUDY BETWEEN TEST AND REFERENCE RASAGILINE (TVP-1012) TABLETS IN HEALTHY MALE AND FEMALE SUBJECTS

Objectives

To compare the bioavailability of rasagiline and its active metabolite, aminoindane (AI) from the test product with that of the reference following single dose administration. To monitor the subjects for adverse events during the study.

Study Design

This was an open-label, randomized, single-dose, two-period, two-treatment, two-sequence crossover study.

Subjects were randomized to receive a single dose of two x 1mg rasagiline tablets on two separate occasions. Subjects received each of the following treatments according to a randomization code produced by _____ using the PROC PLAN procedure of SAS Version 8.2.

Admin 1 (A): 2 x 1mg Rasagiline tablet (To be Marketed Formulation; Test). Batch # MIN 063

Admin 2 (B): 2 x 1mg Rasagiline tablet (Clinical Trial Formulation; Reference). Batch #K-26703

There was a washout period of at least 21 days between doses.

Each in-house study period was of approximately 60 hours duration (48 hours post-dose).

The study took place in the _____ under full medical and nursing supervision.

Subjects were allowed to leave the Clinical Centre at 48 hours post-dose.

Only Caucasian subjects were recruited for this study. Smokers were not excluded from the study design.

Blood samples (7ml) for determination of rasagiline and AI plasma levels were taken into _____ tubes at the following times:

Pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, 24, 36 and 48 hours post dose (19 samples per phase).

Demographic Characteristics

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Male

Age	N	20
	Mean	27.2
	Std Dev	5.0
	Minimum	21
	Maximum	41
Height	N	20
	Mean	1.78
	Std Dev	0.06
	Minimum	1.68
	Maximum	1.92
Weight	N	20
	Mean	72.5
	Std Dev	9.1
	Minimum	58.0
	Maximum	91.1

Female

Age	N	4
	Mean	24.8
	Std Dev	3.6
	Minimum	22
	Maximum	30
Height	N	4
	Mean	1.57
	Std Dev	0.02
	Minimum	1.55
	Maximum	1.60
Weight	N	4
	Mean	53.5
	Std Dev	4.2
	Minimum	48.0
	Maximum	58.0

Bioanalytical Methods-

The analysis was done by _____ under the supervision of _____

Studied Period (years):

Clinical phase June 28-July 26, 2002.

Parameter	Rasagiline	Aminoindan
Method	GC\MS	GC\MS
Sensitivity/LOQ	0.25 ng/ml	0.25 ng/ml
Linearity (Standard curve samples)	0.25 ng/ml-25 ng/ml	0.25 ng/ml-25 ng/ml
Quality Control (QC) Samples	0.75 ng/ml 2.5 ng/ml 22 ng/ml	0.75 ng/ml 2.5 ng/ml 22 ng/ml
Precision of Standards (%CV)	9.5% @ 0.25 ng/ml 3.4% @ 25 ng/ml	3.9% @ 0.25 ng/ml 3.2% @ 25 ng/ml
Precision of QC Samples (%CV)	12.6% @ 0.75 ng/ml 2.57% @ 22 ng/ml	13% @ 0.75 ng/ml 2.3% @ 22 ng/ml
Accuracy of Standards (%)	98.5% @ 0.25 ng/ml 99.6% @ 25 ng/ml	99.5% @ 0.25 ng/ml 99.6% @ 25 ng/ml
Accuracy of QC Samples (%)	94.3% @ 0.75 ng/ml 101.5% @ 22 ng/ml	99.6% @ 0.75 ng/ml 99.2% @ 22 ng/ml
Recovery	79.6% @ 0.75 ng/ml 86.4% @ 22 ng/ml	74.7% @ 0.75 ng/ml 81.4% @ 22 ng/ml
Freeze-Thaw	3 cycles	3 cycles
Long term stability		

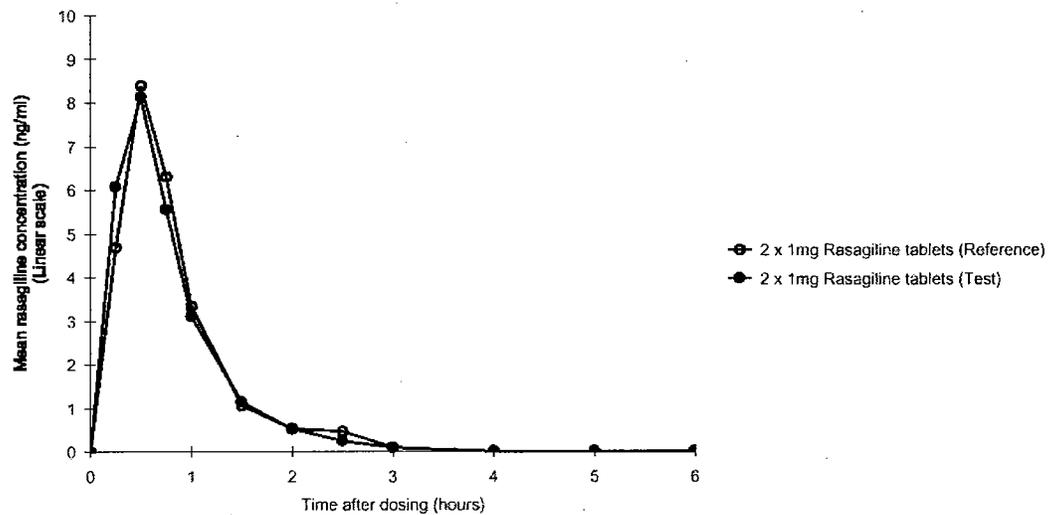
Statistical Analysis

The following rasagiline and AI pharmacokinetic parameters, calculated from the plasma profiles, were subjected to statistical analysis: C_{max}, T_{max}, AUC_T and AUC_∞. Following logarithmic transformation, AUC_T, AUC_∞ and C_{max} values were subjected to an analysis of variance (ANOVA) technique, including terms for sequence, subject within sequence, period and formulation. For comparison, point estimates and 90% confidence intervals for the difference between formulations for rasagiline and AI were constructed using the residual mean square error obtained from the ANOVA. The point and interval estimates were back transformed to give estimates of the ratio of the geometric means and 90% confidence intervals for the ratios of the two formulations in the comparison. T_{max} was analysed using a Wilcoxon rank sum test.

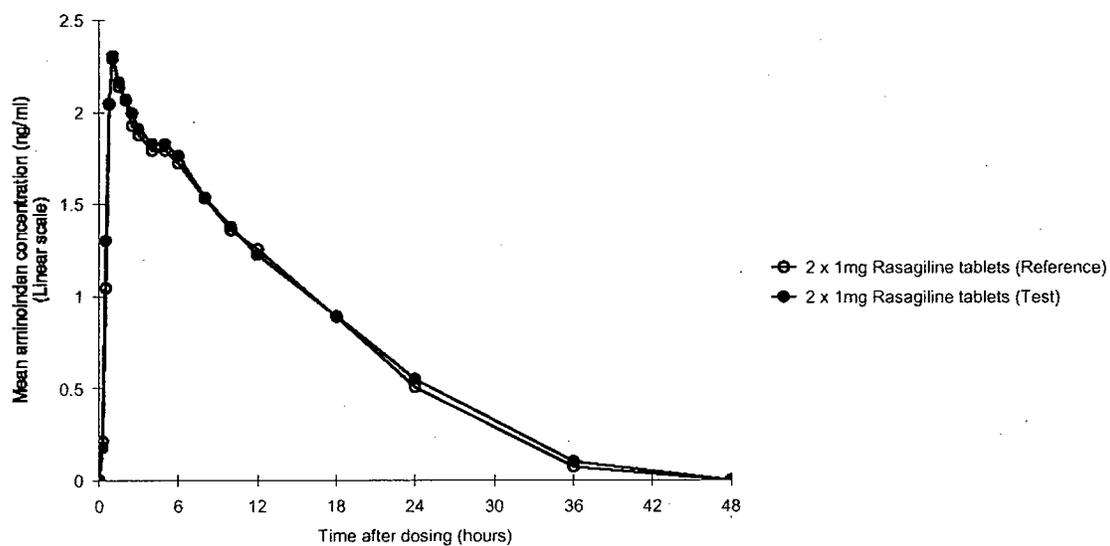
RESULTS

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Mean plasma rasagiline concentrations following single dose oral administration of 2 x 1mg rasagiline tablets (Test) and 2 x 1mg rasagiline tablets (Reference) to twenty-two healthy Caucasian volunteers.



Mean plasma aminoindan (AI) concentrations following single dose oral administration of 2 x 1mg rasagiline tablets (Test) and 2 x 1mg rasagiline tablets (Reference) to twenty-two healthy Caucasian volunteers.



Statistical Results of Rasagiline Pharmacokinetic Data

	Test	Ref	Ratio(%) Test / Ref	90% C.I.s
Geometric LSmeans				
Cmax (ng/ml)	9.89	9.73	101.69	87.05 – 118.79
AUCT (ng.h/ml)	6.78	6.95	97.50	88.93 – 106.91
AUCI (ng.h/ml)	7.04	7.42	94.99	86.57 – 104.23
Median				
Tmax (h)	0.50	0.50	(p=0.2151) *	

Comments:

1. The 90% CI are acceptable and the marketed formulation is BE to the clinical formulation.

STUDY TVP-1012/421-Food Effect Study

AN OPEN, CROSSOVER, FOOD EFFECT STUDY ON BIOAVAILABILITY OF RASAGILINE MESYLATE (TVP-1012) AFTER A SINGLE ORAL DOSE ADMINISTRATION OF 2 MG RASAGILINE MESYLATE IN HEALTHY MALE VOLUNTEERS

Objectives

The aim of this study was to determine the effect of food on the bioavailability of rasagiline by the analysis of pharmacokinetic parameters of rasagiline and its metabolite aminoindan (AI) obtained after administration of 2 mg under fasting and fed conditions.

Study Design

Only Caucasian subjects were recruited and smokers were not excluded.

Eighteen (18) subjects were required to complete the study. The sample size of 18 subjects was considered to be sufficient to detect a 20% difference in AUC and C_{max} of the PAI plasma concentration with probability of 0.80 when testing at the 5% level.

The study drug was administered according to the following regimen :

- Treatment A : one TVP-1012 tablet dosed at 2 mg Rasagiline base (PAI)/tablet, 15 minutes after the beginning of a standard breakfast
- Treatment B : one TVP-1012 tablet dosed at 2 mg Rasagiline base (PAI)/tablet, fasting

On day 1 of each period, blood samples have been collected from all subjects just prior to dosing (T0h), then 10, 20, 30, 45 min, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0 and 12.0 hours after dosing (n = 17).

Demographic and Baseline Characteristics

The mean values (\pm S.D.) of these observed characteristics were :

- Age : 24.2 \pm 3.7 years (range : 20 - 33 years)
- Body weight : 71.4 \pm 9.2 kg (range : 56 - 88 Kg)
- Height : 177.3 \pm 5.6 (range : 165 - 186 cm)

Treatment Administered:

Sample Collection and Handling

Bioanalytical Methods-

Studied Period (years):

Time of clinical part:

Time of analytical part:

Time of pharmacokinetic part:

January 28th-March 27th 1998

March, 1998 - April, 1998

May, 1998

Total storage time=120 days

Parameter	Rasagiline	Aminoindan
Method	GC\MS	GC\MS
Sensitivity/LOQ	0.25 ng/ml	0.25 ng/ml
Linearity (Standard curve samples)	0.25 ng/ml-25 ng/ml	0.25 ng/ml-25 ng/ml
Quality Control (QC) Samples	0.40 ng/ml 2.5 ng/ml 7.5 ng/ml	0.75 ng/ml 2.5 ng/ml 7.5 ng/ml
Precision of Standards (%CV)	4.25% @ 0.25 ng/ml 0.91% @ 10 ng/ml	3.5% @ 0.25 ng/ml 1.7% @ 10 ng/ml
Precision of QC Samples (%CV)	6.8% @ 0.40 ng/ml 2.9% @ 7.5 ng/ml	5.1% @ 0.75 ng/ml 2.2% @ 7.5 ng/ml
Accuracy of Standards (%)	100% @ 0.25 ng/ml 99% @ 10 ng/ml	102% @ 0.25 ng/ml 99% @ 10 ng/ml

Accuracy of QC Samples (%)	103% @ 0.75 ng/ml 97% @ 7.5 ng/ml	89% @ 0.75 ng/ml 91% @ 7.5 ng/ml
----------------------------	--------------------------------------	-------------------------------------

Statistical Analysis

The pharmacokinetic analysis was carried out by —. The pharmacokinetic parameters were calculated, according to standard methods (1)(2), using the — running on a personal computer. The symbols used for pharmacokinetic parameters were those proposed by M. Rowland and G. Tucker (3).

The following pharmacokinetic parameters were derived for each subject after each treatment administered :

* C_{max} , t_{max} :

The maximum plasma concentration (C_{max}) and the time taken to reach C_{max} (t_{max}) were obtained directly from the concentration-time data.

* k_e and $t_{1/2}$:

The terminal rate constant (k_e) was estimated by log-linear regression analysis on data points visually assessed to be on the terminal log-linear phase. The time range used for each calculation of k_e was from the earliest time point possible, commensurate with a high degree of fit and ended with the last time point at which the concentration could be quantifiable. The numerical test of fit was the correlation coefficient (r), the value of which had to be equal to or exceed 0.95. In any case, at least three data points were used for fitting the terminal phase. Also was considered the percentage of extrapolation of $AUC_{0-\infty}$ which should normally not exceed 10%. When the fitting was not acceptable, values of correlation coefficient and/or percentage of extrapolation as close as possible of the target values were retained.

