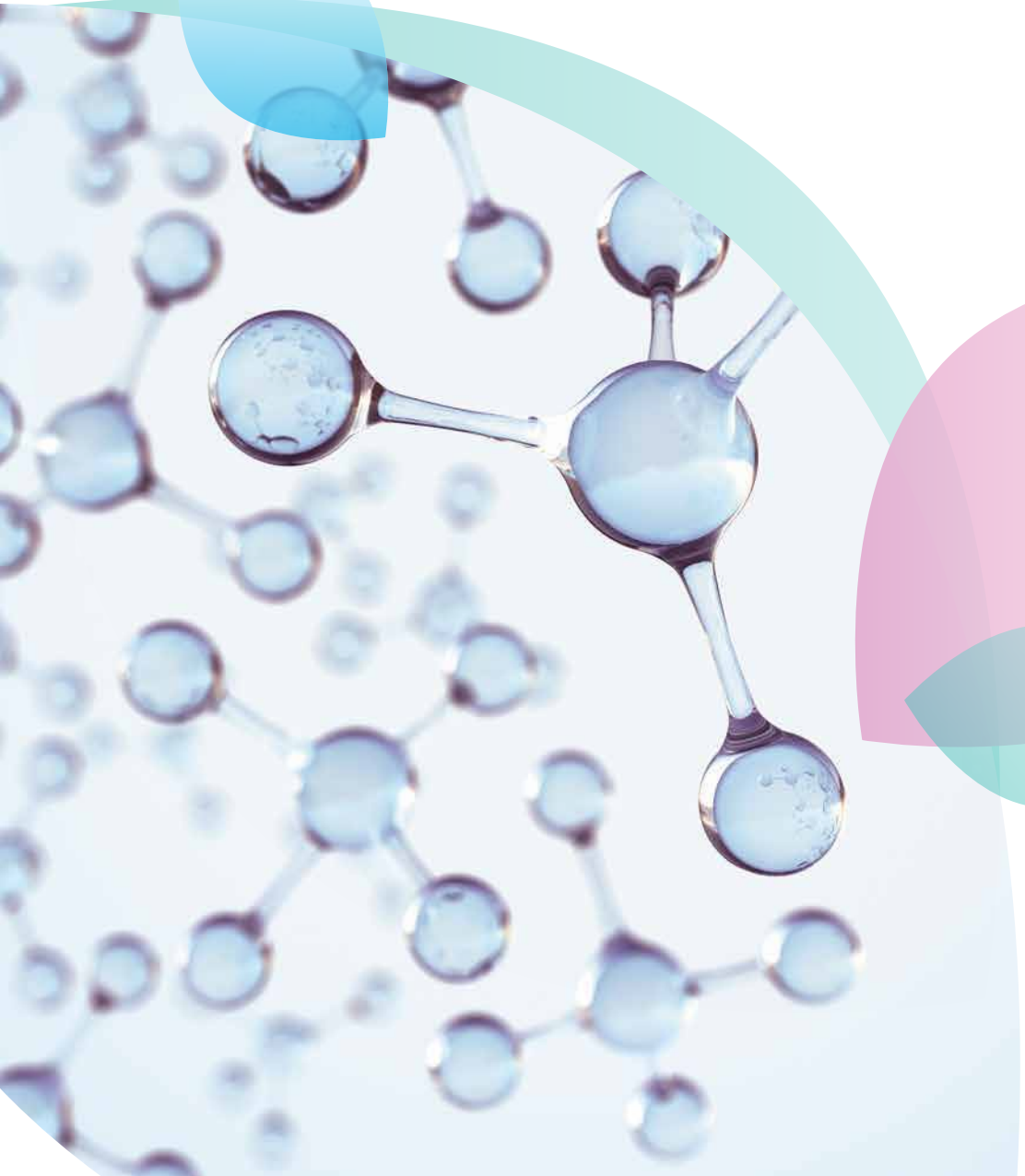
Catira

Dimetilfumarato 120 y 240 mg

Bioequivalence Study Report
Dimethyl Fumarate
240 mg Modified

Release Capsules Under Fed Conditions



Synthon-Bagó

Clinical report

Accutest Study Code: ARL/14/069
Synthon Study Code: CT.DFT.
mrc240.14.002

A Randomized, Two Treatment, Two Period, Two Sequence, Single Dose, Crossover, Bioequivalence Study comparing Dimethyl Fumarate 240 mg modified release capsules to Reference product of Dimethyl Fumarate 240 mg gastro-resistant hard capsules in Healthy, Adult, Male and Female Volunteers under Fed Conditions.

Sponsor: Synthon BV. Microweg 226545 CM Nijmegen. The Netherlands

Study Center: Accutest Research Laboratories (I) Pvt. Ltd., A-31, M.I.D.C, TTC Industrial Area, Khairane

Study Design:

A randomized, two treatment, two period, two sequence, single dose, crossover design.

