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ORIGINAL RESEARCH

Bioequivalence Study of Two Tablet Formulations of Clonazepam 2 mg: A Randomized, Open-Label, Crossover Study in Healthy Mexican Volunteers Under Fasting Conditions

Luis Genis-Najera · Maria Elena Sañudo-Maury

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ABSTRACT

Introduction: The prevalence of neurological disorders is high among the Mexican population. Clonazepam is primarily indicated to treat panic disorders, certain kinds of epilepsy such as status epilepticus, childhood motor seizures (petit mal absence, Lennox–Gastaut syndrome, and infantile spasms), anxiety, and muscle spasm. This study was performed to compare bioequivalence between two oral tablet formulations of clonazepam 2 mg in healthy Mexican volunteers under fasting conditions.

Methods: This phase I, randomized, open-label, two-treatment, crossover study included 30 healthy volunteers. Subjects were randomly assigned to either test or reference formulation of clonazepam 2 mg. Each study period was separated by 21-day washout period. Blood samples were collected at pre-dose and up to 72 h after drug administration. Clonazepam concentrations were determined using a validated ultra-flow liquid chromatography–tandem mass spectrometric method. Pharmacokinetic parameters were determined using a non-compartmental method. Two formulations were considered bioequivalent if geometric mean ratios (test/reference) were between 80% and 125%. Safety was evaluated by recording adverse events.

Results: Pharmacokinetic parameters were comparable between test and reference formulations. The mean maximum plasma concentration (C_{max}) was ≈ 13 ng/mL, area under the plasma concentration–time curve from time 0 to last measurable concentration (AUC_{0-t}) was ≈ 360 ng h/mL, time to reach maximum plasma concentration (T_{max}) was ≈ 3 h, and elimination half-life ($t_{1/2}$) was ≈ 43 h. Geometric mean ratios (90% confidence interval) of C_{max} (99.2–115.3%), AUC_{0-t} (100.6–110.6%), and $AUC_{0-\infty}$ (98.5–111.6%) were within the bioequivalence range. Seven non-serious adverse events (mostly asymptomatic hypotension) were recorded.

Conclusion: The test and reference formulations of clonazepam 2 mg were bioequivalent and well tolerated in healthy Mexican volunteers under fasting conditions.

Protocol Authorization Number: 213301410 B0051 (Approved on April 13, 2021).

Keywords: Clonazepam; Crossover study; Epilepsy; Fasting; Pharmacokinetics; Safety

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L. Genis-Najera (✉)
Industrial Affairs Division, Sanofi, Acueducto del Alto Lerma No. 2, Zona Industrial de Ocoyoacac, Ocoyoacac, Edo CP 52740, Mexico City, De México, Mexico
e-mail: Luis.Genis@sanofi.com

M. E. Sañudo-Maury
Medical Division, Sanofi, Mexico City, Mexico

Key Summary Points

Why carry out this study?

In Mexico, the prevalence of neurological disorders including epilepsy and anxiety disorders is high.

Clonazepam is a US FDA-approved drug for the treatment of seizure and panic disorders.

Bringing in a bioequivalent or a generic formulation of clonazepam with an equivalent safety and tolerability profile will increase its accessibility among the Mexican population.

What was learned from the study?

This is one of the few studies demonstrating the bioequivalence of two oral tablet formulations (test and reference) of clonazepam 2 mg in healthy Mexican volunteers under fasting conditions.

The pharmacokinetic analyses revealed a similar rate and extent of absorption of clonazepam between the two formulations.

The test formulation showed a safety and tolerability profile consistent with the reference formulation.