RESULTS

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RASAGILINE N=18	Cmax (ng.ml ⁻¹)	tmax (h)	AUC ₀₋₁ (ng.ml ⁻¹ .h)	AUC _{0-∞} (ng.ml ⁻¹ .h)	t1/2 (h)
Treatment A 2mg TVP-1012, in fed conditions					
Mean	10.01	0.80	10.02	10.52	0.82
s.d.	5.90	0.78	3.35	3.37	0.23
Median	8.97	0.50	9.37	9.71	0.79
Treatment B 2mg TVP-1012, in fasting conditions					
Mean	24.86	0.50	13.02	13.42	0.81
s.d.	10.83	0.27	3.85	3.96	0.34
Median	20.88	0.50	12.79	12.99	0.76
fed / fasting ratio					
Mean	0.49	-	0.80	0.81	-
s.d.	0.47	-	0.25	0.24	-
Median	0.30	-	0.73	0.77	-
Statistics	p < 0.001 (1)	NS (2)	p < 0.001 (1)	p < 0.001 (1)	NS (2)
90% confidence intervals	0.29-0.50	-	0.70-0.83	0.71-0.85	-

(1) : Analysis of variance (PROC GLM on SAS system) on log-transformed data

(2) : Wilcoxon signed rank test (PROC UNIVARIATE on SAS system) on natural data

The mean maximal plasma concentration decreases of 60 % after concomitant administration with food (p<0.001). The 90% confidence intervals is out of the bioequivalence range. The mean time to reach the maximal plasma concentration is modified : a delay of + 0.3 hour is observed with treatment A but it is not statistically significant. Concomitant administration of 2 mg TVP-1012 with food also significantly decreases both mean AUC values (-23% and -22% for AUC₀₋₁ and AUC_{0-∞}, respectively, with p<0.001). The 90% confidence intervals are out of the bioequivalence range (0.70-0.83 for AUC₀₋₁ and 0.71-0.85 for AUC_{0-∞}). The relative bioavailability (F_{rel}) is 0.81± 0.24.

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ON ORIGINAL**

The batch formula for the commercial batches of 1 mg tablets is identical to the batch formula for the three primary stability batches. It is summarized in the following table.

— The intended batch size is — tablets, which is also the batch size used for the manufacture of the three primary stability batches.

Components	Reference to	Amount Per Batch	
	Quality	Amount Per	tablets)
		Tablet [mg]	
	Standards		
Rasagiline Mesylate	Teva In-House		
Mannitol	USP, Ph. Eur.		
Colloidal Silicon Dioxide	NF, Ph. Eur.		
Starch ³	NF, Ph. Eur.		
Pregelatinized Starch (1500)	NF, Ph. Eur.		
Stearic Acid	NF, Ph. Eur.		
Talc	USP, Ph. Eur.		
Theoretical End Weight		210.0	210

1. Equivalent to 1 mg of rasagiline base (N-Propargyl-1-(R)-aminoindan base).
2. Also named Colloidal Anhydrous Silica (Ph. Eur.).
3. Also named Maize Starch (Ph. Eur.).

Dissolution testing was performed according to Teva's method SI-14329/02 (Dissolution test for 1mg pivotal (primary stability) tablets), which is based on and similar to in-house method SI-10591/14 (Dissolution test for 1mg clinical tablets). The test was conducted on 12 tablets from batch MIN063 (1mg pivotal bio-batch (primary stability) tablets containing stearic acid from a _____), and batch K-26703 (1mg clinical tablets containing stearic acid from _____), respectively

Equipment USP. _____ Apparatus 2 (Paddles),
Dissolution volume 500mL.

Medium 0.1N HCl (aq.)

Rotation speed 50rpm

Temperature 37°C

Sampling time 10, 15, 20 and 30 minutes

Method _____

Tab. #	% RASAGILINE OF LABELED AMOUNT DISSOLVED IN 0.1N HCl							
	10 minutes		15 minutes		20 minutes		30 minutes	
	MIN063	K-26703	MIN063	K-26703	MIN063	K-26703	MIN063	K-26703
1								

2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	96	97	97	97	97	97	97	97
%RSD	1.7	1.9	1.3	1.5	1.4	1.3	1.0	1.2

In the additional dissolution study described in this report dissolution is compared between the batches that were used in the bioequivalence study TVP-1012/427 vs the 1 mg clinical batch produced with  stearic acid., the dissolution profiles of the two batches were compared in three media: 0.1N HCl, buffer at pH 4.5 and buffer at pH 6.8

Table 2A. Comparative Dissolution Results of MIN063 vs. K-26703 in 0.1N HCl									
% RASAGILINE OF LABELED AMOUNT DISSOLVED IN BUFFER in 0.1N HCl									
		10 minutes		15 minutes		20 minutes		30 minutes	
Tab. #	MIN063	K-26703	MIN063	K-26703	MIN063	K-26703	MIN063	K-26703	
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
Average	94	97	95	97	95	97	94	97	
%RSD	1.7	1.2	0.7	1.1	1.4	0.9	1.8	1.1	

Table 3A. Comparative Dissolution Results of MIN063 vs. K-26703 in									
buffer at pH 4.5									
% RASAGILINE OF LABELED AMOUNT DISSOLVED IN BUFFER AT PH									
		10 minutes		15 minutes		20 minutes		30 minutes	
Tab. #	MIN063	K-26703	MIN063	K-26703	MIN063	K-26703	MIN063	K-26703	
1									
2									

3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	94	95	95	96	96	95	96	95
%RSD	1.3	0.8	0.9	0.8	1.2	0.7	2.0	0.9

Table 4A. Comparative Dissolution Results of MIN063 vs. K-26703 in buffer at pH 6.8

% RASAGILINE OF LABELED AMOUNT DISSOLVED IN BUFFER at pH 6.8

Tab. #	10 minutes		15 minutes		20 minutes		30 minutes	
	MIN063	K-26703	MIN063	K-26703	MIN063	K-26703	MIN063	K-26703
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	88	91	89	94	90	94	90	95
%RSD	1.6	1.5	1.1	1.7	1.2	1.4	1.6	1.4

The dissolution profiles of the two batches that were used in the bioequivalence study TVP-1012/427: batch MIN063 1mg DW (primary stability batch) tablets containing stearic acid and batch K-26703 1mg clinical (formulation type II) tablets containing stearic acid, were similar. Additionally, the results show the rapidly dissolving nature of tablets of both formulations.

APPENDIX II
PHARMACOMETRICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

DRUG: Agilect® (Rasagiline Mesylate)

PRIMARY REVIEWER: Andre Jackson

NDA: 21641

TYPE: NDA

FORMULATION: Oral Tablet

STRENGTH: 1 mg

APPLICANT: Teva Neuroscience Submission Date: September 5, 2003

INDICATIONS: Mono and Adjunct Therapy Parkinson's Disease

Generic Name: Rasagiline Mesylate

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Executive Summary

AGILECT (rasagiline mesylate) is a propargylamine-based drug indicated for the treatment of idiopathic Parkinson's disease.

The firm conducted two phase III clinical trials. Tempo was done in early Parkinson's disease (PD) subjects, at doses of 1 and 2 mg/day, that were not being treated with levodopa. The other study Presto was conducted in Parkinson's disease (PD) subjects receiving leodopa, at rasagiline doses of 1 and 2 mg/day. The effect of smoking was also investigated since the drug is metabolized by CYP1A2.

The base model for rasagiline was developed using data from study CD596 which was an extensive sampling Phase I study in normals. For the Tempo study, the model which best described rasagiline was a two-compartment linear model while the metabolite 1-Aminoindan (AI) was best described by a one-compartment model. The significant covariates were weight, age and concomitant levodopa/carbidopa therapy. CL/F (clearance/volume) decreased with age and increased with body weight. Concomitant levodopa/carbidopa therapy caused CL/F to decrease by 31 %.

The Presto study was also described by the same model used for the Tempo study. This study also showed that as exposure increased over time, clearance decreased which was also observed in normals in the Phase I multiple dose study. Apparent rasagiline CL/F was 35% lower than in healthy volunteers after 10 days of dosing. The significant covariate was the presence of entacapone.

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

Introduction

Summary

The objective of this analysis was to perform a population analysis of the pharmacokinetic data that was collected during the clinical trial, TVP-1012/232 (Tempo) and TVP-1012/133 (Presto) rasagiline. A population pharmacokinetic model was developed using rasagiline and aminoindan (AI) concentrations resulting from rasagiline mesylate administration as the dependent variables. The model developed in this analysis was then used to determine the significance of possible covariates to the population pharmacokinetic parameters and to estimate the intersubject variability of the pharmacokinetic parameters. Analysis of the Tempo study for the monotherapy indication indicated that CL/F increased with weight , decreased with age and

was decreased by 30% with concomitant carbidopa/levodopa therapy. On the other hand, for the adjunct therapy study Presto only concomitant entacapone resulted in a 25% increase in CL/F and was the only significant covariate.

STUDY TEMPO-POPULATION PHARMACOKINETIC ANALYSIS OF RASAGILINE AND ITS METABOLITE, AMINOINDAN

ANALYSIS OBJECTIVES

The objective of this analysis was to perform a population analysis of the pharmacokinetic data that was collected during the clinical trial, TVP-1012/232 for rasagiline.

Overall Study Design

Study TVP-1012/232 was a multicenter, double-blind, placebo-controlled, parallel group, Phase III clinical trial of the efficacy, tolerability, and safety of two doses of rasagiline mesylate in early Parkinson's disease (PD) subjects not treated with levodopa. Subjects were randomized to one of two (1 mg or 2 mg/day) dosages of rasagiline or placebo. There was a 1-week titration phase, followed by a 25-week maintenance phase and a 6 month double blind active treatment extension. At the start of the active treatment phase, patients on 1 mg and 2 mg rasagiline continued their original assignment while all placebo patients were rolled over to the 2 mg group. Plasma samples for the measurement of rasagiline and its AI metabolite were collected at Week 14, Week 26, and Week 52 for all subjects, including those assigned to placebo. On the day of these visits, subjects with a study visit prior to 10 am were asked to take their study medication at the study visit. Subjects had a pre-dose blood sample drawn at the beginning of their visit and would then take their study medication followed by a second blood draw. For half the subjects the second blood draw was taken early in the clinic visit (no sooner than one-half hour) and the other half were to have the second blood draw taken at the end of the clinic visit. Subjects with study visits after 10:00 am were asked to take their medication as usual (i.e., in the morning) on the day of their study visit. A blood draw was then taken at the beginning and at the end of this study visit. At week 52, subjects were asked to not take their study medication prior to their study visit (i.e., the last dose of their study medication is taken on the morning of the day before their study visit). One blood draw was taken at any time during this study visit.

Base Pharmacokinetic Model

Study TVP-1012/232 which has approximately 400 subjects was used to define the population PK model.

Estimates of rasagiline compartmental pharmacokinetic parameters were derived from extensively sampled Phase I data (Protocol CD596). The data set was comprised of 371 rasagiline concentration versus time observations originating from 18 subjects, dosed every day for 10 consecutive days at dose levels of 2, 5 and 10 mg (6 subjects per dose level). Extensive PK samples were taken on days 1 and 10 of the study.

The extensive Phase I data were analyzed by population nonlinear mixed-effects

modeling. The choice of model structure was, guided by diagnostic plots and the Akaike Information Criterion (AIC), which is based on the minimum objective function value (MOFV) and number of model parameters (npar); $AIC = MOFV + 2(npar)$. One- and two-compartment linear models parameterized in terms of clearances and volumes of distribution were fitted to the data and compared in the model building process for rasagiline. A one-compartment linear model was used to fit the aminoindan data because of convergence difficulties with more complex model structures. The first order conditional estimation (FOCE/INT) method with eta-epsilon interaction was employed for all Phase I model runs. Goodness of fit was evaluated by examining diagnostic scatter-plots, the minimum objective function value (MOFV) and the AIC. The first order (FO) and FOCE/INT method was used for model development.

The Phase III sparse data were modeled using a two-compartment model for rasagiline and a one-compartment model for aminoindan. The true disposition of l-aminoindan may very well be multi-compartmental, but more complex models exhibited problems with convergence, such as rounding errors which was probably related to the sparseness of the metabolite data. Parent data were analyzed first, with the subsequent simultaneous modeling of parent and metabolite data. The FO and FOCE/INT estimation methods were used. The choice of model structure and estimation method was guided by the minimum objective function value (MOFV), AIC and diagnostic plots as well as parameter estimates, including fixed and random effects parameters.

Statistical Model

The inter-patient variability was modeled using an exponential function in all pharmacokinetic parameters, e.g., for CL:

$$CL_j = CL_{oj} \exp(\eta_i^{CL})$$

where $\exp(\eta_i^{CL})$ denoted the relationship between the true individual parameter (CL_j) and the typical value (CL_{oj}) predicted for an individual with covariates equal to those of patient i . In the base model without covariates, CL_{oj} is the same for all individuals, and it was denoted by CL_o . Inter-patient variability was modeled the same way for the other parameters. The individual random effects, η_i 's (e.g., η_{jCL}), are random variables with a mean of zero and variances of ω^2 (e.g., ω_{CL}^2). Models with both diagonal and block structures for the variance-covariance matrix (Ω) of inter-individual random effects were evaluated. The assumption of an exponential variance model is consistent with the observation that pharmacokinetic parameters in a population typically follow a log-normal distribution. This assumption was also tested by investigating distributions of resulting η_i estimates. Random residual variability was modeled using a combined additive and constant CV error model:

$$Y_{ij} = F_{ij} + F_{ij} \varepsilon^P_{ij} + \varepsilon^A_{ij}$$

Y_{ij} and F_{ij} were the j^{th} measured and model predicted plasma concentrations for the i^{th} patient, respectively. The parameters ε^P_{ij} and ε^A_{ij} denoted the random residual error for the constant coefficient of variation (CV) and additive portion of the error, respectively. Means of all the residual random effects were assumed to be equal to zero; variances were denoted as σ^2_p and as σ^2_A , respectively. The random variables ε^P_{ij} and ε^A_{ij} were assumed to be independent. A proportional error model only (without the additive part) was also tested.

