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Research Article

# Bioequivalence of Two Perampanel 12mg Tablets in Healthy, Adult, Human Subjects under Fed Conditions - An Open Label, Cross Over Study

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**Keywords**

- Bioequivalence
- Perampanel
- Epilepsy
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**Abstract**

**Background:** Perampanel is a glutamate non-competitive receptor antagonist that is effective as adjunctive therapy for epilepsy. The main objective of the present research is to compare the bioavailability and to evaluate the bioequivalence between the test and reference product. The secondary objective is to assess the safety and tolerability of the drug.

**Methods and findings:** The study design was an open label, randomized, two treatment, two sequence, two period, single dose, cross over, oral bioequivalence study of the two formulations in single dose of 12mg. The study was conducted in 28 healthy, adult, human subjects, aged between 22 to 44 years, under fed conditions with a washout period of 42 days in between doses. Blood samples were collected up to 72 hours post-dose for measurement of pharmacokinetic parameters in each period. Safety evaluation was done by assessing clinical examinations, vital signs assessment, clinical laboratory parameters and monitoring subject's well-being, symptoms and signs for adverse events. A validated LC-MS/MS method was used to determine the plasma concentrations of Perampanel. Bioequivalence between both the products was established by calculating 90% confidence intervals for the ratio of $C_{max}$ and $AUC_{0-72}$ values for the test and reference products. The 90% confidence intervals found for the relation of Test/Reference were $C_{max}$ 90.23% - 107.9% and $AUC_{0-72}$ 92.02% - 104.12%.

**Conclusion:** According to FDA's guidelines for Bioequivalence research, the confidence intervals for $C_{max}$ and $AUC_{0-72}$ ranged between 80.00-125.00%. The above limits obtained for Perampanel were within the accepted bio-equivalence limits. Thus, bio-equivalence was demonstrated between Perampanel 12mg Tablets of Abbott Laboratories de Colombia and Fycompa® (Perampanel 12mg) tablets of Eisai Europe Limited in healthy, adult, human subjects under fed conditions.

## INTRODUCTION

Perampanel is an anti-epileptic drug which is used in the treatment of seizure. It is a highly selective, non-competitive AMPA receptor antagonist that supresses neuronal hyper excitation which is associated with seizures by targeting the activity of glutamate at postsynaptic AMPA receptors [1].

Perampanel is approved for the adjunctive treatment of partial-onset seizures, with or without secondarily generalised seizures, and for primary generalised tonic-clonic (PGTC) seizures in patients with epilepsy aged 12 years and older [2].

During the course of treatment, the drug is highly absorbed after being orally administered. Based on the tolerability of the drug, the maximum recommended dose of Perampanel is 12 mg which can be gradually increased by 2mg initially on a daily dosing regimen depending upon the patient's response to the drug [3]. The half-life of Perampanel is relatively long, which is 105 hours, hence it is suggested to be given once daily for a higher dose [4].

The safety and tolerability of Perampanel was studied in various stages of development including the phase trials [5]. Perampanel was tolerable in healthy subjects and the US drug agency (USFDA) recommends conducting bioequivalence studies in healthy subjects [6].

Bioequivalence studies provide interchangeability between generic products and reference products without reiterating clinical trials in patients [7]. According to U.S. Food and Drug Administration bioequivalence between two drug products will solely be assumed when the characteristic parameters of bioavailability show no more than a defined difference, which depends upon the characteristics of the drug, the clinical end point and population of the subject [8].

## METHODS

### Volunteers

A total of 28 subjects were selected and allowed to participate in the study.

Inclusion criteria for this study were:

a) Healthy male literate volunteers of 20 to 45 years (both years inclusive) with BMI of 18.50 – 29.99 Kg/$m^2$.

b) Healthy volunteers as evaluated by medical history, vitals, and general clinical examination and laboratory assessments.

c) Volunteers with no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure (BP) and pulse rate (PR) measurement, electrocardiogram (ECG) and clinical laboratory tests.

d) Volunteers who can give written informed consent form and communicate effectively.

