2. SYNOPSIS

NAME OF SPONSOR/COMPANY: **Teva Pharmaceutical Industries** NAME OF FINISHED PRODUCT: Azilect NAME OF ACTIVE INGREDIENT(S): Rasagiline mesilate	INDIVIDUAL STUDY TABLE REFERRING TO PART .. OF THE DOSSIER Volume .. Page ..	(FOR NATIONAL AUTHORITY USE ONLY)

Study Title

A PHASE I, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED (WITHIN EACH GROUP) STUDY TO EVALUATE THE INTERACTION BETWEEN ORALLY ADMINISTERED TYRAMINE HYDROCHLORIDE AND RASAGILINE MESILATE IN HEALTHY SUBJECTS

Study Code

Sponsor code : TVP-1012-120-TYR
PRA code : TEV62061-062061

Sponsor

Teva Pharmaceutical Industries, Ltd., Israel
Sponsor's contact : PPD

Study Centre

Pharmaceutical Research Associates International (PRA), Stationsweg 163, 9471 GP Zuidlaren, The Netherlands; Location: Hanzeplein 1, 9713 BZ Groningen, The Netherlands
Project Manager : PPD (until 23 August 2007), PPD (from 23 August 2007)

Medical Investigator : S.P. van Marle, M.D.

Publication : None at time of writing this report

Study Period : Date of first screening to last follow-up: 12 December 2006 – 11 February 2008

Clinical Phase : Phase I

Objectives

Primary objective : To assess tyramine sensitivity when administered with rasagiline, and the selectivity of rasagiline for monoamine oxidase type B (MAO-B)
Secondary objectives : To investigate orthostatic blood pressure (BP) and pulse timed to rasagiline dosing

Methodology

Design : Double-blind, placebo-controlled, randomized (within each group), positive and comparator control, multiple dose study in healthy subjects.
Study groups:
Group 1: 45 mg/day phenelzine (positive control)
Group 2: 10 mg/day selegiline (comparator) and matching placebo
Group 3: 1 mg/day rasagiline and matching placebo
Group 4a and 4b: 2 mg/day rasagiline and matching placebo
Group 5: 4 mg/day rasagiline and matching placebo
Group 6: 6 mg/day rasagiline and matching placebo

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Each group proceeded with 3 periods:

1: a run-in tyramine challenge test during which tyramine was administered in escalating doses without the study drug for maximally 10 days.
2: a treatment period during which a MAO inhibitor (MAOI) or placebo was administered for 14 days or 30 days (see below).
3: a treatment period during which a MAOI or placebo was administered concomitantly with escalating doses of tyramine for maximally 11 days.

The study was executed in 2 steps:

Step 1: Groups 4a and 4b on 2 mg rasagiline with 14 days of rasagiline dosing in Period 2 for Group 4a, and 30 days of rasagiline dosing in Period 2 for Group 4b.
Step 2: The remaining groups were dosed for the duration of 14 days in Period 2.

Study Populations

		Population				
Group	**Planned**	**Primary**	**AST**	**MIT**	**TO**	**PK**
Group 1	16	15	17	16	1	0
Group 2	24	22	24	22	2	0
Group 3	24	22	25	23	2	16
Group 4a	24	22	28	24	4	14
Group 4b	24	23	29	23	6	14
Group 5	24	24	27	24	3	17
Group 6	24	21	29	24	5	14
Total	160	149	179	156	23	75

AST = all subjects treated; MIT = MAO inhibitor treated; TO = tyramine only

Main Criteria for Inclusion

Subjects :Healthy male or female volunteers
Age :40 - 70 years, inclusive
Body mass index :19.0 – 30.0 kg/m^2
Gender :Male to female ratio between 60/40 and 40/60 in each treatment group
Other criteria :At least 85% non-smokers, at most 15% smokers (up to 10 cigarettes/day until screening; smoking not allowed during the study); up to 3 subjects who were smokers were allowed per treatment group