Covariate Model Identification

Once an appropriate base pharmacokinetic model (including inter-individual and residual variance models) had been developed, empirical Bayes estimates of individual model parameters were generated using the POSTHOC subroutine in NONMEM and relationships between covariates and individual PK parameters were graphically explored. The effects of the following covariates were evaluated: age, weight, creatinine clearance, ALT, AST, race, (1=Caucasian, 2=Black, 3=Oriental, 4=Hispanic, 94=Other), gender (0=male, 1=female). In addition, the following concomitant medications: carbidopa/levodopa (1 = present, 0= not present, COM1), omeprazole (1 = present, 0= not present, COM2), beta-blockers (1 = present, 0 = not present, COM3), NSAIDs (1 = present, 0= not present, COM4) and aspirin (1 = present, 0 = not present, COM5).

Possible covariates for the rasagiline population pharmacokinetic model were first selected by identifying covariates of interest and by eliminating any highly correlated or collinear covariates. Gender and the presence of concomitant medications were modeled as categorical covariates. Race was not included because the majority of (~95%) of patients were of the same race (Caucasian). For the continuous covariates, ALT (liver enzyme) was used to represent both AST and ALT because of their strong correlation. Age and CRCL also appeared to be somewhat correlated but both were included because of the considerable variability in the relationship between these two variables. The other covariates were modeled as continuous. Continuous covariates were centered about the median (or a reference value close to the median) of the distribution of the respective covariate in the population. A power model was used to describe the relationship between parameters and continuous covariates. The influence of weight on clearance CL_j was modeled as:

$$CL_j = CL_0 \times (WT_j/70)^{CLWT}$$

where CL_j was the typical value of clearance predicted for an individual with covariates equal to those of patient i , CL_0 denoted the typical clearance for an individual with the median value of weight, and $CLWT$ was an estimated power parameter for the effect of weight on clearance. The term $(WT_j/70)$ represents the relationship between the predicted clearance of the individual with WT_j and the typical clearance of the population.

Categorical covariate effects were described with a proportional model:

$$CL_j = CL_0 \times (1 + CL_{GEN} \times GEN)$$

where CL_j was the typical value of clearance predicted for an individual with covariates equal to those of patient i , CL_0 denoted the typical clearance for an individual with the null value of the categorical covariate (in this case, $GEN=0$), and CL_{GEN} was an estimated model parameter for the proportional effect of gender on clearance.

The statistical significance of each covariate-parameter relationship was investigated in several steps. Modeling of rasagiline concentration-time data proceeded with the construction of a full covariate model and subsequent stepwise backward elimination of non-significant covariate-parameter relationships. Due to multiple comparisons and the known anti-conservative nature of the FO method in NONMEM, a significance level of

$p < 0.001$ was defined a priori for model comparisons with the Likelihood Ratio Test. This translates to a difference in minimum objective function values (MOFV) of at least 10.8 for nested models with 1 degree of freedom (difference in number of parameters between two models is 1). Covariate-parameter relationships for the apparent clearance of 1-aminoindan (CLM) were investigated by a stepwise backward elimination method, using the simultaneous parent-metabolite model. The full model included all covariates in the reduced rasagiline model plus all possible covariates on CLM.

Model Evaluation

A predictive check technique was employed to evaluate the combined parent-metabolite population model. For each simulated data set, the median, first quartile and third quartile concentrations were calculated by dose level. The same calculations were repeated for the single observed data set.

RESULTS

Study Population

Demographic Characteristics

Overall, the mean age of patients was 60 years with a range from 32 to 79 years. The mean height was 171.7 cm with a range from 147.5 to 192.0 cm, and the mean weight was 78.2 kg with a range from 45 to 139 kg. There were 123 females (35%) and 229 males (65%) in the study. The majority of patients 334 (94.9%) were Caucasian, 6 (1.7%) were Black, 4 (1.14%) were Hispanic, 7 (1.99%) were Asian, and 1 (0.284%) were identified as 'other'.

Population Pharmacokinetic Modeling Results

Extensive Phase I Pharmacokinetic Data

Estimates of rasagiline (rasagiline) compartmental pharmacokinetic parameters were derived from data obtained in an extensively sampled Phase I study. Choice of model structure was guided by the minimum objective function value (MOFV) and diagnostic plots. The log-likelihood difference (LLD) was computed from the MOFV of two nested models and the Likelihood Ratio Test was used for model comparison. The first-order conditional estimation method with eta-epsilon interaction (FOCE/INT) was employed for all Phase I model runs. A two-compartment model resulted in a statistically significant improvement ($p < 0.001$; Likelihood Ratio Test) in model prediction of rasagiline concentration when compared to a one-compartment model, MOFV of 1290 and 1476, respectively. Additionally, there was no statistically significant improvement associated with inter-individual variance parameters on peripheral volume of distribution and inter-compartmental clearance. The two-compartment model with first-order absorption was parameterized in terms of an absorption rate constant (k_a), apparent

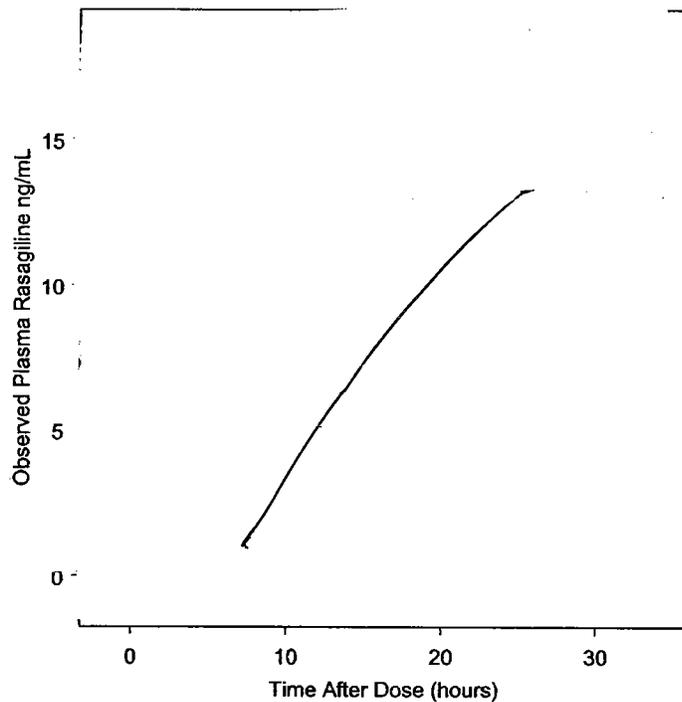
oral clearance (CL/F), apparent central volume of distribution (V₂/F), apparent peripheral volume of distribution (V₃/F) and apparent inter-compartmental clearance (Q/F). Inter-individual random effects were assumed to follow a log-normal distribution (exponential error model) and residual variability was modeled with a combination additive and proportional variance model. Following an oral dose, absorption from the gut was rapid, as evidenced by the magnitude of the absorption rate constant.

Sparse Population Pharmacokinetic Data: Rasagiline

A combined parent-metabolite population PK data set was created. Rasagiline plasma concentration, dosing and covariate data from Protocol TVP-1012/232 were extracted and analyzed separately from the metabolite, l-aminoindan, data. Several modeling attempts were performed using 1- and 2-compartment models, with both the first-order (FO) and FOCE/INT estimation methods. Irrespective of model and estimation method, it was apparent that some data points were not at all consistent with the model prediction, as indicated by excessively high weighted residuals (WRES). Estimation runs with these data were also characterized by convergence difficulties and unrealistic parameter estimates. Inspection of the data revealed a problem common to these time points. Several concentration observations at the end of the dosing interval (e.g. greater than 20 hours after dosing) were unrealistically high when compared to the typical trough concentrations. The following figure of the observed C_{min} values shows the normal and outlier values.

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Observed rasagiline plasma concentration data are plotted vs. time after dose (in hours). Data points are labeled by individual NONMEM ID numbers.



Further inspection of the data set revealed that the large WRES were not related to any measured covariate factors and it was assumed that errors in recording sampling or dosing times might be responsible for these outliers. Outliers were identified as data points with WRES less than -10 and greater than 10. were identified and inspected. Any observations of metabolite (l-aminoindan) on the same dosing occasion were also commented-out of the source data set. In all, 44 of the 2005 total observations of rasagiline or l-aminoindan were removed from the analysis data set. The resulting corrected data set was used for all subsequent modeling. Subsets for parent rasagiline and combined parent-metabolite models were created from the corrected data set.

As seen with the extensively sampled Phase I PK data, a two-compartment model with first-order absorption was also the best structural model for the sparse population data. Because of study design and PK sampling limitations, it was not possible to obtain stable estimates of k_a or V_3/F for the sparse data. Very few plasma concentrations were obtained during the rapid absorption phase of the concentration-time profile. In addition, all concentration observations were obtained at steady-state, so there was little information about the peripheral distribution and accumulation of drug. Consequently, both k_a and V_3/F parameters were fixed to the point estimates obtained from the Phase I model, 6.20 hr⁻¹ and 3,300L, respectively. The firm contends that the large estimate of V_3/F was consistent with the finding that rasagiline undergoes significant, irreversible specific binding in peripheral tissues. The base model for the sparse population PK data was characterized with the same fixed-effects model structure that was used

for the Phase I data, but an additional term describing covariance between CL/F and V2/F inter-individual random effects was added to the random model hierarchy. Estimation with NONMEM's FOCE/INT method resulted in convergence difficulties and it was necessary to conduct model building with the FO method. Possible covariates for the rasagiline population PK model were first selected by identifying covariates of interest and by eliminating any highly correlated or collinear covariates. Covariates available for inclusion in the population PK model were (with units and NMTRAN data item name): age (yrs., AGE), weight (kg, WT), height (cm., HT), creatinine clearance (mL/min, CRCL), serum alanine aminotransferase (U/L, AST), serum aspartate aminotransferase (U/L, AST), gender (0 = male, 1 = female, GEN), race (1 = Caucasian, 2 = Black, 3 = Asian, 4 = Hispanic, 94 = Other, RACE) and five possible concomitant medications. Concomitant medications studied were: carbidopa/levodopa (I = present, 0 = not present, COM1), omeprazole (I = present, 0 = not present, COM2), beta-blockers (I = present, 0 = not present, COM3), NSAIDs (I = present, 0 = not present, COM4) and aspirin (I = present, 0 = not present, COM5). Because some individuals may have received concomitant medications on one occasion, but not on another, the number (N) and percent (%) of concomitant medications refers to the number or percent of patients having received the concomitant medication was recorded.

The reduced rasagiline population PK model identified a increase in CL/F with WT and an decrease in CL/F with AGE, CRCL, and COM1. V2/F decreased with AGE and CRCL, but increased with COM3 and COM4.

Sparse Population Pharmacokinetic Data: Combined Parent-Metabolite Model

Rasagiline and 1-Aminoindan population PK data were simultaneous analyzed with a parent-metabolite model. The model structure consisted of the rasagiline two-compartment disposition with first-order absorption, and a one-compartment disposition for 1-aminoindan. As in the case of the parent model PK parameters, estimates of metabolite parameters were also confounded with oral bioavailability of the administered drug. Because of limitations in the available observed data (more specifically, a lack of a complete mass-balance), it was necessary to make some assumptions about the parent-metabolite model in order to avoid a priori parameter identifiability problems. It was assumed that the rasagiline elimination mechanism was entirely via biotransformation to 1-aminoindan. Any inaccuracies in this assumption would result in an overestimation of the fraction of rasagiline converted to 1-aminoindan and would be reflected by an increase in the estimate of volume of distribution of the metabolite. Therefore, the estimate of metabolite volume of distribution (VM) is an apparent estimate. Similarly the estimated clearance of metabolite (CLM) is relative to the formation fraction and is an apparent estimate only. Without any strong prior knowledge of the relative disposition of rasagiline and 1-aminoindan in humans, it was necessary to make such an assumption. Covariate-parameter relationships for the apparent clearance of 1-aminoindan (CLM) was also investigated by a stepwise backward elimination method, using the simultaneous parent-metabolite model. The full model included all covariates in the reduced rasagiline model plus all possible covariates on CLM.

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Combined Rasagiline/1-Aminoindan model
Initial Model determined with FO with final model analysis by FOCE/INT.

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FULL MODEL			
ka = θ_1			
CL/F = $\theta_2 \cdot (WT/70)^{0.66} \cdot (AGE/60)^{0.7} \cdot (CRCL/100)^{0.66} \cdot (1 + COM1 \cdot \theta_9) \cdot e^{\eta_1}$			
V2/F = $\theta_3 \cdot (AGE/60)^{0.10} \cdot (CRCL/100)^{0.11} \cdot (1 + COM3 \cdot \theta_{12}) \cdot (1 + COM4 \cdot \theta_{13}) \cdot e^{\eta_2}$			
V3/F = θ_4			
Q/F = θ_5			
CLM/F = $\theta_{14} \cdot (WT/70)^{0.16} \cdot (AGE/60)^{0.17} \cdot (1 + COM5 \cdot \theta_{24}) \cdot e^{\eta_3}$			
V4/F = $\theta_{15} \cdot e^{\eta_4}$			
RUN	MODEL DESCRIPTION	MOFV	Δ OFV
551	Full Model	-79.820	N/A
553	Full Model, $\theta_9 = 0$	-78.654	1.166
554	Full Model, $\theta_{13} = 0$	-78.742	1.078
555	Full Model, $\theta_{24} = 0$	-77.358	2.462
556	Full Model, $\theta_7 = 0$	-71.759	8.062 ^a
557	Full Model, $\theta_{10} = 0$	-65.336	14.484 ^a
558	Full Model, $\theta_{11} = 0$	-79.515	0.305
559	Full Model, $\theta_{16} = 0$	-29.240	50.580 ^a
560	Full Model, $\theta_{17} = 0$	-62.039	17.782 ^a
561	Full Model, $\theta_9 = 0$	-59.620	20.201 ^a
562	Full Model, $\theta_{12} = 0$	-74.173	5.647
563	Full Model, $\theta_6 = 0$	-46.945	32.875 ^a
564	Full Model, $\theta_8, \theta_{13}, \theta_{24}, \theta_{11} \text{ \& } \theta_{12} = 0$	-69.159	10.661 ^b
REDUCED MODEL			
ka = θ_1			
CL/F = $\theta_2 \cdot (WT/70)^{0.66} \cdot (AGE/60)^{0.7} \cdot (1 + COM1 \cdot \theta_9) \cdot e^{\eta_1}$			
V2/F = $\theta_3 \cdot (AGE/60)^{0.10} \cdot e^{\eta_2}$			
V3/F = θ_4			
Q/F = θ_5			
CLM/F = $\theta_{14} \cdot (WT/70)^{0.16} \cdot (AGE/60)^{0.17} \cdot e^{\eta_3}$			
V4/F = $\theta_{15} \cdot e^{\eta_4}$			

^asignificant change in MOFV at p<0.005, 1 df (critical value=7.88)

^bchange in MOFV not significant at p<0.005, 5 df (critical value=16.75)

Final population pharmacokinetic model parameters, FOCE/Interaction: combined Rasagiline/1-Aminoindan model are presented in the following Table.