Exclusion criteria for this study were:

a) Volunteers who had undergone any major surgical procedure in the past 3 months, with history of any clinically significant cardiac, gastrointestinal, respiratory, hepatic, renal, endocrine, neurological, metabolic, psychiatric, hematological diseases, chronic alcoholism/chronic smoking/drug abuse.

b) Volunteers with present or past history of intake of drugs or any prescription drug or over the counter (OTC) drugs within 7 days which potentially modify kinetics / dynamics of Perampanel or any other medication judged to be clinically significant by the investigator.

c) Subjects who consumed grapefruit and/or its products within 10 days prior to the start of study.

d) Subjects who had bled (350 ml) in the past 3 months from the date of start of study either for blood donation or for any other reason.

## Informed Consent

The protocol and informed consent forms (ICFs) were reviewed and approved by an independent ethics committee: Independent Ethics Committee, Chennai (Ethics Committee re-registration No. ECR/lll/Indt/TN/2013/RR-16 issued under Rule 12200 of the Drugs & Cosmetics Rules, Ministry of Health & Family Welfare, Directorate General of Health Services, Office of the Drugs Controller General (India), Central Drugs Standard Control Organization), prior to study initiation. The study informed consent documents were distributed to all the eligible subjects. The consent documents were read and explained by the staff. Subjects were given adequate time to read and understand the consent documents. Illiterate volunteers were explained vocally by the investigator in their vernacular language. Individual counseling was then given to the willing volunteers by the Investigator in private and any questions and concerns were addressed prior to obtaining consent.

Prior to initiation of the study a written informed consent was acquired from each one of them and the study was conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines and national regulatory requirements [9,10].

## Study design

An open label, randomized, two treatment, two sequence, two period, single dose, cross over, oral bioequivalence study of test product Perampanel 12mg Tablets of Abbott Laboratories de Colombia with the reference product Fycompa® (Perampanel 12mg) tablets of Eisai Europe Limited in healthy, adult, human subjects under fed conditions.

Study subjects received either test or reference in each period as per the randomization schedule. The randomization schedule was generated by using SAS® software and each study subject was randomly assigned to one of the sequences of test product (T) and reference product (R) for the study.

## Drug administration

After an overnight fasting of 10 hours, the subjects were provided with a high fat high calorie breakfast about 30 minutes prior to dosing. The subjects were administered with a single oral dose of either test product or reference product with 200 mL of water as per the randomization schedule in sitting posture at fixed time in each period. Washout period of 42 days was maintained between the treatments. Compliance to dosing following drug administration was assessed by examination of the oral cavity. Drug dosing details were recorded in the individual case report forms. The Principal Investigator and/or Sub investigator/Physician was present throughout the conduct of the study. All the subjects remained in supine posture for 08 hours post dosing. During this period of time, subjects were allowed to rise only with assistance and also during the first rising after completion of 08 hours. The subjects were permitted to rise/walk for short intervals of time for reasons such as but not limited to the following - natural exigencies, blood sampling and vitals measurement activity during this period. Water restriction of 01 hour prior to and post dose was followed as per the protocol by all the subjects and were allowed to consume water ad libitum thereafter. The subjects received standard food approximately at 04.00, 08.00 and 12.00 hours post-dose with time flexibility of +15 minutes.

## Blood sampling

A total of 18 blood samples of 05 mL each at 00.00 (Pre-dose), 00.50, 01.00, 01.50, 02.00, 02.50, 03.00, 04.00, 06.00, 08.00, 12.00, 24.00, 48.00 and 72.00 hours post-dose were collected for measurement of pharmacokinetic parameters in both periods. The pre dose samples were collected 02 hours prior to the drug administration.