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Study Medication

Active substance	: Rasagiline mesilate
Activity	: MAO-B inhibitor
Indication	: Parkinson's disease
Strength	: 1 and 2 mg (rasagiline base)
Dosage form	: Tablet
Batch numbers	: K-35167 (1 mg), K-35168 (2 mg)
Active substance	: Placebo for rasagiline mesilate
Activity	: Not applicable
Indication	: Not applicable
Strength	: Not applicable
Dosage form	: Tablet
Batch number	: K-35166
Active substance	: Phenelzine sulphate
Activity	: MAOI
Indication	: Depression
Strength	: 15 mg (phenelzine)
Dosage form	: Tablet
Batch number	: 519039
Active substance	: Selegiline hydrochloride
Activity	: MAO-B inhibitor
Indication	: Parkinson's disease
Strength	: 5 mg (selegiline hydrochloride, equaling 4.2 mg selegiline base)
Dosage form	: Encapsulated tablet
Batch number	: 1067S
Active substance	: Placebo for selegiline hydrochloride
Activity	: Not applicable
Indication	: Not applicable
Strength	: Not applicable
Dosage form	: Tablet
Batch number	: K-37455
Active substance	: Tyramine hydrochloride
Activity	: Monoamine oxidase (MAO) substrate
Strength	: 5, 12.5, 25, 100 mg tyramine hydrochloride (1 mg tyramine hydrochloride equals 0.79 mg free tyramine)
Dosage form	: Tablet
Batch numbers	: K-37082 (5 mg), K-37083 (12.5 mg), K-37085 (25 mg), K-37086 (100 mg)

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Outcome Measures

Primary outcome measure : TYR30 ratio, calculated as the tyramine dose associated with an increase from baseline in SBP of ≥ 30 mmHg maintained for at least 3 consecutive measurements in a period of 10 minutes or more in Period 1, divided by the dose associated with the same change in SBP in Period 3

Secondary outcome measures

: Orthostatic BP timed to rasagiline dosing

Pharmacodynamics : Plasma DHPG concentrations

Pharmacokinetics Plasma tyramine, rasagiline and 1-aminoindan (1-AI) concentrations, PK parameters

Safety and tolerability measures

: AEs, vital signs, ECG-parameters, clinical laboratory parameters, physical examination

Statistical Methods

Sample size : 160 subjects were planned to be enrolled in Period 2; no formal statistical analysis was planned for this study, hence no power calculation was performed. All provided p-values (as requested by FDA) are given without Type I error correction for multiplicity.

Primary endpoint : TYR30 ratio, calculated as the tyramine dose associated with an increase from baseline in SBP of ≥ 30 mmHg maintained for at least 3 consecutive measurements in a period of 10 minutes or more in Period 1, divided by the dose associated with the same change in SBP in the Period 3, are presented for each subject. Individual values of TYR30 and TYR30 ratios (i.e., TSF) are presented, together with descriptive statistics describing the number of subjects, geometric mean, minimum, median and maximum by treatment group.

Secondary endpoint : Orthostatic hypotension (Groups 3 - 6) is defined as a change in BP from supine to standing position of ≥ 20 or ≥ 40 mmHg for SBP and ≥ 10 or ≥ 20 for DBP, measured after 5 minutes at supine position and after 2 minutes at standing position

Pharmacokinetic/ pharmacodynamic evaluation

: The pharmacodynamic evaluation was performed for the primary study population (i.e, subjects who completed all 3 periods of the study). The DHPG plasma concentrations are listed and descriptive statistics are presented by treatment group and time point. Results for rasagiline treated subjects of Groups 4a and 4b are presented both separately and pooled.
All subjects who received rasagiline treatment and for whom the PK data were considered to be sufficient and interpretable and who did not have any protocol violations interfering with pharmacokinetics, were included in the pharmacokinetic statistical analyses.

Evaluation of safety and tolerability parameters

: AEs, clinical laboratory data, ECG parameters, physical examination, and early terminations due to AEs were assessed.

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Results

Primary Endpoint

The geometric mean and median TYR30 ratios were highest for the non-selective comparator phenelzine (17.32 and 17, respectively) and lowest for the pooled placebo group (1.50 and 1, respectively).

The geometric mean and median TYR30 ratios for the marketed dose of 1 mg rasagiline were 2.03 and 2, respectively, while those for pooled placebo were 1.50 and 1, respectively. These were clearly lower than the TYR30 ratios of the non-selective comparator phenelzine (17.32 and 17). Even for the highest rasagiline dose of 6 mg the TYR30 ratios (5.10 and 5, respectively) were lower than those of phenelzine.

A 5 mg twice daily dose of selegiline resulted in comparable geometric mean and median TYR30 ratios (2.47 and 2, respectively) to those of 1 mg rasagiline.

A positive association was evident between rasagiline dose and geometric mean TYR30 ratios with values ranging between 2.03 and 5.10, and a slope of 1.25 ($p<0.0001$) – i.e., an increase of 25% in the geometric mean TYR30 ratio for each 1 mg increase in the rasagiline dose. Based on the TYR30 ratios the selectivity of rasagiline seems to wane at rasagiline doses above 2 mg.

The geometric mean and median TYR30 ratios following 30 days of treatment with 2 mg rasagiline (2.45 and 3, respectively) were not any higher than those following 14 days of treatment with 2 mg rasagiline (3.33 and 4, respectively). This indicates that the effect reaches steady state within 2 weeks of treatment with rasagiline; therefore, the 14 day results can be extrapolated to longer administration.