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Structural Model and Interindividual Variance Parameters

Parameter	Typical Value (%RSE*)	Interindividual CV% (%RSE*)
ka (hr ⁻¹)	6.20	NE
CL/F (L/hr) ^a	58.5 (2.80%)	30.6% (14.8%)
V2/F (L) ^a	125 (6.58%)	73.8% (13.0%)
V3/F (L)	3300	NE
Q/F (L/hr)	46.4 (4.33%)	NE
CL~WT	0.541 (16.0%)	N/A
CL~AGE	-0.403 (35.0%)	N/A
CL~COM1	-0.310 (13.8%)	N/A
V2~AGE	-0.785 (40.6%)	N/A
CLM ^b	27.5 (1.89%)	26.5% (10.6%)
VM ^b	270 (4.37%)	41.0% (17.3%)
CLM~WT	0.732 (12.2%)	N/A
CLM~AGE	-0.358 (22.2%)	N/A

Residual Error	
Parameter	Estimate (%RSE ^a)
Σ _{1,1 prop}	CV%=29.1% (6.51%)
Σ _{3,3 prop}	CV%=17.7% (5.11%)
Σ _{4,4 add}	SD=0.194 (18.7%)

*%RSE: percent relative standard error of the estimate = SE/parameter estimate * 100

^aCovariance of etas for CL/F and V2/F was 0.164 (correlation coefficient = 0.725)

^bCovariance of etas for CLM and VM was 0.00962 (correlation coefficient = 0.0887)

NE: not estimable

N/A: not applicable

Model Evaluation: Sensitivity Analysis for Fixed Model Parameters

One of the assumptions of the model building process was that any minor inaccuracies in the fixed estimates of ka and V3/F would not have a significant impact on other model parameter estimates. In order to explore this assumption, a fixed-point sensitivity analysis was conducted. The fixed values of ka and V3/F were altered to reflect the range of parameter uncertainty as defined by the standard error of the estimate (SE) from the Phase I PK model. A low parameter value was defined as the point estimate minus SE and a high parameter value was defined as the point estimate plus SE. Separate estimation runs with the final combined PK model were conducted with different fixed values of ka (3.62, 6.2 and 8.78 hr⁻¹) and V3/F (2050, 3300 and 4550 L) and the resulting estimates for other model parameters (and % change from the final model) were tabulated. The majority of parameter estimates were insignificantly affected by the changes in the fixed parameters as indicated by the % change from final estimate. The parameter that was most sensitive to the values of ka and V3/F was the covariance between CLM and VM random effects (ω_{4,3}). The magnitude of this covariance was small and possibly insignificant to begin with. The sensitivity analysis results indicated that the model and parameter estimates were robust to moderate changes in both ka and V3.

Model Evaluation: Predictive Check

A predictive check technique was employed to evaluate the combined parent-metabolite population model. One hundred replicates of the TVP-101/232 population PK data set were generated via Monte Carlo Simulations with the combined parent-metabolite model. The resulting simulations were summarized and compared to summary statistics of the observed data set. For each simulated data set, the median, first quartile and third quartile concentrations were calculated. The same calculations were repeated for the single observed data set. Most of the results were reasonable but there were several cases where the observed results for the first quartile, median and third quartile were not centered in the distribution. The firm contends that perhaps with another measure such as clearance the predictions may have been more consistent. Even when the firm used FOCE/Interaction many of the predictions still were not centered. (vol. 52, figures 8.1.14 and 8.1.15 pages 63 and 64 of 92).

DISCUSSION

The pharmacokinetic parameter estimates were comparable with what had previously been observed for rasagiline from the intensive sampling studies. A comparison of the estimates for CL from the population analysis and what has previously been reported is presented in the following Table 1 which demonstrates the comparability of this analysis with previous reports

Table 1. Comparison of CL estimates from the population analysis with study CD596

Dose	Study CD 596 CL, L/hr	Population
5 mg	90.4	84.6 L/hr
10 mg	85.9	

The rasagiline CL/F estimate for a 70 kg, 60 year-old individual, with no concomitant medications, was 58.5 L/hr. Variability across the population in rasagiline CL/F was related to weight, age and concomitant levodopa/carbidopa therapy. A decrease in CL/F was associated with increasing age. For example, the expected CL/F for a typical 79 year-old individual would be about 11% less than a typical 60 year-old and approximately 30% less than a 32 year-old individual. Table presents a tabulation of the effect of the covariates on rasagiline pharmacokinetic parameters.

Table 2. Effect of Covariates on Rasagiline/1AI Pharmacokinetic parameters as function of significant covariates in the final population model.

		CL/F (L/hr)			Weight ^a		
		min	ref	max	min	ref	max
Age ^b	min	57.4	75.4	109.9	39.6	52.0	75.8
	ref	44.5	58.5	85.3	30.7	40.4	58.8
	max	39.9	52.4	76.3	27.5	36.1	52.7
		COM1 = 0			COM1 = 1		

V2/F(L)		
Age ^b		
min	ref	max
205	125	101

		CLM(L/hr)		
		Weight ^a		
		min	ref	max
Age ^b	min	23.8	34.4	57.4
	ref	19.0	27.5	45.8
	max	17.2	24.9	41.5

^a Minimum = 42.3 kg, reference = 70 kg, maximum = 140.5 kg

^b Minimum = 32 yr., reference = 60 yr., maximum = 79 yr.

The concomitant use of carbidopa/levodopa was related to a decrease in rasagiline CL/F of 31% (with an approximate 95% confidence interval of 23% to 39%). The mechanism for this interaction is not apparent and it may be that this covariate is correlated with a decrease in CL/F.

Although several covariate factors were eliminated as significant predictors of rasagiline and l-aminoindan pharmacokinetic parameters, this may or may not be evidence of a finding of no relationship. An alternative interpretation is that the study design, covariate range (or count), and analysis method were not sufficient to detect an effect if indeed one were present. Although the clinical significance of covariate effects on rasagiline and l-aminoindan pharmacokinetics is unknown, the pharmacokinetic variability may be of minimal importance at the intended therapeutic dose range.

ADDENDUM TO TEMPO STUDY

SUBSEQUENT TO THIS INITIAL ANALYSIS OF THE TEMPO DATA SET BY THE FIRM THEY WERE REQUESTED BY FDA TO ANALYZE THE DATA FOR SMOKERS SINCE THE DRUG IS METABOLIZED BY CYP1A2.

Smoking Firm's Method

Evaluation of the effect of tobacco smoking on the pharmacokinetics of rasagiline mesylate in TVP-1012/232 (TEMPO)

RATIONALE FOR ANALYSIS

Tobacco smoke is a known inducer of cytochrome P450. Since rasagiline is primarily metabolized by cytochrome P450 1A2, a pharmacokinetic analysis was performed to evaluate the effect of tobacco smoking on the pharmacokinetics of rasagiline using data collected during a clinical trial (TVP-1012/232) of rasagiline in early Parkinson's Disease subjects not treated with levodopa.

ANALYSIS OBJECTIVE

The specific objective of the analysis was to evaluate whether clearance of rasagiline was increased in subjects who were classified as current tobacco smokers in the TVP-1012/232 clinical trial database.

Data

A variable describing smoking status was appended to the data sets used for the original population pharmacokinetic analysis of rasagiline and combined analysis of rasagiline and AI. The variable, SMOK, was coded as follows: 0 – nonsmoker, 1 – current smoker, 2 – former smoker.

Table 3 presents the numbers of nonsmokers, smokers and former smokers in the TVP-1012/232 study population.

Table 3. Smoking status, summarized by category

	Nonsmokers	Smokers	Former Smokers
N (%)	209 (59.1%)	17 (4.8%)	128 (36.2%)

EVALUATION OF SMOKING STATUS ON RASAGILINE CLEARANCE

Several analyses were performed to evaluate the possible effect of tobacco smoking on rasagiline clearance.

Exploratory Graphical Evaluation of Rasagiline Clearance vs. Smoking Status

A box plot (Figure 1) of rasagiline clearance vs. smoking status was examined in an initial exploratory analysis. Empirical Bayes estimates of individual rasagiline clearances were generated using the base population pharmacokinetic model for rasagiline alone and the POSTHOC subroutine in NONMEM.

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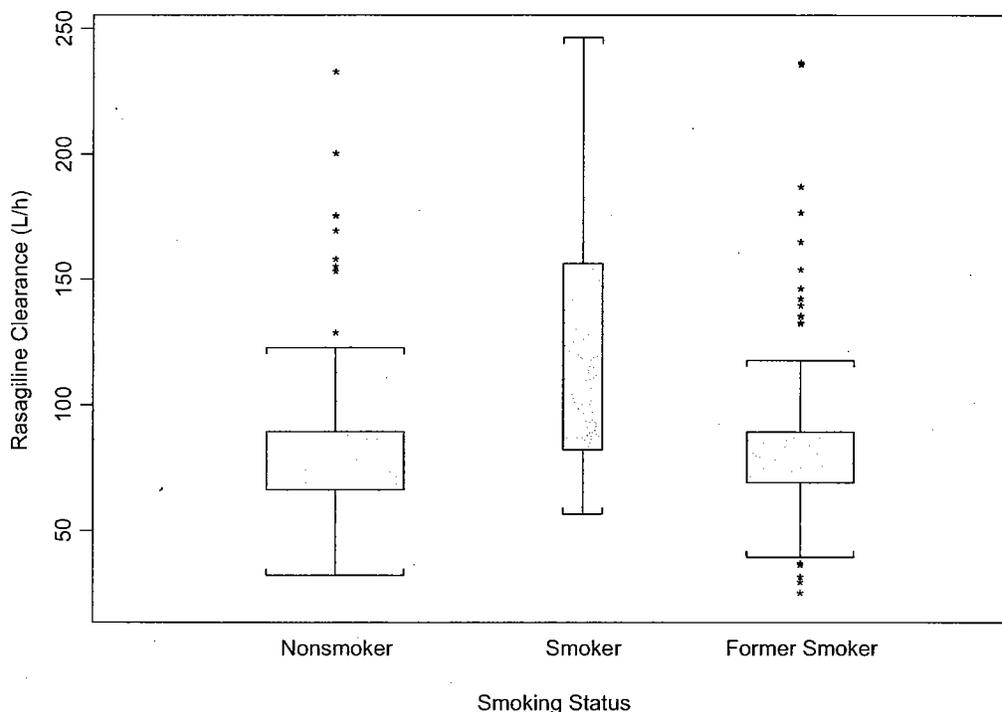


Figure 1. Box plot of rasagiline clearance by smoking status category, showing median (white line) and interquartile range (IQR, box). The whiskers span 1.5 times IQR. Outliers are shown by asterisks. Box width is proportional to the number of observations in each category. The results of the graphical analysis showed no difference in rasagiline clearance for the nonsmoker and former smoker categories. Smokers were shown to have more variable rasagiline clearances.

Hypothesis Testing Using the Likelihood Ratio Test in NONMEM

The final population pharmacokinetic model for rasagiline, including all significant covariate effects (model 302), was used to evaluate the statistical significance of smoking status on rasagiline clearance. The likelihood ratio test in NONMEM and a significance level of $\alpha < 0.001$ was used. Table 4 details the models that were tested.

Table 4. Results of Hypothesis Testing in Study TVP-1012/232
All final runs were done with FOCE

Model	Model Tested	OFV	Comment
302	Final Population PK Model for Rasagiline	-157.860	Reference model
302s	Add smoking status (2 parameters)	-174.777	Significant compared to run 302
302s1	Drop SMOK=1 (smokers)	-160.270	Significant compared to run 302s
302s2	Drop SMOK=2 (former smokers)	-172.985	Not significant compared to run 302s
302s3	Add effect of currently smoking (1 parameter)	-172.985	Significant compared to run 302

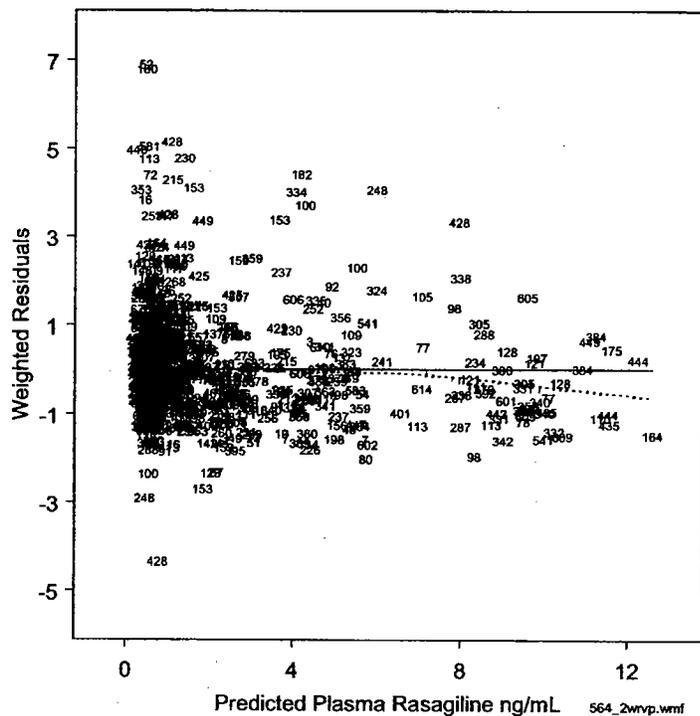
The results of the hypothesis testing show that there is a significant effect of currently smoking tobacco on rasagiline clearance. In subjects who were currently smoking tobacco, there was an estimated increase in rasagiline clearance of 39.1% (95% confidence interval: 13.2%, 65.0%) relative to nonsmokers and former smokers (model 302s3, Listing 1).