The post dose in-house samples were collected within 02 minutes from the scheduled time and the ambulatory samples were collected within ± 01 hour from the schedule time. Any delay from these was recorded as protocol deviation. The samples were collected from intravenous cannula or by direct vein puncture into pre-labeled $K_3$EDTA vacutainers. The samples were then centrifuged at 4000 rpm for 10 minutes at 4°C. The plasma was separated into two aliquot: 01 mL in first aliquot

and remaining in the second aliquot. The $K_3$EDTA vacutainers and polypropylene tubes were pre-labeled with Subject Number, Study Number, Study Period, Time point and Aliquot Number. The samples were stored at -70°C in an ultra-low temperature freezer. The plasma samples were quantified using validated bio-analytical method.

### Analytical method

Liquid-Liquid Extraction was chosen for sample preparation to extract the analyte of Perampanel. A validated LC-MS/MS bio-analytical method was used for estimation of Perampanel in plasma. Bioanalytical method validation was done as per FDA's Bioanalytical Method Validation guidance on Specificity, Sensitivity, Precision and Accuracy, Stability, Recovery, Dilution Integrity and Linearity range. Samples of subjects who completed the entire duration of study were analysed. All samples from one subject were analyzed with the same single standard curve. Sample concentration above upper limit of the standard curve from validated range was analysed by diluting the sample with drug free biological matrix and assayed.

### Pharmacokinetic parameters and statistical analysis

For Perampanel, analysis of variance (ANOVA) was performed on the Ln-transformed data of $C_{max}$ and $AUC_{0-72}$ using PROC GLM of SAS® (version 9.4) software. The analysis of variance model included sequence, period and formulation (treatment) as fixed effect and the subjects nested within the sequence as random effect. The sequence effect was tested at the 0.10 level of significance using the subjects nested within sequence mean square from the ANOVA as the error term. All other main effects were tested at the 0.05 level of significance against the residual error (mean square error/MSE) from the ANOVA as the error term using 90% confidence interval approach [11]. Based on comparisons of the test and reference product for Ln-transformed $C_{max}$ and $AUC_{0-72}$ data, the ratio of the least square mean was calculated, as well as the 90% confidence intervals for Ln-transformed $C_{max}$ and $AUC_{0-72}$ was determined.

The ANOVA was performed on the Ln-transformed $C_{max}$ and $AUC_{0-72}$ parameters. The least-square mean ratios, 90% CI and intra-subject CVs were also determined for $C_{max}$ and $AUC_{0-72}$ of Perampanel for test and reference products.

To establish bioequivalence of the test product with that of reference product, 90% CI for the ratio (Test/Reference) of Least Square Means of the Ln transformed PK parameters ($C_{max}$ and $AUC_{0-72}$) must fall between 80.00% and 125.00%.

### Safety Analysis

Safety was assessed via continuous health monitoring and scheduled recording of safety measurements throughout the study. Staffs monitored and recorded the pulse rate, oral temperature, blood pressure and subjects' well-being during check-in, at 00.00 (pre dose), 02.00, 08.00 and 23.00 hours post-dose and during ambulatory. The pre dose (00.00 hour) vital parameters were recorded within two hours prior to drug administration and the post dose vitals with a flexibility of ± 30 minutes of each time point. During ambulatory visits, the vital parameters were recorded at the actual time of visit before blood sampling.

General examination and systemic examination of subjects were performed during check-in of each period by the physician/investigator/sub-investigator to ensure safety. Subjects were instructed to inform clinic personnel of any untoward medical symptoms and/or events that arose during the course of the study. Prior to period II check in, subjects were questioned concerning unusual symptoms that may have occurred after the previous administration of the study drug.

The Principal Investigator/sub-investigator/study physician evaluated the relationship of all adverse events to the study drugs. The adverse events were graded as mild, moderate or severe as per standard operating procedure. The Principal Investigator/sub-investigator also evaluated the subjects for subsequent dosing. Post-clinical laboratory tests (hematology and serum chemistry), post-study general and systemic examination including vital sign measurements (blood pressure, pulse rate and temperature) were performed.

## RESULTS

### Demographic characteristics

The mean age, height, weight and BMI of the 25 subjects who completed the study are presented in Table 1. All the subjects included in the study were Male and Asians.