INTRODUCTION

Epilepsy is a neurological disorder affecting 50 million people worldwide [1]. In Mexico, the prevalence of epilepsy is estimated between 1 and 2 million people [2]. The Mexican National Comorbidity Survey reported a high lifetime prevalence of psychiatric disorders in the Mexican population, the most common being anxiety (14.3%) and mood disorders (9.2%) [3]. About 35.8% of Mexican adolescents suffered from depression or generalized anxiety disorder [4]. Clonazepam is a high-potency and long-acting benzodiazepine; it has gamma-aminobutyric acid A receptor agonist and serotonergic (by increasing serotonin synthesis) activities [5]. Clonazepam is approved by the US Food and Drug Administration (FDA) for the treatment of seizure and panic disorders [6] and is marketed in the USA and Mexico. It is used in the treatment of status epilepticus [7] and childhood motor seizures such as petit mal absence, Lennox–Gastaut syndrome, and infantile spasms [5]. Clonazepam is also prescribed for the treatment of panic disorder in patients with or without agoraphobia [8]. The pharmacological properties of clonazepam include antimanic, sedative, muscle relaxant, and anxiolytic effects, which are common in benzodiazepines [9, 10].

The absorption of clonazepam after oral administration is rapid with bioavailability in excess of 80% [11]. The maximum plasma concentration (C_{max}) of clonazepam is reached within 1–4 h; the plasma protein binding is high ($\approx$ 85%) [5]. It is extensively metabolized by hepatic cytochrome P450, particularly by CYP3A [5]. The major metabolites are 7-aminoclonazepam and 7-acetamidoclonazepam [12]. The elimination half-life ($t_{1/2}$) is about 30–40 h [5]. The distribution half-life is $\approx$ 0.5–1 h. There is a linear relationship between the dose and plasma concentration of clonazepam [13].

Although the pharmacokinetic profile of clonazepam had previously been studied [6, 11, 14–17], no data are available for pharmacological equivalence between different formulations of clonazepam in the Mexican population. Moreover, bringing in a bioequivalent or a generic formulation of clonazepam will increase the accessibility of this drug with an equivalent safety and tolerability profile. Therefore, this phase I trial was undertaken to demonstrate the bioequivalence between two oral tablet formulations of clonazepam 2 mg (test and reference) in healthy Mexican volunteers under fasting conditions.

METHODS

Study Design

This was a phase I, randomized, prospective, open-label, single-dose, two-treatment (test and reference), crossover study of clonazepam 2 mg tablet. The study was conducted at the Desarrollos Biomédicos y Biotecnológicos de México S.A. de C.V. (DEBBIOM) research center in healthy Mexican volunteers under fasting conditions. Subjects were randomly assigned (1:1) to either test or reference formulation. Each study period was separated by a 21-day washout period to eliminate carryover effects from the previous period (Fig. 1).

Ethical Considerations

This study was performed in compliance with the principles of the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice, the Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS – Federal Committee for Protection from Sanitary Risks) regulatory requirements, the Mexican guidance NOM 177-SSA1-2013 that establishes the requirements for bioequivalence studies, and the Mexican Regulation of the General Health Law Regarding Health Research. The study protocol (213301410B0051) was approved by the Research Ethics Committee of DEBBIOM (April 13, 2021). An informed consent form was signed by all volunteers before their participation in this study.

Study Participants

Healthy volunteers (both male and female) aged 18–55 years and with body mass index (BMI) between 18.0 and 27.0 kg/m^2 were included. The investigator performed a clinical examination to check for any abnormality. Volunteers were excluded due to hypersensitivity to clonazepam; sleep apnea; history of severe respiratory or hepatic impairment and cardiovascular, renal, metabolic or gastrointestinal, or neurological diseases; history of alcoholism and/or drug of abuse (urine test); being tested positive for the coronavirus (SARS-CoV-2) infection; pregnancy; and breastfeeding. The use of investigational drug within 3 months or any drug or consumption of alcohol or tobacco 24 h prior to the study was prohibited.

Study Drugs

The test formulation used was clonazepam 2 mg tablet manufactured by Sanofi Aventis, S.A. de C.V., Mexico. The reference formulation was clonazepam 2 mg tablet manufactured by Roche, S.A. de C.V., Mexico.