Primary Objective To assess the bioequivalence between test product versus reference product Methodology A total of eighty (80) healthy, adult, male and female subjects were enrolled in the study. The subjects were confined within the facility from at least 11 hours before dosing until 12.00 hours post-dose in each study period. After an overnight fast of at least 10 hours all subjects were given a high-fat and high-calorie breakfast, 30 minutes prior to drug administration.

All subjects had to finish the breakfast within 30 minutes. 30 minutes after start of the breakfast, all subjects were administered the study drug [a single oral dose of test product or reference product according to the randomization schedule] in sitting position, with 200 ± 2 mL of water at ambient temperature, in each study period. A total of 21 blood samples (6 mL each) were collected from the subjects in pre-cooled NaF/Potassium Oxalate vacutainers during each study period at pre-dose (collected within 1 hr prior to dosing), 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 9.00, 10.00, 11.00 and 12.00 hours post-dose. All activities related to handling of investigational products, dosing, blood sample collection, sample handling, processing and sample analysis were carried out under sodium vapour lamp. Analysis of plasma concentrations of monomethyl fumarate was done by a validated LC-MS/MS analytical method. Statistical comparison of Cmax, AUCo_t and AUCo_irif of the test and reference formulation was performed to assess the bioequivalence of monomethyl fumarate.

Number of Subjects

(planned and analysed):

A total of one hundred and twenty eight (128) subjects were screened in order to enroll eighty (80) subjects for the study.

Subject no. 06 was withdrawn from the study due to adverse event after dosing in period I, subject no. 58 was dropped out from Period II as the subject did not report to study center and subject no. 75 was withdrawn from the study due to adverse event in wash out of period I.

A total of seventy seven (77) subjects completed the clinical phase of the study successfully and received test and reference products. The plasma samples of seventy nine (79) subjects (excluding subject no. 58 but including subject no. 06 and 75) were included in sample analysis. As per section 6.3 of protocol, 'Samples to be analysed' Plasma samples from dropouts due to an adverse event were analysed and evaluated for safety reasons, but not included in the statistical evaluation of bioequivalence. Hence subject nos. 06 and 75 were analysed for safety reasons. A total of seventy seven (77) subjects were considered for pharmacokinetic analysis.

Diagnosis and main criteria for inclusion:

It was decided to include, healthy, nonsmoking adult, male and non pregnant female subjects aged between 18 to 45 years (inclusive) with a body mass index (BMI) in a range of 18.5 kg/m2 to 30 kg/m2, who provided his/her written informed consent and who were willing to follow the protocol requirements. The subjects were enrolled in the study when the following inclusion screening test were determined and accepted by the Principal Investigator: breath alcohol test, demographic examination, BMI, clinical history, physical examination (including vital signs assessment), 12-lead ECG, clinical laboratory tests [haemogram, biochemistry, infectious disease screening (HIV, Hepatitis B and Hepatitis C), urinalysis and urine screen for drug abuse], female subjects were tested for pregnancy by Serum Beta (B)-hCG and when they met the inclusion criteria and none of the exclusion criteria. All the subjects who were enrolled in the study were healthy male and non pregnant female subjects within age range of 19 to 40 years and within the BMI range of 18.69 kg/m2 to 29.67 kg/m2.

Criteria for evaluation:

Bioequivalence:

Assessment of bioequivalence was done by comparing pharmacokinetic parameters of the Test Product (A): Dimethyl fumarate 240 mg modified release capsules (manufacturer: Rider Synthon Ltda, Chile) with the Reference Product (B): Reference product of Dimethyl Fumarate 240 mg gastroresistant hard capsules (MAH: Biogen Idec Ltd., United Kingdom) Bioequivalence was concluded if the 90% confidence intervals of the ratio of Least square mean (test/reference) of Cmax, AUCO-t and AUCo-mrare within the acceptance range of 80.00 ¬ 125.00% for Monomethyl fumarate.

Safety:

Safety measurements included monitoring of adverse events, physical examination

Assessment, well being assessment, vital signs assessment, 12-lead ECG and clinical laboratory tests.

Statistical methods:

For the primairy endpoints: ANOVA was performed on Ln-transformed pharmacokinetic parameters C., AUCo_t and AUCo_inf for Monomethyl fumarate. Median difference of Tmax between the Investigational products was analyzed by nonparametric Wilcoxon test.

The 90% confidence interval was constructed for the ratio of geometric least square mean of the test and reference product, obtained from the Ln-transformed pharmacokinetic parameters Cmax, AUC04 and AUCo-inf. All pharmacokinetics and statistical analysis have been performed by the use of SAS® 9.2.