Similar results were obtained when an effect of currently smoking tobacco was tested on rasagiline clearance in the final combined Tempo population pharmacokinetic model for rasagiline and AI (model 565). In that analysis, the inclusion of an effect of smoking tobacco on rasagiline clearance resulted in a decrease in the MOFV of 12.02 ($p < 0.001$, 1 df) and rasagiline clearance was estimated to be increased by 33.3%.

The following GOODNESS OF FIT PLOTS WERE USED TO EVALUATE THE QUALITY OF THE FITS.

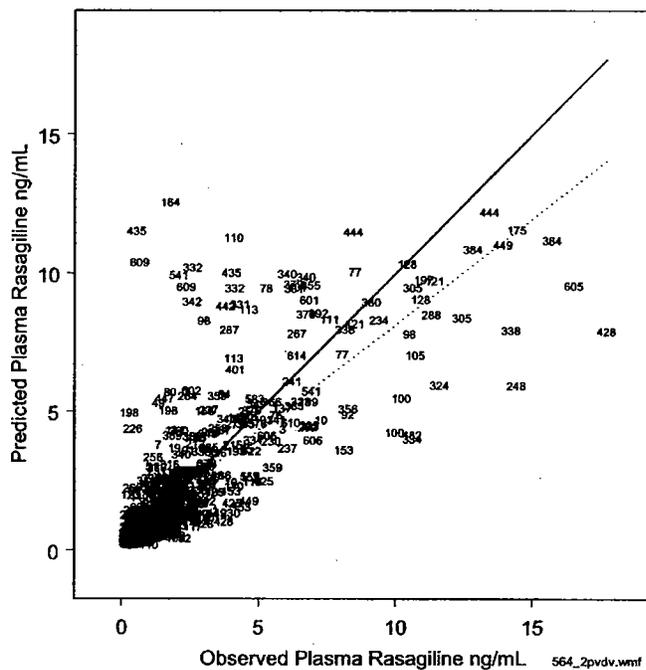
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Residuals vs. predicted concentrations are indicated by NONMEM ID number. A reference line at $y = 0$ (solid line) and a cubic spline trend-line (dotted line) are also plotted.



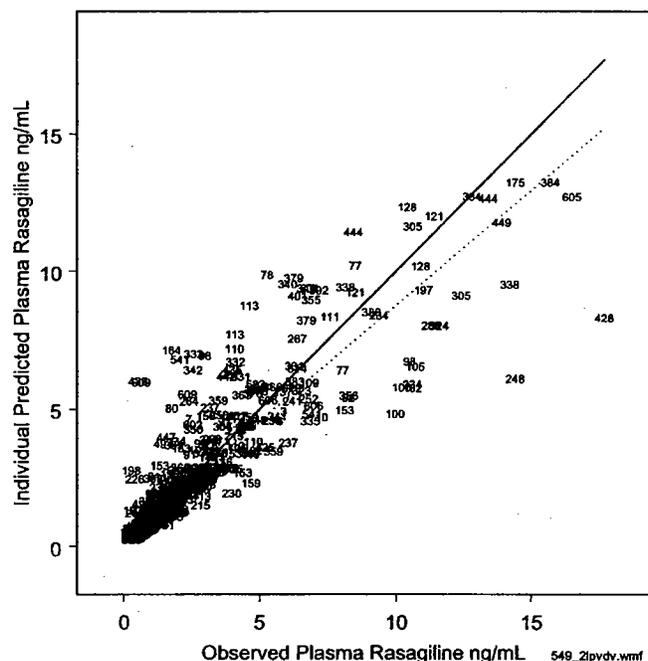
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Population predicted concentrations vs. observed data points are indicated by NONMEM ID number. A reference line of identity (solid line) and a linear trend-line (dotted line) are also plotted.



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Individual-predicted concentrations vs. observed data points are indicated by NONMEM ID number. A reference line of identity (solid line) and a linear trend-line (dotted line) are also plotted.



DISCUSSION

The results of this analysis indicate that the clearance of rasagiline was increased in subjects who were classified as current tobacco smokers in the TVP-1012/232 clinical trial database.

However, the firm stated that the results of this analysis should be interpreted cautiously for the following two reasons:

1. In the TVP-1012/232 study population, tobacco smokers represented less than 5% of the overall study population. Given the small number of tobacco smokers (17 out of 352 subjects) and the large interindividual variability in rasagiline clearance in this group (Figure 1), the data may be insufficient to reliably determine the effect of smoking on rasagiline clearance in study TVP-1012/232 (Aarons et al., *Eur. J. Clin. Pharmacol.* 1996).

CONCLUSIONS

1. The population pharmacokinetics of rasagiline and l-aminoindan were characterized by a linear model with a two-compartment disposition for parent drug and a one-compartment disposition model for the metabolite.

2. The pharmacokinetic parameter estimates were comparable with what has previously been observed for rasagiline following intense sampling protocols.

3. The rasagiline CL/F estimate for a 70 kg, 60 year-old individual, with no concomitant medications, was 58.5 L/hr. Variability across the population in rasagiline CL/F was related to weight, age and concomitant levodopa/carbidopa therapy.

4. A decrease in CL/F was associated with increasing age.

5. Weight affected CL/F in a positive manner.

6. The apparent clearance CL/F of the metabolite, l-aminoindan, was also affected negatively by age and positively by weight. The magnitude of these effects were also similar to the effects on rasagiline CL/F.

7. The effect of tobacco smoking on the clearance of rasagiline in study TVP-1012/232 was examined using exploratory graphical techniques and the likelihood ratio test in NONMEM. The results of the analysis indicate that rasagiline clearance is increased in tobacco smokers by 30-40%. The clinical significance of this result is unclear. In addition, this result should be interpreted cautiously due to the small number of tobacco smokers included in the study population and the large interindividual variability observed in this group.

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**COMPARISON OF RESULTS FROM THE SPONSOR AND FDA ANALYSIS FOR
TEMPO- ALL FINAL MODELS ANALYZED WITH FOCE**

Base Model Dense Sampling Firm Study CD596	Base Model Dense Sampling FDA-Study CD596	COMMENTS
OBJ VALUE 1290.467 Table 7.1.2 page 32 of 92, Vol. 52- Run 002	OBJ VALUE 1290.467 Base_Mod.DF agrees with values in Table 7.1.2, Vol. 52 for base model	There were minor differences in the values of parameters that had smaller values (ie < 10 ⁻³) PARENT DATA ONLY File folder Base mod.DF
Final Parent Model Sparse Sampling Firm- Study 232	Final Parent Model Sparse Sampling FDA-Study 232	COMMENTS
OBJ VALUE -157.86 All structural parameters and variances in Table 7.1.10, Vol. 52 pg 40 for base structural model –Additive + proportional error- Run 302B	OBJ VALUE -157.86 All structural parameters and variances in file folder 302B.DF agrees with values in Table 7.1.10, Vol. 52 pg 40 for Additive + proportional error model	Parent Data Only
COMBINED PARENT AND METABOLITE MODEL-FIRM Method FO	COMBINED PARENT AND METABOLITE MODEL-FDA Method FO	COMMENTS
OBJ VALUE -169.25 All structural parameters and variances in Table 7.1.12, Vol. 52 for combined parent and metabolite –Study 232- Run 550	OBJ VALUE -169.25 All structural parameters and variances parameters in file folder (out.550-nmv.run)agree with values in Table 7.1.12, Vol.52 pg 42 for the combined parent and metabolite – Study 232	Outlier subjects have been deleted from this analysis.
COMBINED PARENT AND METABOLITE MODEL-FIRM Method FOCE/INT	COMBINED PARENT AND METABOLITE MODEL-FDA Method FOCE/INT	COMMENTS
OBJ VALUE -79.82 All structural parameters and variances in Table 7.1.16, Vol. 52 pg 46 for combined parent and metabolite –Study 232- Run 551	OBJ VALUE -79.82 All structural parameters and variances parameters in file folder (out.551-nmv.run)agree with values in Table 7.1.16, Vol.52 for the combined parent and metabolite – Study	Outlier subjects have been deleted from this analysis
COMBINED PARENT AND METABOLITE MODEL-FIRM Method FOCE/INT-COV Step	COMBINED PARENT AND METABOLITE MODEL-FDA Method FOCE/INT- COV Step	COMMENTS
OBJ VALUE -69.15 Run 551	OBJ VALUE -69.15 Parameters agree with the firm's.	
Inclusion of Smoking as a Covariate-Firm	Inclusion of Smoking as a Covariate-FDA	
OBJ VALUE -174.77 Run 302s	OBJ VALUE -172.985	

STUDY PRESTO

RASAGILINE MESYLATE IN LEVODOPA TREATED PARKINSON'S DISEASE PATIENTS WITH MOTOR FLUCTUATIONS

Analysis Objectives

The purpose of this analysis was to develop a population pharmacokinetic model for rasagiline mesylate (rasagiline) and its major metabolite, I-R-aminoindan (AI), using data collected during a clinical trial (TVP-1012/133) of rasagiline in Parkinson's Disease subjects treated with levodopa and experiencing motor fluctuations. The specific objectives of the analysis were to:

- a. estimate population pharmacokinetic parameters describing the disposition of rasagiline and AI in the study population, and
- b. investigate possible covariate-parameter relationships within the population that may account for interindividual variability in the population pharmacokinetic parameter estimates.

Overall Study Design

Study TVP-1012/133 was a multicenter, randomized, double-blind, placebo-controlled, parallel group, phase III clinical trial of the efficacy, tolerability, and safety of two doses of rasagiline mesylate in Parkinson's disease (PD) subjects treated with levodopa and experiencing motor fluctuations. Subjects were randomized to one of two dosages of rasagiline (0.5 mg or 1 mg/day) or placebo. There was a 6 week levodopa adjustment period during which the levodopa dosage could be decreased, at the discretion of the investigator, followed by a 20 week period during which the levodopa dosage remained constant. The dosage regimen of all other anti-PD drugs was not allowed to be changed. Subjects returned to the study center during weeks 3, 6, 10, 14, 20, and 26 weeks after baseline for safety and efficacy monitoring.

Blood samples for measurement of rasagiline and AI plasma concentrations were collected during study weeks 10 and 26 for all subjects, including those assigned to placebo. On the day of the week 10 visit, two samples were obtained, as follows: subjects with a scheduled visit prior to 10 AM were asked to take their study medication during the study visit and blood samples for pharmacokinetic analysis were drawn just before dose administration and between 0.5 and 2 h post-dose. If the visit was scheduled after 10 AM, the daily dose was administered at home and the blood samples were obtained at the beginning and end of the visit. During week 26, only one PK blood draw was obtained. If a subject's scheduled visit was before 10 AM, the subject did not take the study medication at home, but at the study site. The blood was collected post dose, at least 30 minutes but no more than 2 hours after the study medication was taken. If a subject's scheduled visit was after 10 AM, the subject took the study medication as prescribed, and the PK blood draw was obtained any time during the visit.

Data Included in Data Sets

Subjects in study TVP-1012/133 who received at least one dose of study medication and with at least one rasagiline or AI plasma concentration measurement, and complete documentation of the dates and times of the dose and concentration measurement(s), were included in the analysis. If the dosing history information for a subject was missing, plasma concentrations relative to the missing dose were not included in the analysis. Missing rasagiline or AI concentrations were not imputed nor used in the analysis. Similarly, observations that were below the quantitation limit (BQL) for rasagiline ($\ll 0.25$ ug/mL) and AI ($\ll 0.5$ ug/mL) were not included in the final data set.

Covariates that were explored as possible sources of variability in the pharmacokinetics of rasagiline and AI for all subjects included in the TVP-1012/133 study population included age (years); weight (kg); race; sex; creatinine clearance (mL/min), calculated using the Cockcroft-Gault equation; rasagiline dose (0.5 mg or 1.0 mg); levodopa dose; aspartate transaminase (AST) (U/L); alanine transaminase (ALT) (U/L); total protein (mg/dL); serum albumin (mg/dL); smoking status and concomitant medications.

BASE PHARMACOKINETIC MODEL

SEQUENCE OF ANALYSIS

Pharmacokinetic models for rasagiline and AI were developed sequentially. First, the structure of the pharmacokinetic model for rasagiline and AI was determined using extensively sampled phase I data (study CD596). Subsequently, rasagiline dosing records and extensively sampled plasma concentrations from the phase I study (CD596) together with sparsely sampled data from the phase III study (TVP-1012/133) were combined and analyzed by mixed-effects modeling to determine the population pharmacokinetic parameters for rasagiline (without the inclusion of covariates).

Once the population pharmacokinetic model for rasagiline had been determined, the pharmacokinetic model for AI was developed, conditioning on the rasagiline model. The population pharmacokinetic model for AI was developed using the same approach as that for rasagiline. Thus, the base model for AI (without the inclusion of covariates) was developed using the combined data from the phase I and phase III studies (CD596 and TVP-1012/133, respectively). This was the same procedure used in the TEMPO study.