Study Conduct and Procedures

All subjects were admitted to the study center 1 day prior to the study drug administration;

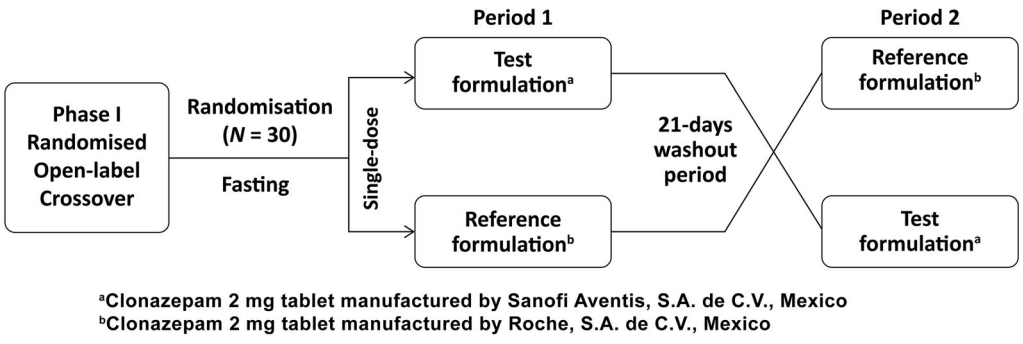

Fig. 1 Study design: Randomization of test and reference formulations of clonazepam 2 mg tablet in healthy Mexican volunteers

they underwent screening and physical examination to confirm their eligibility. Subjects remained fasted (without food and water) overnight for a minimum of 10 h before administering the drug. A single-dose of study drugs was administered along with 250 mL of non-carbonated water. After the drug administration, they were provided with a standard diet of breakfast, lunch, and dinner. The breakfast was given 4 h after the drug administration, and consisted of one cup of rice cereal, one banana, one apple, and one glass of milk (250 mL). The subjects were under medical supervision throughout the study period. In each study period, 22 blood samples were collected (≈ 6 mL each) into a heparinized vacuum tube at pre-specified sampling time: pre-dose (before drug administration, 0 h) and at 0.50, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 48.00, and 72.00 h after drug administration. Vital signs were measured at the time of admission and at pre-defined time points. The blood samples were centrifugated at 3500 rpm for 10 min at room temperature to obtain plasma samples and stored in a deep freezer at − 70 °C ± 20 °C until analysis.

Sample Extraction and Analysis

Clonazepam was extracted from human plasma (400 µL aliquot) using liquid–liquid extraction with an ethyl acetate solvent and voriconazole as internal standard.

The chromatographic separation was obtained on a Zorbax Eclipse Plus C18 Rapid Resolution HT column (4.6 × 50 mm, 1.8 µm). Mobile phase consisted of acetonitrile/ammonium acetate 5 mM pH 4 (80:20, v/v); flow rate was 0.500 mL/min. The autosampler and column temperatures were maintained at 8 °C and 40 °C, respectively. The compounds were detected in positive electrospray ionization; multiple reaction monitor transitions for clonazepam and voriconazole were *m*/*z* 316.0–270.1 and *m*/*z* 350.1–127.1, respectively. The method was linear over the concentration range of 0.25–50.00 ng/mL for clonazepam. Analytical data were processed using the Analyst IntelliQuan® software. The within-run coefficient of variation (CV) for precision and accuracy for all quality control samples was less than 11%. The between-run CV for precision and accuracy was 14.66% for the lower limit of quantitation (LLOQ), and 10.37%, 10.96% and 9.58% for nominal concentrations of low- (LQC), middle- (MQC) and high- (HQC) quality control samples, respectively (Supplementary Table S1).

The clonazepam concentration was determined using an ultra-flow liquid chromatography–tandem mass spectrometry method. The bioanalytical method was validated as per local regulatory guidance defined in NOM-177-SSA1-2013. The acceptance and rejection of the analytical run, and reanalysis criteria were in accordance with NOM-177-SSA1-2013. The reliability of clonazepam concentrations obtained from the study samples was verified by

Table 1 Pooled analysis of intra-subject CV for C_{max} and AUC_{0-t} from bioequivalence studies of clonazepam 2 mg under fasting conditions

Study	*N*	C_{max} (Intra-subject CV)	AUC_{0-t} (Intra-subject CV)
González et al. (2007) [17]	26	0.22	0.17
Cavedal et al. (2007) [14]	33	0.22	0.08
Davanço et al. (2019) [11]	31	0.19	0.06
Clonazepam TioFarma (2012) [18]	24	0.17	0.13
Pooled	114	0.19	0.11

AUC_{0-t}= area under the plasma concentration–time curve from time 0 to last measurable concentration, C_{max}= maximum plasma concentration, CV = coefficient of variation

incurred sample reanalysis performed according to the US FDA guidance on bioanalytical method validation.

