6.0 SUMMARY AND CONCLUSION

Several regulatory agencies (US: FDA; DCGI and EMEA) consider two products to be bioequivalent if they yield comparable bioavailability (rate and extent of drug absorption) when administered to the same individuals in the same dose and under similar conditions. The formulations thus deemed to be bioequivalent are therapeutically interchangeable.

In the present study we compared the rate and extent of absorption of Rasagiline between the two tablets of test formulation of Rasagiline 1 mg (containing rasagiline mesylate equivalent to 1mg of rasagiline base; total dose rasagiline 2mg) of Ranbaxy Laboratories Limited, with two tablets of Azilect tablets 1 mg (containing rasagiline mesylate equivalent to 1mg of rasagiline base; total dose rasagiline 2mg) of Teva Neuroscience, Inc., in healthy, adult, human male subjects under fasting condition.

The clinical study was carried out in accordance with ICH Good Clinical Practices. The study protocol and the informed consent forms were approved by the Jamia Hamdard Institutional Review Board. Each of the subjects was required to understand and give his consent to participate in the study by signing the informed consent form. The signed original copy was retained and a copy was given to each study subject for record. The washout period maintained between the each period was of seven days.

Bioequivalence was assessed by measuring the pharmacokinetic parameters namely $C_{\text{max}}$, $T_{\text{max}}$, $\text{AUC}_{0-\text{t}}$, $\text{AUC}_{0-\infty}$ for Rasagiline 1mg tablets.

The complete study could be summarized as follows:

- The clinical study was carried out in accordance with ICH Good Clinical Practices.

- The protocol and informed consent form for this study was approved by Jamia Hamdard Institutional Review Board (JHIRB) and approved protocol was used for the conduct of study.

- The study design selected was an open label, balanced, randomized, crossover design under fasting conditions.

- Eighteen healthy, adult male, human subjects, who met the inclusion and exclusion criteria as described in the protocol, were enrolled in the study.
The order of receiving the test and reference products for each subject was determined according to a SAS generated randomization schedule.

The standard SOP’s of the clinical pharmacology unit (CPU) and Clinical Pharmacology and Pharmacokinetics (CPP), Ranbaxy have been adhered during the clinical, analytical, pharmacokinetic and statistical analysis.

There was no protocol deviation during study.

A suitable LC/MS/MS method was developed and validated for the analysis of plasma samples to estimate the Rasagiline concentration in human plasma.

The method was validated in terms of selectivity, precision, accuracy, linearity, recovery, dilution integrity, effect of anti-coagulant, ruggedness and stability studies.

- Stability studies includes freeze-thaw, bench top, ininjector, long term and stock solution.

Analysis of subject samples was done using the validated method. All the batches met pre defined acceptance criteria and there was no repeat analysis. Final concentration data was used for pharmacokinetic and statistical analysis.

Pharmacokinetic evaluation was carried out by determination of parameters, viz. $T_{\text{max}}$ (hrs), $C_{\text{max}}$ (ng/ml), $\text{AUC}_{0-t}$ (ng.hr/ml), and $\text{AUC}_{0-\infty}$ (ng.hr/ml) after administration of two tablets of Rasagiline 1mg both for reference and test (Reference R, Test T).

Statistical analysis was performed on various pharmacokinetic parameters.

The following conclusion was drawn from the study:

- Intrasubject CV was <30% for all pharmacokinetic parameters.
- Power was less than 90% for $C_{\text{max}}$ i.e. 68.20 and for $\text{AUC}_{0-t}$ and $\text{AUC}_{0-\infty}$ it was more than 90% i.e. 99.22 and 99.21 respectively.
- The 90% confidence intervals of $C_{\text{max}}$ (T/R ratio) were 74.73- 100.81 which were not falling in the acceptable range. While 90% confidence intervals of $\text{AUC}_{0-t}$ and $\text{AUC}_{0-\infty}$ (T/R ratio) were 87.78- 103.15 and 87.96- 103.39 respectively which were within the 80-125% acceptable range.
• The test and reference products were well tolerated by the study subjects.

Finally it can be concluded that the test product (T) of rasagiline in the present study did not satisfy the criteria for pharmacokinetic bioequivalence in comparison to reference product (R), since the 90% confidence interval of C\text{max} for T/R ratio was not within 80-125%. However, for AUC\text{0-t} and AUC\text{0-∞} it was within the specified range.