### Pharmacokinetics and statistics

In the present study, 28 subjects participated of which 25 subjects completed. Thus, the pharmacokinetic analysis of Perampanel was performed using the concentration data obtained from 25 subjects. The statistical analysis was done using the concentration data of 23 subjects (excluding subjects S12 and S24, who had pre-dose concentration of more than 5% of $C_{max}$ in period II). Sequence effect was insignificant for $C_{max}$ and $AUC_{0-72}$ with respect to p - value 0.6570 and 0.2764 respectively.

Period effect was insignificant for $C_{max}$ and significant for $AUC_{0-72}$ with respect to p - value 0.0669 and 0.0289 respectively. Formulation effect was insignificant for $C_{max}$ and $AUC_{0-72}$ with respect to p - value 0.7992, and 0.5565 respectively.

The plasma concentration vs. time curve of test and reference

**Table 1:** Summarized Demographic Profile of Subjects who completed the study

| Parameter | Mean | SD | Min | Max |
|---|---|---|---|---|
| **Age (years)** | 33 | 07 | 22 | 44 |
| **Height (m)** | 1.688 | 0.063 | 1.590 | 1.800 |
| **Weight (Kg)** | 68.9 | 10.2 | 51.2 | 90.0 |
| **BMI (Kg/m2)** | 24.14 | 3.01 | 18.57 | 29.50 |

in fed conditions is presented in (Figure 1). The Geometric mean ratios, 90% CI, power and intra-subject coefficient of variation of test and references for Ln transformed pharmacokinetic parameters $C_{max}$ and $AUC_{0-72}$ for Perampanel are presented in (Figure 2) Table 2.

## SAFETY

### Brief Summary of Adverse Events:

Safety was evaluated throughout the study and there were three adverse events experienced by 02 subjects; two adverse events with reference product and one adverse event following administration of test product. No serious adverse events were reported in this study. Thus, both the test and reference products were well tolerated.

List of adverse events with relation to the drug product – Reference and test are given in the Table 3 and Table 4, respectively.

## DISCUSSION

This study was conducted to obtain a marketing approval for a generic drug which is used to treat seizures. This generic drug will be marketed as a low cost alternate to the innovator product with the same efficacy and tolerability. This cost reduction would help the patients who need the treatment with this drug and cannot afford treatment with innovator product.

28 subjects in the age group of 22 to 44 years, who met the study eligibility criteria, participated in the study and 25 subjects completed the study. The clinical study was conducted over a period of 45 days. Blood sampling was done at pre-defined intervals up to 72.00 hours in both periods, separated by a washout period of 42 days between each period. The plasma concentrations of Perampanel were measured for 25 subjects.

The pharmacokinetic analysis of Perampanel was performed using the concentration data obtained from 25 subjects. The statistical analysis of Perampanel was performed using the concentration data obtained from 23 subjects, excluding subjects S12 and S24 who had pre-dose concentration of more than 5% of $C_{max}$ in period II. The results of the pharmacokinetic analysis of Perampanel with the test product were comparable to the reference product.

90% CI of $C_{max}$ and $AUC_{0-72}$ were 90.23% - 107.9% and 92.02% - 104.12% for Perampanel, which were within the acceptable limit of 80.00 % to 125.00 %.

## CONCLUSION

According to FDA's guidelines for Bioequivalence research, the confidence intervals for $C_{max}$ and $AUC_{0-72}$ ranged between 80.00-125.00%. The above limits obtained for Perampanel were within the accepted bio-equivalence limits. Thus, bio-equivalence was demonstrated between Perampanel 12mg Tablets of Abbott Laboratories de Colombia and Fycompa® (Perampanel 12mg) tablets of Eisai Europe Limited in healthy, adult, human subjects under fed conditions.