The choice of model structure was, guided by diagnostic plots and the Akaike Information Criterion (AIC), which is based on the minimum objective function value (MOFV) and number of model parameters (npar); $AIC = MOFV + 2(npar)$. One- and two-compartment linear models parameterized in terms of clearances and volumes of distribution were fitted to the data and compared in the model building process for rasagiline. A one-compartment linear model was used to fit the AI data because of convergence difficulties with more complex model structures. The first order conditional estimation (FOCE/INT) method with eta-epsilon interaction was employed for all Phase I model runs.

Individual pharmacokinetic parameter estimates were obtained by Bayesian estimation from the population pharmacokinetic model. Next, an exploratory analysis was conducted to identify relationships between the pharmacokinetic parameters for rasagiline and AI and the covariates of interest in the TVP-1012/133 study population. Significant covariate-parameter relationships were incorporated into the population pharmacokinetic model.

Goodness of fit was evaluated by examining diagnostic scatterplots, the minimum objective function value (MOFV) and the AIC. The first order (FO) was used to determine initial estimates with the FOCE/INT method was used for final model development. A decrease in the AIC as well as improvements in diagnostic goodness-of-fit plots guided the base model selection. The Phase III sparse data were modeled using a two-compartment model for rasagiline and a one-compartment model for aminoindan. It is likely that the true disposition of l-aminoindan may very well be multi-compartmental, but more complex models exhibited problems with convergence, such as rounding errors which may be related to the sparseness of the metabolite data. Parent data were analysed first, with the subsequent simultaneous modelling of parent and metabolite data, The FO and FOCE/INT estimation methods were used. The choice of model structure and estimation method was guided by the minimum objective function value (MOFV), AIC and diagnostic plots as well as parameter estimates, including fixed and random effects parameters.

The difference in the NONMEM objective function is approximately chi-square distributed with n degrees of freedom, where n is the difference in the number of parameters between the hierarchical models and was used to compare models. A decrease of ≥ 3.84 in the value of the NONMEM objective function, which is minus twice the maximum logarithm of the likelihood of the data, is significant under the likelihood ratio test ($n=1$, $p<0.05$).

AI

Once a final population pharmacokinetic model for rasagiline had been established, the metabolite model was developed. Individual pharmacokinetic parameters for rasagiline were determined using Bayesian estimation from the population pharmacokinetic model and appended to the combined (CD596 and TVP-1012/133) data set. The metabolite model was subsequently developed, conditioning on the population pharmacokinetic model for rasagiline. Initially, the structural model for AI was identified using dosing records and AI plasma concentration vs. time data collected in the extensively sampled phase I study, CD596. Subsequently, AI plasma concentrations, rasagiline dosing records and covariate data for the phase I CD596 and phase III (TVP-1012/133) studies were included in the data set for the development of the base population PK model for AI.

Covariate Model

After an appropriate base population pharmacokinetic model (including interindividual and residual variability models) had been developed, individual model parameters were obtained by Bayesian estimation in NONMEM and relationships between covariates and individual pharmacokinetic parameters in the TVP-1012/133 study population were explored graphically. Covariates that were evaluated in this analysis are listed in the following Table 1 which summarizes covariates:

Continuous Variables	Median	Range
Body weight (kg)	77.3	43.0 – 129.7
Age (y)	63	33 – 83
Baseline ALT (IU/L)	13	3 – 68
Baseline AST (IU/L)	19	9 – 67
Baseline serum albumin (g/dL)	4.1	3.5 – 4.8
Baseline total protein (g/dL)	7.0	6.0 – 9.3
Baseline creatinine clearance (mL/min) ^a	93.1	22.6 – 224.3
Categorical Variables	Count	%
Sex (males, females)	179, 97	65%, 35%
Race (Caucasian, Black, Hispanic, Asian, Native American, Other and Unknown)	249, 3, 15, 6, 1, 2	90%, 1%, 5.5%, 2%, 0.5%, 1%
Smoking Status (Never, Current, Former)	141, 13, 122	51%, 5%, 44%
Rasagiline Dose/Day (0.5 mg, 1 mg)	139, 137	50%, 50%
Levodopa Dose/Day (<400 mg, ≥400 – <600 mg, ≥600 – <900 mg, ≥900 mg)	43, 64, 91, 78	16%, 23%, 33%, 28%
Concomitant medication, beta blockers	12	4%
Concomitant medication, NSAID	57	21%
Concomitant medication, aspirin	66	24%
Concomitant medication, paracetamol (acetaminophen)	48	17%
Concomitant medication, sildenafil citrate	17	6%
Concomitant medication, quinolones	2	1%
Concomitant medication, benzodiazepines except clonazepam	26	9%
Concomitant medication, amantadine HCl	52	19%
Concomitant medication, entacapone	93	34%
Concomitant medication, pergolide	44	16%
Concomitant medication, pramipexole	100	36%
Concomitant medication, ropinirole	38	14%
Concomitant medication, diphenhydramine	9	3%
Concomitant medication, lipid lowering drugs (statins)	16	6%
Concomitant medication, COX-2 inhibitors	18	7%
Concomitant medication, Angiotensin converting enzyme inhibitors and Angiotensin II blockers	30	11%
Concomitant medication, estrogens	34	12%

^a calculated using Equation 4

These included demographic variables and laboratory markers of organ function. Concomitant medications were also examined for possible interactions influencing rasagiline and l-R-aminioindan clearance.

Creatinine clearance was estimated using the Cockcroft-Gault equation:

$$CLCR = ((140 - \text{Age}) \cdot \text{WT}/\text{Scr}) \cdot (x) \quad (1)$$

Where:

CLCR = creatinine clearance (mL/min)

Age = age (years)

WT = actual body weight (kg)
SCR = serum creatinine (mg/dL)
x= 1 for males, 0.85 for females

Exploratory analyses of relationships between covariates and individual pharmacokinetic parameter estimates were carried out using generalized additive models (GAM) and exploratory graphical techniques in S-PLUS 2000. Results of this analysis were used to guide the covariate model building process in NONMEM. Continuous covariates were entered into the model according to the following equation :

$$P = \theta_1 + \theta_2 \cdot (\text{COV} - \text{COV}_m) \quad (2)$$

Where:

P = the individual estimate of the parameter

θ_1 = the typical value of the parameter (when $\text{COV} = \text{COV}_m$)

θ_2 = the slope of the effect of the covariate on the parameter

COV = the value of the covariate

COV_m = the median value of the covariate in the study population

Categorical covariates were included in the model using indicator variables as shown in Equation 3:

$$P = \theta_1 + \theta_2 \text{ IND} \quad (3)$$

Where:

P = the individual estimate of the parameter

θ_1 = the typical value of the parameter when $\text{IND} = 0$

θ_2 = the effect of the covariate (when $\text{IND} = 1$) resulting in a fractional change in the value of P

IND = an indicator variable, which has a value of 1 when the covariate is present, otherwise $\text{IND} = 0$

Race, sex, rasagiline dose, smoking status and the presence of concomitant medications were modeled as categorical covariates. Because the majority of study participants (90%) were Caucasian, race was modeled as a binary covariate, Caucasian ($\text{IND} = 0$) and other races ($\text{IND} = 1$). Levodopa dose was evaluated as a categorical covariate and also a continuous covariate. Table 1. All other covariates were modeled as continuous covariates. The statistical significance of each covariate-parameter relationship was investigated in several steps. In the first step, the statistical significance of each covariate-parameter relationship was screened individually in NONMEM. The model with the lowest objective function value was carried forward to the next step of the analysis in which significant covariate-parameter relationships were added, in a stepwise fashion, to the model. This process was repeated to obtain a "full" population pharmacokinetic model, which included all significant covariate-parameter relationships.

Hypothesis testing to discriminate among alternative hierarchical models was performed

using the likelihood ratio test. Differences in the NONMEM objective function of two alternative models are approximately chi-squared distributed with n degrees of freedom, where n is the difference in the number of parameters between hierarchical models. A decrease of ~3.84 in the value of the NONMEM objective function was considered to be significant under the likelihood ratio test (n= 1, p<0.05).

Statistical Model

In the development of the random effects models, all pharmacokinetic parameters were assumed to be log-normally distributed and exponential interindividual variability terms were included on the pharmacokinetic parameters in the model. The form of the exponential error model was:

$$P_i = P' \exp(\eta_i P) \quad (4)$$

where:

P_i = the true parameter value for individual i

P' = the typical value (population mean) of the parameter

$\eta_i P$ = the difference between the true value for individual i and the typical value for the population, with a mean of 0 and a variance of ω

Various residual error models were tested, including additive, proportional, and combined additive and proportional error models. The form of the combined model, showing the additive and proportional error components, is illustrated in the following equation:

$$C_{ij} = C_{ij}' \cdot (1 + \epsilon_{1ij}) + \epsilon_{2ij} \quad (5)$$

where:

C_{ij} = the jth measured observation (plasma concentration) for individual i

C_{ij}' = the jth model predicted value (plasma concentration) for individual i

ϵ_{1ij} = the proportional residual error for the jth measurement for individual i, and is normally distributed with a mean of 0 and a variance of σ_1^2

ϵ_{2ij} = the additive residual error for the jth measurement for individual i, and is normally distributed with a mean of 0 and a variance of σ_2^2

Population pharmacokinetic parameters, without covariates, were estimated. Estimates of the pharmacokinetic parameters for each individual were subsequently obtained using Bayesian estimation.

Final Population Pharmacokinetic Model

The final combined rasagiline -AI population pharmacokinetic model included the structural pharmacokinetic model definition, estimates of the population mean and individual fixed effects parameters, and estimates of the random effects parameters.

Model Evaluation

The same procedures were used as for study TVP-1012/132.

RESULTS

Subjects who received at least one dose of rasagiline and with at least one plasma concentration measurement, and documentation of the dates and times of the dose and concentration measurement(s), were included in the population pharmacokinetic analysis (TVP-1012/133PPK). Consequently, the evaluable TVP-1012/133PPK study population included data for 276 subjects who provided 421 quantifiable rasagiline plasma concentrations and 671 quantifiable AI plasma concentrations. The subjects were equally distributed among the two dose groups, with 139 receiving a daily dose of 0.5 mg rasagiline and 137 subjects receiving 1 mg rasagiline. There were 356 rasagiline values excluded since they were BLQ.

Subjects median age was 63 years (range: 33 -83 years) and the median body weight was 77.3 kg (range: 43.0- 129.7 kg). The TVP-1012/133PPK study population included 97 (35%) females and the majority were Caucasian (249 subjects, 90%).

Imputed body weights were generated for a total of 3 subjects. For these subjects, the missing covariate was replaced with the median value of the covariate for subjects in the same study of the same sex. There were no missing categorical covariates.

CD596

Eighteen healthy volunteers participated in the CD596 study. Subjects received a single dose of 2, 5 or 10 mg rasagiline for 10 consecutive days. Extensive blood samples for pharmacokinetic analysis were collected on days 1 and 10 of the study. The data set was comprised of 373 rasagiline plasma concentration measurements and 575 AI plasma concentration measurements .

Structural Model Development: Phase I (CD596) Data

The structure of the rasagiline and AI compartmental pharmacokinetic model was determined from data obtained in an extensively sampled phase I study (CD596). The extensive phase I data were analyzed using a nonlinear mixed-effects modeling approach, as previously described. Based on goodness of fit criteria, including diagnostic plots, the objective function value in NONMEM and the Akaike Information Criterion (AIC), a two compartment model with first order absorption and first order elimination provided the best fit to the extensively sampled phase I rasagiline plasma concentration vs. time data collected in study CD596. Since there were no intravenous data, this analysis was confounded by oral bioavailability similar to the analysis of TVP-1012/132 which was previously described. Allowing apparent oral clearance (CL/F) and the apparent intercompartment clearance (Q/F) to decrease following the 10th consecutive dose on study day 10 relative to the 1 st dose on study day 1 provided a substantial improvement in the fit of the model to the data, based on the likelihood ratio test and diagnostic plots. The data did not support inclusion of interindividual variance parameters on the central or the peripheral compartment apparent volumes or the

apparent intercompartment clearance.

Inter-individual random effects were assumed to be log-normally distributed (exponential error model) and residual variability was modeled with a proportional error model. Diagnostic plots illustrated the goodness of fit of the model to the rasagiline plasma concentration vs. time data. Subsequently, AI plasma concentration vs. time data collected in study CD596 were analyzed, conditioning on the rasagiline pharmacokinetic model. Because of a lack of a complete mass-balance, it was necessary to make the assumption that rasagiline elimination was entirely via biotransformation to AI in order to avoid a priori parameter identifiability problems. Therefore, the estimate of metabolite volume of distribution (VM) is an apparent estimate (VM/F_M). Similarly, estimated AI clearance (CL_M) is relative to the formation fraction and is an apparent estimate. One and two compartment models were fit to AI plasma concentration vs. time data. A model in which the apparent AI clearance and apparent volume of distribution decreased between study day one and study day ten provided the best fit to the data. The one compartment model for AI was parameterized using apparent volume of distribution (V_M/F_M) and apparent clearance (CL_M/F_M) terms. Inter-individual random effects were assumed to be log-normally distributed (exponential error model) and residual variability was modeled with a proportional error model. Diagnostic plots (predicted vs observed and residual vs predicted vol 52, pg 57 of 73) illustrated the goodness of fit of the model to the AI plasma concentration vs. time data.