Summary – Conclusion

Bioequivalence Results:

All plasma concentrations of subject no. 35 in period II were below the quantification (BLQ). As there were no significant clinical observations, data 35 were considered for pharmacokinetic and statistical analysis. Hence, data were considered for pharmacokinetic and statistical analysis. However, analysis was also performed excluding subject no. 35 for information purpose.

The 90 % confidence intervals of Ln-transformed parameters for Monomethyl fumarate are summarized below:

Safety results:

A total of eight (08) adverse events were reported during the clinical phase of the study, of which four (04) adverse event were probably related to the study drug, three (03) adverse events were unrelated and one (01) adverse event was possibly related to the drug. All the adverse events were mild to moderate in severity and were resolved.

No serious adverse events were observed during the study periods.

Conclusion:

Bioequivalence between Test Product: Dimethyl fumarate 240 mg modified release capsules (manufacturer: Rider Synthon Ltda, Chile) and reference Product: Tecfidera® 240 mg gastroresistant hard capsules (MAH: Biogen Idec. Ltd. , United Kingdom) was demonstrated in this study.

Least square mean (test/reference) of Cmax, AUCO-t and AUCo-mrare within the acceptance range of 80.00 ¬ 125.00% for Monomethyl fumarate.

Safety:

Safety measurements included monitoring of adverse events, physical examination

Assessment, well being assessment, vital signs assessment, 12-lead ECG and clinical laboratory tests.

Statistical methods:

For the primairy endpoints: ANOVA was performed on Ln-transformed pharmacokinetic parameters C., AUCo_t and AUCo_inf for Monomethyl fumarate. Median difference of Tmax between the Investigational products was analyzed by nonparametric Wilcoxon test.

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Table of Geometric Means and 90% Confidence Interval for Monomethyl fumarate
Test Product (A) Versus vs. Reference Product (B) (N=77)
All evaluable subjects included

Parameters	*Geometric mean		%T/R Ratio	90 % Confidence Interval for Ln-transformed data	
	Test	Reference		Lower Limit	Upper Limit
AUComiF	4029.49	3915.04	102.9234	97.9895	108.1057
AUCo-t	3860.69	3604.93	107.0947	102.1830	112.2424
Cmax	1898.86	1715.08	110.7153	101.4719	120.8007

*Geometric mean was taken as the antilog (exponential) of the Least square mean of the ln-transformed data.

Table of Geometric Means and 90% Confidence Interval for Monomethyl fumarate
Test Product (A) Versus vs. Reference Product (B) (N=76)
Excluding Subject no: 35

Parameters	*Geometric mean		%T/R Ratio	90 % Confidence Interval for Ln-transformed data	
	Test	Reference		Lower Limit	Upper Limit
AUComiF	4033.89	3922.87	102.8300	97.8870	108.0225
AUCo-t	3862.74	3607.95	107.0619	102.1399	112.2210
Cmax	1902.19	1722.50	110.4321	101.1880	120.5206

*Geometric mean was taken as the antilog (exponential) of the Least square mean of the ln-transformed data.

Catira

Dimetilfumarato 120 y 240 mg

- Dimetilfumarato baja el riesgo de recaída a la mitad. [1]
- Dimetilfumarato disminuye el riesgo de discapacidad en un 38%. [1]
- Más del doble de pacientes libres de lesiones comparado con placebo a dos años. [2]

PRESENTACIÓN:
Catira 120 mg, envases conteniendo 14 cápsulas.
Catira 240 mg, envases conteniendo 60 cápsulas.

1. Placebo-Controlled Phase 3 Study of Oral BG-12 for Relapsing Sclerosis Ralf Gold, M.D., Ludwig Kappos, M.D., Douglas L. Arnold, M.D., Amit Bar-Ot, M.D., Gavin Giovannoni, M.D., Krzysztof Selmaj, M.D., Carlo Tornatore, M.D., Marianne T. Sweetser, M.D., Ph.D., Minhua Yang, M.S., Sarah I. Sheikh, M.D., and Katherine T. Dawson, M.D., for the DEFINE Study Investigators
N Engl J Med 2012; 367:1098-1107September 20, 2012DOI: 10.1056/NEJMoa1114287

2. Placebo-Controlled Phase 3 Study of Oral BG-12 or Glatiramer in Multiple Sclerosis Robert J. Fox, M.D., David H. Miller, M.D., J. Theodore Phillips, M.D., Ph.D., Michael Hutchinson, F.R.C.P., Eva Havrdrova, M.D., Mariko Kita, M.D., Minhua Yang, M.S., Kartik Raghupathi, M.S., Mark Novas, M.D, Marianne T. Sweetser, M.D., Ph.D., Vissia Viglirtta, M.D., Ph.D., and Katherine T. Dawson, M.D., for the CONFIRM Study Investigators.
N Engl J Med 2012; 367:1087-1097 September 20, 2012DOI: 10.1056/NEJMoa1206328

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