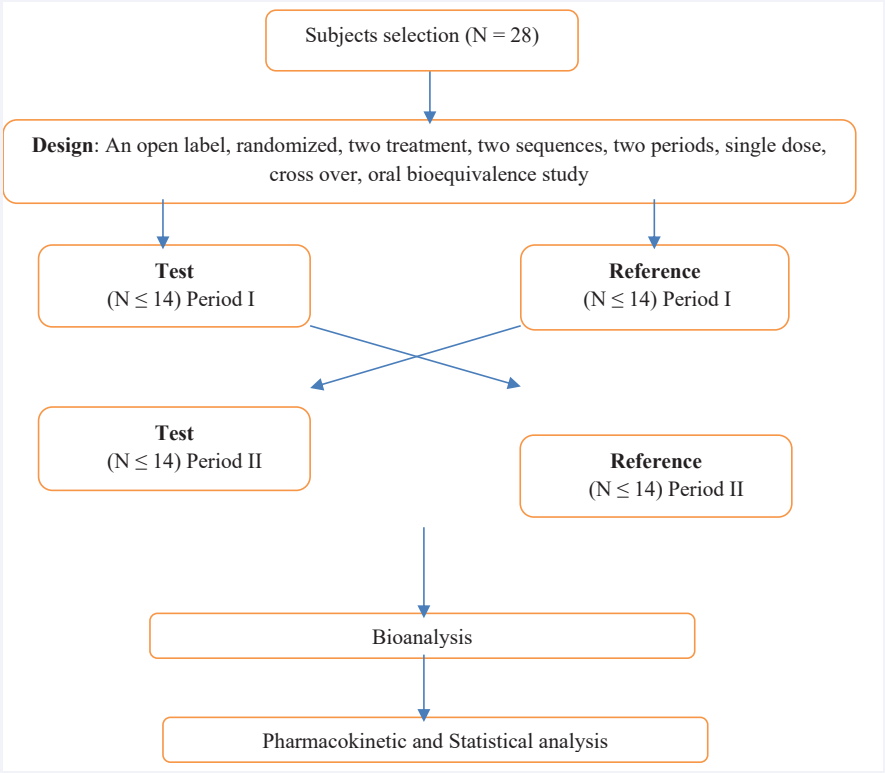


**Figure 1** Study design.

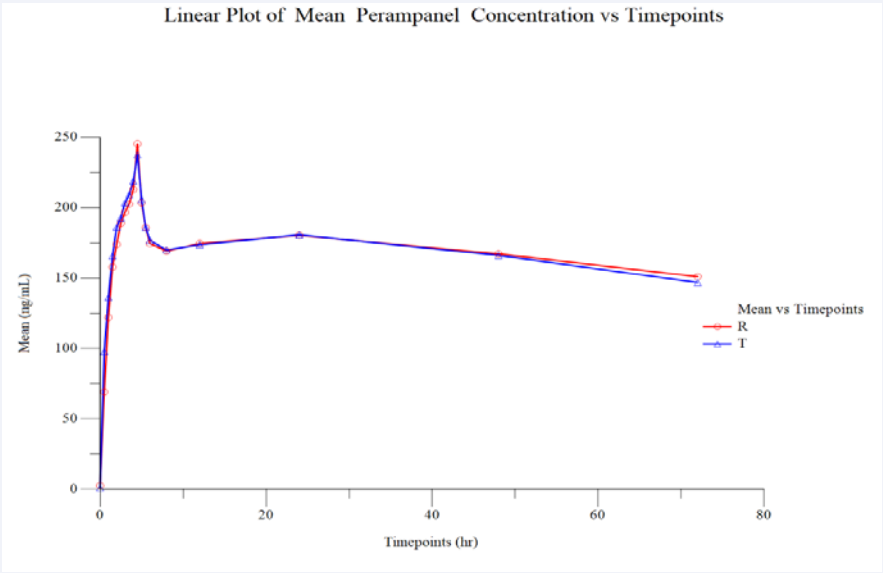


**Figure 2** Bioavailability curve (Mean plasma concentration vs. Time) of test and reference.

**Table 2:** The Geometric mean ratios, 90% CIs, power and intra subject coefficient of variation of test and reference for Ln transformed pharmacokinetic parameters $C_{max}$ and $AUC_{0-72}$ for Perampanel 12mg are presented below.