Base Population Pharmacokinetic Model Development for Rasagiline

A two-compartment model with first-order absorption and first order elimination was fit to rasagiline plasma concentration vs. time data collected in studies CD596 and TVP-1012/133. Because of the limited number of samples collected during the rapid absorption phase in TVP-1012/133, it was not possible to obtain stable estimates of the absorption rate constant, K_a, for the combined data. Consequently, the population estimate for K_a was fixed to the estimate obtained from the analysis of the phase I data alone, 8.7 h⁻¹. Differences in rasagiline pharmacokinetics between the healthy volunteers in study CD596 and patients with Parkinson's Disease (PD) in the TVP-1012/133 study population were explored in the model building process. A significant difference was found in apparent rasagiline clearance between healthy subjects and PD patients. Thus, the median apparent clearance (CL/F) for rasagiline in the phase III study population was estimated to be 69.8 L/h, approximately 30% lower than that estimated for healthy subjects in the phase I study after 10 consecutive daily doses of rasagiline. The median apparent volume of the central compartment (V/F) was estimated to be 118 L and the median apparent volume of the peripheral compartment (V_p/F) was estimated to be 240 L. The large apparent volume of distribution was consistent with the finding that rasagiline undergoes significant, irreversible specific binding in peripheral tissues. All pharmacokinetic parameters were precisely estimated, as shown by percentage relative standard errors (RSE) of less than 19%. Interindividual variability in the absorption rate constant, K_a, was large (81.6%) while the interindividual variability in apparent rasagiline clearance (CL/F) was estimated to be 38.6%. Separate residual error models were included for the phase I (CD596) and phase III (TVP-1012/133) data. Residual variability was estimated to be 37.1- 44.6%.

Results from the base model are presented in the following Table for the Rasagiline Base Pharmacokinetic Model CD 596 and TVP-1012/133.

Structural Model Parameter	Median Value (RSE)
Ka (h ⁻¹)	8.7
CL/F on study day 1 (L/h)	225.0 (8.1%)
CL/F on study day 10 (L/h)	101.0 (3.6%)
CL/F in phase III study (L/h)	69.8 (4.3%)
Q/F on study day 1 (L/h)	47.3 (10.8%)
Q/F on study day 10 in phase I study and phase III study (L/h)	56.6 (13.3%)
V _d /F (L)	118.0 (5.4%)
V _p /F (L)	240.0 (19.0%)

Interindividual Variability	Estimate (RSE)	Interindividual CV
Ka (h ⁻¹)	0.67 (35.9%)	81.6%
CL/F (L/h)	0.15 (19.4%)	38.6%
Q/F (L/h)	NE ^a	NE ^a
V _d /F (L)	NE ^a	NE ^a
V _p /F (L)	NE ^a	NE ^a

^anot estimated

Residual Error	Estimate (RSE)	Intraindividual CV
$\sigma^2_{prop - study CD596}$	0.20 (14.0%)	44.6%
$\sigma^2_{prop - study TVP-1012/133}$	0.14 (10.0%)	37.1%

Base Population Pharmacokinetic Model for AI

Individual pharmacokinetic parameters for rasagiline were determined using Bayesian estimation from the population pharmacokinetic model and appended to the combined (CD596 and TVP-1012/133) data set. The metabolite model was subsequently developed, conditioning on the population pharmacokinetic model for rasagiline. The model structure consisted of the rasagiline two compartment disposition with first-order absorption and first order elimination, and a one compartment open pharmacokinetic model for AI. Model selection for AI was based on evaluation of Results from the base model are presented in the following Table for the Aminoindan Base Pharmacokinetic Model CD 596 and TVP-1012/133.

Structural Model Parameter	Median Value (RSE)	
CL _M /F _M on study day 1 in phase I study (L/h)	38.6	(4.4%)
CL _M /F _M on study day 10 in phase I study and phase III study (L/h)	27.8	(2.5%)
V _M /F _M on study day 1 in phase I study (L)	502.0	(5.4%)
V _M /F _M on study day 10 in phase I study (L)	331.0	(5.1%)
V _M /F _M in phase III study (L)	492.0	(10.7%)

Interindividual Variability	Estimate (RSE)	Interindividual CV
CL _M /F _M (L/h)	0.09 (12.6%)	29.8%
V _M /F _M (L)	0.04 (43.2%)	20.9%

Residual Error	Estimate (RSE)	Intraindividual CV
$\sigma^2_{prop - study CD596}$	0.05 (13.1%)	22.1%
$\sigma^2_{prop - study TVP-1012/133}$	0.04 (13.2%)	19.9%

Differences in AI pharmacokinetics between the healthy volunteers in study CD596 and patients with Parkinson's Disease (PD) in the TVP-1012/133 study population were explored in the model building process. Apparent AI clearance did not differ between healthy volunteers at steady-state (after the 10 consecutive daily dose) and at steady-state in PD patients. However, the apparent AI volume of distribution differed between healthy volunteers and PD patients. The median estimated AI CL_M/F_M was 27.8 L/h and estimated V_M/F_M was 492 L in the phase III study population. All pharmacokinetic parameters were precisely estimated, as shown by percentage relative standard errors (RSE) of less than 11%. Estimates of interindividual variability in AI CL_M/F_M and V_M/F_M were 29.8% and 20.9%, respectively, in the combined CD596 and TVP-1012/133 populations. Residual variability was estimated to be approximately 20% for both studies (CD596 and TVP-1012/133).

Final Model

Model Refinement

The combined rasagiline -AI population pharmacokinetic model was re-evaluated to define the most parsimonious model. During the development of the rasagiline population pharmacokinetic model intercompartment clearance was assumed to differ at steady-state (after the 101h consecutive dose in the phase 1 (CD596) study and in the phase III (TVP-I 0 12/133) study relative to the estimated intercompartment clearance after the first dose in the phase I study. This was deemed a reasonable assumption based on the analysis of the CD596 data alone and because the sparseness of the phase III data did not support inclusion of a separate parameter for estimation of the intercompartment clearance in the TVP-1012/133 study population. However, whereas the estimate of Q/F was reduced by approximately 36% at steady-state relative to the first dose in the phase I study, estimated

Q/F increased by approximately 20% for the combined phase I and phase III data set. Consequently, the model was simplified to include a constant intercompartment clearance in the model. Based on the likelihood ratio test, the data supported a single estimate of the intercompartment clearance for the combined CD596 and TVP-1012/133 data sets. The data did not support simplification of the residual error model despite similar estimates for the phase I and the phase III studies (44.7% and 36.6%, respectively).

The population pharmacokinetic model for AI was conditioned on the refined population pharmacokinetic model for rasagiline. As with the rasagiline model, estimates of the residual error for the AI population pharmacokinetic model were similar for the phase I and phase III studies (22.2% and 19.8%, respectively). However, the data did not support simplification of the residual error model. In addition, hypothesis tests confirmed that while the apparent AI volume of distribution differed between healthy volunteers and PD patients, apparent AI clearance did not differ between healthy volunteers at steady-state (after the 10th consecutive daily dose) and at steady-state in PD patients. The refined model was deemed the final rasagiline -AI population pharmacokinetic model. Population pharmacokinetic parameter estimates for the final combined model are listed in the following Table.

Table 7.1.16 Final Population Pharmacokinetic Model Parameters, FOCE/INTERACTION: Combined Rasagiline/1-Aminoindan Model (Protocol TVP-1012/232)

Structural Model and Interindividual Variance Parameters		
Parameter	Typical Value (%RSE*)	Interindividual CV% (%RSE*)
ka (hr ⁻¹)	6.20	NE
CL/F (L/hr) ^a	58.5 (2.80%)	30.6% (14.8%)
V2/F (L) ^a	125 (6.58%)	73.8% (13.0%)
V3/F (L)	3300	NE
Q/F (L/hr)	46.4 (4.33%)	NE
CL~WT	0.541 (16.0%)	N/A
CL~AGE	-0.403 (35.0%)	N/A
CL~COM1	-0.310 (13.8%)	N/A
V2~AGE	-0.785 (40.6%)	N/A
CLM ^b	27.5 (1.89%)	26.5% (10.6%)
VM ^b	270 (4.37%)	41.0% (17.3%)
CLM~WT	0.732 (12.2%)	N/A
CLM~AGE	-0.358 (22.2%)	N/A
Residual Error		
Parameter	Estimate (%RSE^a)	
Σ _{1,1 prop}	CV%=29.1% (6.51%)	
Σ _{3,3 prop}	CV%=17.7% (5.11%)	
Σ _{4,4 add}	SD=0.194 (18.7%)	

*%RSE: percent relative standard error of the estimate = SE/parameter estimate * 100

^aCovariance of etas for CL/F and V2/F was 0.164 (correlation coefficient = 0.725)

^bCovariance of etas for CLM and VM was 0.00962 (correlation coefficient = 0.0887)

NE: not estimable

N/A: not applicable

Table 7.1.17 Effect of Covariates on Rasagiline/1-Aminoindan Pharmacokinetic Parameters
 Expected values of rasagiline clearance (CL/F), central volume of distribution (V2/F) and 1-aminoindan clearance (CLM) are presented as a function of significant covariates in the final population PK model.

		CL/F (L/hr)			CL/F (L/hr)		
		Weight ^a			Weight ^a		
		min	ref	max	min	ref	max
Age ^b	min	57.4	75.4	109.9	39.6	52.0 ^v	75.8
	ref	44.5	58.5	85.3	30.7	40.4	58.8
	max	39.9	52.4	76.3	27.5	36.1	52.7
		COM1 = 0			COM1 = 1		

V2/F(L)		
Age ^b		
min	ref	max
205	125	101

		CLM(L/hr)		
		Weight ^a		
		min	ref	max
Age ^b	min	23.8	34.4	57.4
	ref	19.0	27.5	45.8
	max	17.2	24.9	41.5

^a Minimum = 42.3 kg, reference = 70 kg, maximum = 140.5 kg

^b Minimum = 32 yr., reference = 60 yr., maximum = 79 yr.

In the PRESTO study (TVP-1012/133), there was a similar proportion of tobacco smokers (13 out of 276 subjects, 5% of the study population). In that study, there was no significant effect of tobacco smoking on rasagiline clearance. The effect of smoking status on rasagiline clearance was evaluated using the likelihood ratio test and the final population pharmacokinetic model for rasagiline and AI (model 621, Table 5 in report TVP 1012/133PPK). The change in MOFV was 0.157 (2 df, not significant). See the following Table on the results of hypothesis testing in study 133.

Results of Hypothesis Testing in Study TVP-1012/133

Model	Model Tested	OFV	Comment
621p	Final Population PK Model for Rasagiline and AI	833.583	Reference model
621psmok	Add smoking status (2 parameters)	833.426	Not significant compared to model 621p

Graphical analysis of goodness of fit

Figure 11-4 Diagnostic Plots for Rasagiline Base Population Pharmacokinetic Model (studies CD596 and TVP-1012/133)
= ID number; solid line is line of identity.

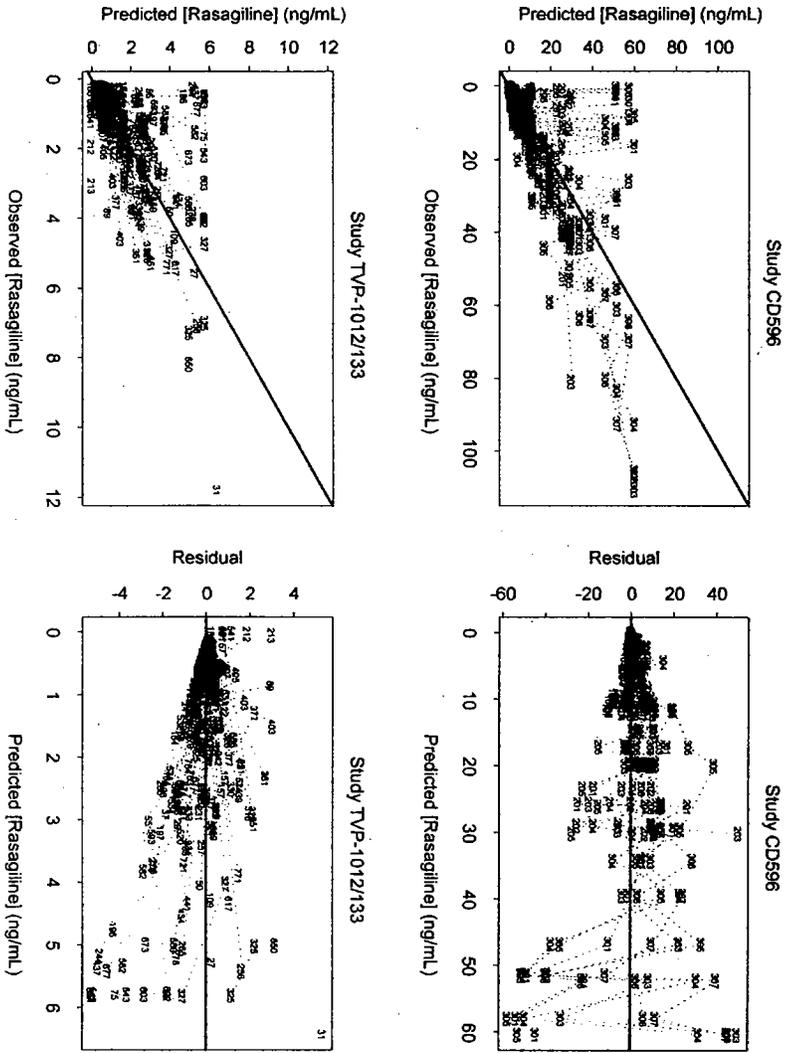
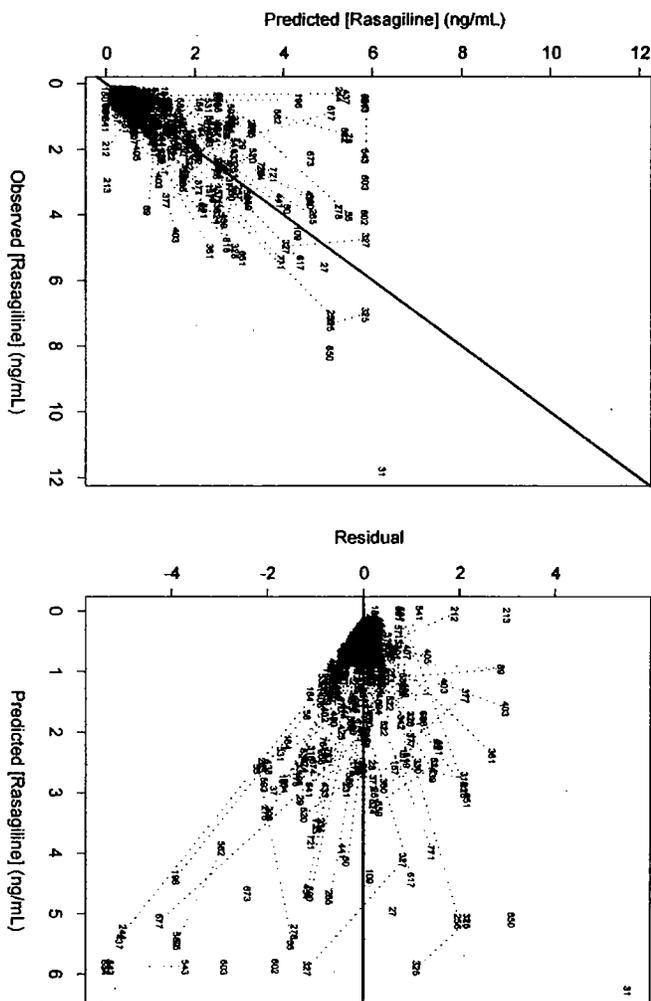


Figure 11-11 Diagnostic Plots for Final Rasagiline – AI Population Pharmacokinetic Model (TV-P-1012/133)

= ID number; solid line is line of identity. Upper panel: rasagiline data, lower panel: 1-R-aminoindan data.