Summary Table of Mean and Median TYR30 Ratios

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

Secondary Endpoint

There was no evidence of higher orthostatism in rasagiline-treated subjects compared to placebo subjects, and no evidence of dose response.

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Pharmacokinetics

After multiple daily administration of rasagiline, a dose-dependent increase in mean C_{max} and AUC plasma rasagiline values was observed in the dose range of 1 mg to 6 mg rasagiline. The median t_{max} for plasma rasagiline was approximately similar across the dose range studied, ranging from 0.33 h to 0.55 h. The geometric mean $t_{1/2}$ was between 1.19 h to 6.78 h across the dose range studied. The PK parameters were similar after 13 days and 29 days of dosing with 2 mg rasagiline.

As for rasagiline, a dose-dependent increase in mean C_{max} and AUC plasma 1-AI values (main metabolite of rasagiline) was observed across the dose range studied. The median t_{max} for plasma 1-AI ranged from 1.07 h to 2.07 h. The geometric mean $t_{1/2}$ was between 11.0 h to 15.8 h across the dose range studied.

Overall the PK profile of rasagiline and 1-AI is consistent with the profile seen in previous studies with rasagiline.

Pharmacodynamics

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

Safety

Overall, during Periods 2 and 3, there were 2 treatment-emergent AEs (TEAEs) of severe intensity (including intervertebral discitis [Subject PPD and disturbance in attention [Subject PPD 24 TEAEs of moderate intensity (especially headache, nausea and vomiting) and the remainder (538 TEAEs) were of mild intensity.

Three subjects had one or more serious AEs (SAEs) during the study. In Period 1, Subject PPD (tyramine only) had one event of ventricular tachycardia (VT) of mild intensity. In Period 3, Subject PPD (2 mg rasagiline + tyramine) had intervertebral discitis. In Period 3, Subject PPD (6 mg rasagiline + tyramine) had one event of acute coronary syndrome of moderate intensity and post-procedural haemorrhage of moderate intensity.

For 5 subjects, study medication administration was prematurely discontinued because of TEAEs. This included in Period 1 VT of mild intensity (SAE in Subject PPD ECG ST segment depression of mild intensity (Subject PPD multiple ectopic ventricular beats (Subject PPD see Note to File No. 28) and atrioventricular block of second degree of mild intensity (Subject PPD In Period 3 this included influenza like illness of moderate intensity (Subject PPD which started at the end of Period 2 and continued in Period 3. For 1 subject (Subject PPD dosing with selegiline was temporarily interrupted during Period 2 (one evening dose) due to nausea of moderate intensity and somnolence, headache, dizziness and hyperhidrosis of mild intensity.

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Overall, the most frequently reported TEAEs of the MIT population were nervous system disorders (185 TEAEs reported by 83 subjects [53%]; mainly headache, dizziness and somnolence), general disorders and administration site conditions (106 TEAEs reported by 65 subjects [42%]; especially fatigue) and gastrointestinal disorders (103 TEAEs reported by 54 subjects [35%]; especially nausea).There was no clear difference between active and placebo treated subjects, with the exception of the nervous system disorders which were reported more often during treatment with phenelzine than during treatment with selegiline, rasagiline or placebo.

With regard to administration with study medication (rasagiline, phenelzine or selegiline), there were no findings of clinical relevance with respect to 12-lead ECG, continuous ECG monitoring, clinical laboratory and physical examination.

Conclusions

Primary Endpoint

- The geometric mean and median TYR30 ratios were highest for the non-selective comparator phenelzine and lowest for the pooled placebo group.
- The geometric mean and median TYR30 ratios for rasagiline 1 mg were 2.03 and 2, while those for pooled placebo were 1.50 and 1, respectively. These were clearly differentiated from the results for phenelzine (17.2 and 20). Even for the highest rasagiline dose of 6 mg the TYR30 ratios were lower than those of phenelzine.
- Sensitivity analyses support the conclusions from the primary analysis.

Secondary Endpoint

- There was no evidence of orthostatism in rasagiline-treated subjects compared to placebo subjects.

Safety

- There was no clear difference between rasagiline and placebo treated subjects with respect to AEs.

Pharmacodynamics

- Treatment with 1 mg rasagiline, similar to placebo, did not cause a decrease in mean DHPG levels, in contrast to the non-selective comparator phenelzine where a clear decrease in mean DHPG levels was observed.

Pharmacokinetics

- Overall the PK profile of rasagiline and 1-AI is consistent with the profile seen in previous studies.

Summary Conclusions

- In conclusion, the primary endpoint and all supportive sensitivity analyses, together with the results from DHPG assessment provide evidence for the MAO-B selectivity of 1 mg rasagiline.

Date of report: 22 January 2009