| Parameters | Antilog Least Square Mean | | T/R Ratio (%) | 90% Confidence Interval (%) | Intra subject CV (%) | Power (%) |
|---|---|---|---|---|---|---|
| | Test Product (T) | Reference Product (R) | | | | |
| Ln ($C_{max}$) | 257.7471 | 261.2224 | 98.67 | 90.23% - 107.9% | 17.75 | 99.11 |
| Ln ($AUC_{0-72}$) | 11475.856 | 11724.266 | 97.88 | 92.02% - 104.12% | 11.87 | 99.99 |

**Table 3:** List of adverse events with relation to the Drug product – Reference

| Subject | Preferred Terminology PT) | Number of events | Intensity | Relationship to the drug product |
|---|---|---|---|---|
| S24 | Arthralgia | 01 | Moderate | Probable |
| S25 | Headache | 01 | Moderate | Probable |

**Table 4:** List of adverse events with relation to the Drug product – Test

| Subject | Preferred Terminology (PT) | Number of events | Intensity | Relationship to the drug product |
|---|---|---|---|---|
| S24 | Arthralgia | 01 | Moderate | Probable |

As the product is bioequivalent to the reference product, the sponsor could get marketing authorization for the test product, which in turn reduces the cost of the products in the market.

## CONFLICT OF INTEREST DISCLOSURE

This scientific article was made with funding from Abbott Laboratories of Colombia, whose participation was related to financial support and document review. All technical, clinical and analytical execution of the bioequivalence studies were performed independently by Azidus Laboratories LTD.

## REFERENCES

1. Hanada T, Hashizume Y, Tokuhara N, Takenaka O, Kohmura N, Ogasawara A, et al. Perampanel: a novel, orally active, noncompetitive AMPA-receptor antagonist that reduces seizure activity in rodent models of epilepsy. Epilepsia. 2011; 52: 1331-40.
2. Usui N, Akamatsu N, Nakasato N, Ohnishi A, Kaneko S, Hiramatsu H, et al. Long-term tolerability, safety and efficacy of adjunctive perampanel in the open-label, dose-ascending Study 231 and extension Study 233 in Japanese patients with epilepsy. Seizure. 2018; 62: 26-32.
3. Yerino GA, Feleder EC, Otero AM, Diaz L, Sakson M. Comparative Bioavailability of Two Oral Perampanel Formulations in Healthy Subjects: A Randomized, Open Label, Single-Dose, 2-Way Crossover Study. J Bioequiv Availab. 2017; 9: 501-8.
4. Gidal BE, Majid O, Ferry J, Hussein Z, Yang H, Zhu J, et al. The practical impact of altered dosing on perampanel plasma concentrations: pharmacokinetic modeling from clinical studies. Epilepsy Behav. 2014; 35: 6-12.
5. Food US. Drug Administration Center for Drug Evaluation and Research: Clinical Pharmacology and Biopharmaceutics review(S); 202834Orig1s000. 2012.
6. Food US. Drug Administration Center for Drug Evaluation and Research: Product-Specific Guidances for Generic Drug Development.
7. https://www.medicines.org.uk/emc/product/4276/smpc
8. Perry R. Perspectives on the bioequivalence and therapeutic equivalence of generic formulations: An overview of the landscape. Clin Ther. 2010; 32: 1796-7.
9. World Medical Association. Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 59th WMA General Assembly, Seoul, and October 2008.

10. Singh J. International conference on harmonization of technical requirements for registration of pharmaceuticals for human use. J Pharmacol Pharmacother. 2015; 6: 185-7.

11. Food US. Drug Administration Center for Drug Evaluation and Research: Guidance for industry: statistical approaches to establishing bioequivalence. Washington, DC: US Department of Health and Human Services. Food and Drug Administration Center for Drug Evaluation and Research. 2001.