DISCUSSION

The population pharmacokinetics of rasagiline and l-aminoindan were characterized by a linear model with a two-compartment disposition for parent drug and a one-compartment disposition model for the metabolite. The pharmacokinetic parameter

estimates were comparable with what has previously been observed for rasagiline, intense sampling studies. Inclusion of covariates in the population model resulted in an improved predictive ability and identified possible sources of variability in rasagiline and AI pharmacokinetics. The rasagiline CL/F estimate for a 70 kg, 60 year-old individual, with no concomitant medications, was 58.5 L/hr. Variability across the population in rasagiline CL/F was related to weight, age and concomitant levodopa/carbidopa therapy. Inclusion of these covariates as predictors of clearance reduced the random unexplained variance parameter estimate from 0.124 to 0.094 (a 25% reduction). A decrease in CL/F was associated with increasing age. Weight affected CL/F in a positive manner. The concomitant use of carbidopa/levodopa was related to a decrease in rasagiline CL/F of 31%.

The ISS reported on page 134 of 379 that fluctuating PD patients in whom rasagiline was added to LD therapy showed a dose response in the adverse effects between the 0.5 mg and 1 mg groups. However this seems to be of little clinical importance since carbidopa/levodopa and rasagiline are metabolized by different enzyme systems(the former by dopa-decarboxylase the latter by CYP1A2). The adverse effects (AE's) observed in the LD adjunct subjects from the ISS was discussed with the Medical Officer and she believes that many of them may be related to the progressed stage of the disease in the adjunct patients. She also pointed out that many of these may be related to other PD meds since in the adjunct study 65% of the subjects were taking concomitant dopamine agonists while for monotherapy the figure was 46-53%.

Although several covariate factors were eliminated as significant predictors of rasagiline and I-aminoindan pharmacokinetic parameters, this may or may not be evidence of a finding of no relationship. An alternative interpretation is that the study design, covariate range (or count), and analysis method were not sufficient to detect an effect if indeed one were present. In clinical trials performed to date, the safety profile of rasagiline mesylate was good in subjects with doses ranging from 0.5 to 20 mg per day . Clinical studies have also demonstrated an inability to distinguish efficacy between 1 mg and 2 mg daily doses.

Although the clinical significance of covariate effects on rasagiline and AI pharmacokinetics is unknown, the lack of a demonstrated efficacy exposure-response relationship suggest that pharmacokinetic variability may be of minimal importance at the intended therapeutic dose range.

CONCLUSIONS

1. The final population pharmacokinetic model was characterized by a two-compartment model with first order absorption and first order elimination for rasagiline and a one-compartment model with first order formation from rasagiline and first order elimination for I-R-aminoindan.

2. Absorption of rasagiline from the oral tablet formulation was rapid, but varied substantially among individuals. The disposition of both rasagiline and I-R-aminoindan was characterized by a large apparent volume of distribution. Apparent rasagiline clearance was approximately 35% lower than that in healthy volunteers while apparent clearance of I-R-aminoindan was similar to that in healthy subjects after 10 consecutive daily doses of rasagiline.

3. Three covariates were retained in the final population pharmacokinetic model for

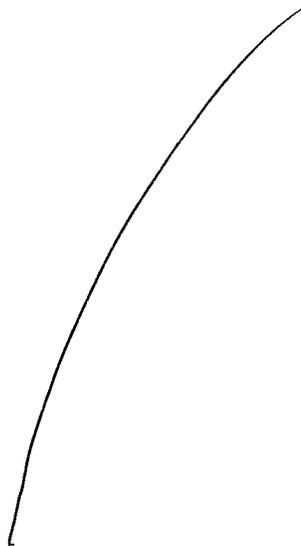
rasagiline and AI. Concomitant entacapone was correlated with apparent rasagiline clearance, body weight was correlated with apparent AI clearance and gender was

COMPARISON OF RESULTS FROM THE SPONSOR AND FDA ANALYSIS FOR PRESTO- ALL FINAL MODELS ANALYZED WITH FOCE

Base Structural Model Dense Sampling Firm-Parent	Base Structural Model Dense Sampling FDA-Parent	COMMENTS
Method 1 OBJ=1002.57 Run 073	Method 1 OBJ=1002.57	All parameter values agree
Base Structural Model Dense Sampling Firm-Metabolite	Base Structural Model Dense Sampling FDA-Metabolite	COMMENTS
Method 1 OBJ=757.67 Run 112c	Method 1 OBJ=757.67	All parameter values agree
Base Population Model Firm-Parent + Metabolite	Base Population Model FDA-Parent + Metabolite	COMMENTS
Method 1 OBJ=108.62 Run 510A	Method 1 OBJ=108.62	Fit uses different clearance values for times > 48 hrs than for times < 48 hrs.
Final Population Model Firm-Parent + Metabolite	Final Population Model FDA-Parent + Metabolite	COMMENTS
Method 1 OBJ=-27.78 Run 930	Method 1 OBJ=-27.78 Run 930	All parameter values agree

APPENDIX 1-TEMPO CONTROL STREAMS

1.CONTROL FOR RUN 002-STRUCTURAL MODEL DENSE SAMPLING



15 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

APPENDIX III
OCPB FILING REVIEW

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission				
	Information		Information	
NDA Number	21641	Brand Name	Agilect®	
OCPB Division (I, II, III)	I	Generic Name	Rasagiline Mesylate	
Medical Division	Neuropharmacology	Drug Class	MAO Inhibitor	
OCPB Reviewer	Andre Jackson	Indication(s)	Mono&Adjunct Therapy Parkinson's Disease	
OCPB Team Leader	Ray Baweja	Dosage Form	Tablet	
		Dosing Regimen	1 mg QD	
Date of Submission	9/5/03	Route of Administration	Oral	
Estimated Due Date of OCPB Review		Sponsor	Teva Neuroscience	
PDUFA Due Date		Priority Classification		
Division Due Date				
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:	X	2		Study TVP-1012/422 Study TVA 158/012831
Isozyme characterization:	X	2		Studies WUJ 00801& WUJ00401
In vivo conversion R to S	X	1		RSqIn 2
Plasma protein binding:	X	2		TVA 108/951876 TVA 116/972994
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	X	1		CC547
multiple dose:	X	1		CD 596
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	2		Tyramine -Normals PD patients on LD/CD
In-vivo effects of primary drug:	X	2		Ciprofloxacin-TVA1012/426 Theophylline-TVA1012/430
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	X	1		TVP-1012/425
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				

PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				
Filability and QBR comments				
	"X" if yes	Comments		
Application fileable ?		Reasons if the application is not fileable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA HFD-850 (Electronic Entry or Lee), HFD-120 (CSO), HFD-860 (), CDR (Biopharm-CDR)

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this page is the manifestation of the electronic signature.**

/s/

Andre Jackson
5/13/04 08:19:25 AM
BIOPHARMACEUTICS

Jogarao Gobburu
5/13/04 10:22:41 AM
BIOPHARMACEUTICS

Raman Baweja
5/13/04 12:15:15 PM
BIOPHARMACEUTICS

**Office of Clinical Pharmacology and Biopharmaceutics
Pharmacometrics Consult Request Form**

NDA:	21641	Sponsor:	Teva
IND:			
Brand Name:	Agilect	Priority Classification:	1S
Generic Name:	Rasagiline Mesylate	Indication(s):	Parkinson's disease mono & adjunct therapy
Dosage Form:	Tablet	Date of Submission:	9/5/03
Dosing Regimen:	1 mg QD	Due Date of PM Review:	4/30/04
Division:	Neuropharmacology	Medical Division:	Neuropharmacology
Reviewer:	Andre Jackson	Team Leader:	Ray Baweja; Joga Gobburu

Tabular Listing of All Human Studies That Contain PK/PD information (This can be requested at the pre-NDA stage as indicated on the PM roadmap)

(may attach tabular summary of all studies from NDA to this document)

TVP-1012/232 TEMPO

TVP-1012/133 PRESTO

TVP-10129(P94159)

List the following for this compound (if known. The list will be confirmed by PM Scientist during the review):

Clinical endpoint(s):	UPDR-Unified Parkinson's Disease Rating Scale; ON Time
Surrogate endpoint(s):	None
Biomarker(s):	None
Any reported optimal dose based on PK/PD ?:	No
Any reported dose/concentrations associated with efficacy/ toxicity ?:	No
Principal adverse event(s):	For 2 mg dose abnormal dreams and vomiting

Pharmacometrics Request: (Jointly filled out with PM Scientist)

(Briefly state the objective(s) of the consult. The request should be as explicit as possible, and should state whether a review or additional analysis is needed. An assessment of the impact that the data will have on labeling should be included (Questions to be answered in QBR). The proposed labeling and the HPK Summary along with the relevant volumes should be available to the PM Scientist.)

The major emphasis of the consult will be to establish a pk/pd relationship to aid in dose/dosing regimen selection.

Due Date to the Reviewer 3/15/04

The PM Scientist or the _x_ Primary Reviewer (select one) will perform the PM Review

PM Briefing or PM Peer Review _x_ requested (for criteria see the PM Road Map of QA/QC process)

Primary Reviewer Andre Jackson
Date 11/3/04

Signature _____

PM Scientist Andre Jackson
Date 11/3/04

Signature _____

CC: HFD-860(Jackson, Sahajwalla, Mehta, Gobburu,Baweja) HFD-850 (Lee)

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/s/

Andre Jackson
11/4/03 10:21:44 AM
BIOPHARMACEUTICS

Jogarao Gobburu
11/7/03 08:53:23 AM
BIOPHARMACEUTICS

Raman Baweja
11/7/03 09:27:56 AM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

Information		Information	
NDA Number	21641	Brand Name	Agilect®
OCPB Division (I, II, III)	I	Generic Name	Rasagiline Mesylate
Medical Division	Neuropharmacology	Drug Class	MAO Inhibitor
OCPB Reviewer	Andre Jackson	Indication(s)	Mono&Adjunct Therapy Parkinson's Disease
OCPB Team Leader	Ray Baweja	Dosage Form	Tablet
		Dosing Regimen	1 mg QD
Date of Submission	9/5/03	Route of Administration	Oral
Estimated Due Date of OCPB Review	4/30/04	Sponsor	Teva Neuroscience
PDUFA Due Date	7/4/04	Priority Classification	1S
Division Due Date	5/15/04		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:	X	2		Study TVP-1012/422 Study TVA 158/012831
Isozyme characterization:	X	2		Studies WUJ 00801& WUJ00401
In vivo conversion R to S	X	1		RSqln 2
Plasma protein binding:	X	2		TVA 108/951876 TVA 116/972994
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		CC547
multiple dose:	X	1		CD 596
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	2		Ciprofloxacin-TVA1012/426 Theophylline-TVA1012/430
In-vivo effects of primary drug:	X	2		Tyramine -Normals PD patients on LD/CD
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	X	1		TVP-1012/425
hepatic impairment:	X	1		TVP-1012/424
PD:				
Phase 2:	X	4		PD PD on chronic LD Dose Finding
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				

Population Analyses -				
Data rich:				
Data sparse:	X	2		PD rasagiline w/concomitant LD PD rasagiline w/chronic LD
II. Biopharmaceutics				
Absolute bioavailability:	X	1		TVP-1012/423
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		TVP-1012/427
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		TVP-1012/421
Dissolution:	X	1		
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References N=29		1		Vol 25
Total Number of Studies		27		
Filability and QBR comments				
	"X" if yes	Comments		
Application fileable ?	X			
Comments sent to firm ?	No			
QBR questions (key issues to be considered)	1.Do the application studies support monotherapy for Rasagiline in PD? 2.Do the application studies support adjunct therapy for PD in the presence of Levodopa? 3.For adjunct therapy should there be any reduction in Levodopa dosage levels? 4.Is an adjustment in Rasagiline dose required with the decrease in oral clearance with age ?			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 21641 HFD-850 (Lee), HFD-120 (CSO), HFD-860 (Jackson,Sahajalla, Baweja, Mehta,Gobburu), CDR (Biopharm-CDR)

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/s/

Andre Jackson
11/3/03 12:49:27 PM
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OCPB Memo to file for filing NDA 21641, Rasagiline Mesylate

Raman Baweja
11/3/03 12:56:50 PM
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