Safety Assessments

For safety evaluation, adverse events (AEs, by system organ class) and serious AEs were recorded along with their severity related to the study drug. Additionally, clinical laboratory data for hematology, blood chemistry, vital signs (blood pressure, heart rate, respiratory rate, and body temperature), and electrocardiogram was collected for the safety assessment.

Sample Size Calculation

The highest pooled intra-subject CV for C_{max} and area under the plasma concentration versus time curve from time 0 to last measurable concentration ($AUC_{0–t}$) from four clonazepam 2 mg bioequivalence studies are presented in Table 1 [11, 14, 17, 18]. The highest pooled intra-subject CV for C_{max} was 0.19. Considering a 5% true difference between geometric means of formulations, a total of 24 subjects were required to demonstrate the bioequivalence between test and reference formulations with a power of at least 90%. Six additional subjects were included to account for possible AEs or dropouts (mainly for pandemic issues), resulting in a total sample size of 30 healthy volunteers.

Table 2 Baseline characteristics of healthy Mexican volunteers enrolled in the study

Baseline characteristics (mean ± SD)	Total (N = 30)
Sex	
Male (N, %)	20 (66.7)
Female (N, %)	10 (33.3)
Age (years)	29.80 ± 8.97
Body weight (kg)	63.87 ± 10.94
BMI (kg/m^2)	23.06 ± 2.44
Height (m)	1.66 ± 0.09
Systolic blood pressure (mmHg)	109.20 ± 11.93
Diastolic blood pressure (mmHg)	66.60 ± 6.33
Heart rate (beats per minute)	81.33 ± 8.08
Respiratory rate (breaths per minute)	17.43 ± 0.77
Body temperature (°C)	36.80 ± 0.08

BMI = body mass index, SD = standard deviation

Pharmacokinetic and Statistical Analyses

The parameters for pharmacokinetic evaluation included C_{max}, area under the plasma concentration versus time curve (AUC) from time 0 to last measurable concentration at 72 h ($AUC_{0–t}$) and from time 0 to infinity ($AUC_{0–\infty}$), time to reach maximum plasma concentration (T_{max}), and $t_{1/2}$. These parameters were derived from plasma concentration–time curves using a non-compartmental method with a log-linear terminal phase assumption and summarized using descriptive statistics, namely, arithmetic and geometric means, standard deviation (SD), and CVs. The Schuirmann "double unilateral" t-hypothesis test was used for C_{max} and $AUC_{0–t}$, with $P < 0.05$. C_{max} and T_{max} were directly obtained from the concentration–time curves. $AUC_{0–t}$ was calculated using the linear trapezoidal method, and $AUC_{0–\infty}$ was calculated as the sum of $AUC_{0–t}$ and ratio of the last observed plasma concentration (C_{last}) to the terminal rate constant (λ_z) (i.e., $AUC_{0–t} + C_{last}/\lambda\_z$). Any concentration below LLOQ was set to 0 for pharmacokinetic and statistical analyses.

The analysis of variance (ANOVA), which included sequence, subjects nested within sequence, period, formulation, and residual, was carried out for log (ln)-transformed C_{max}, $AUC_{0–t}$, and $AUC_{0–\infty}$. The 90% confidence intervals (CIs) of the geometric mean ratios (GMRs) of test/reference formulation of these parameters were determined using ln-transformed data. Test and reference formulations were bioequivalent if the 90% CIs of these parameters were within the acceptable bioequivalence range of 80–125%. The Phoenix 64^{TM} WinNonlin® 8.1 software was used to

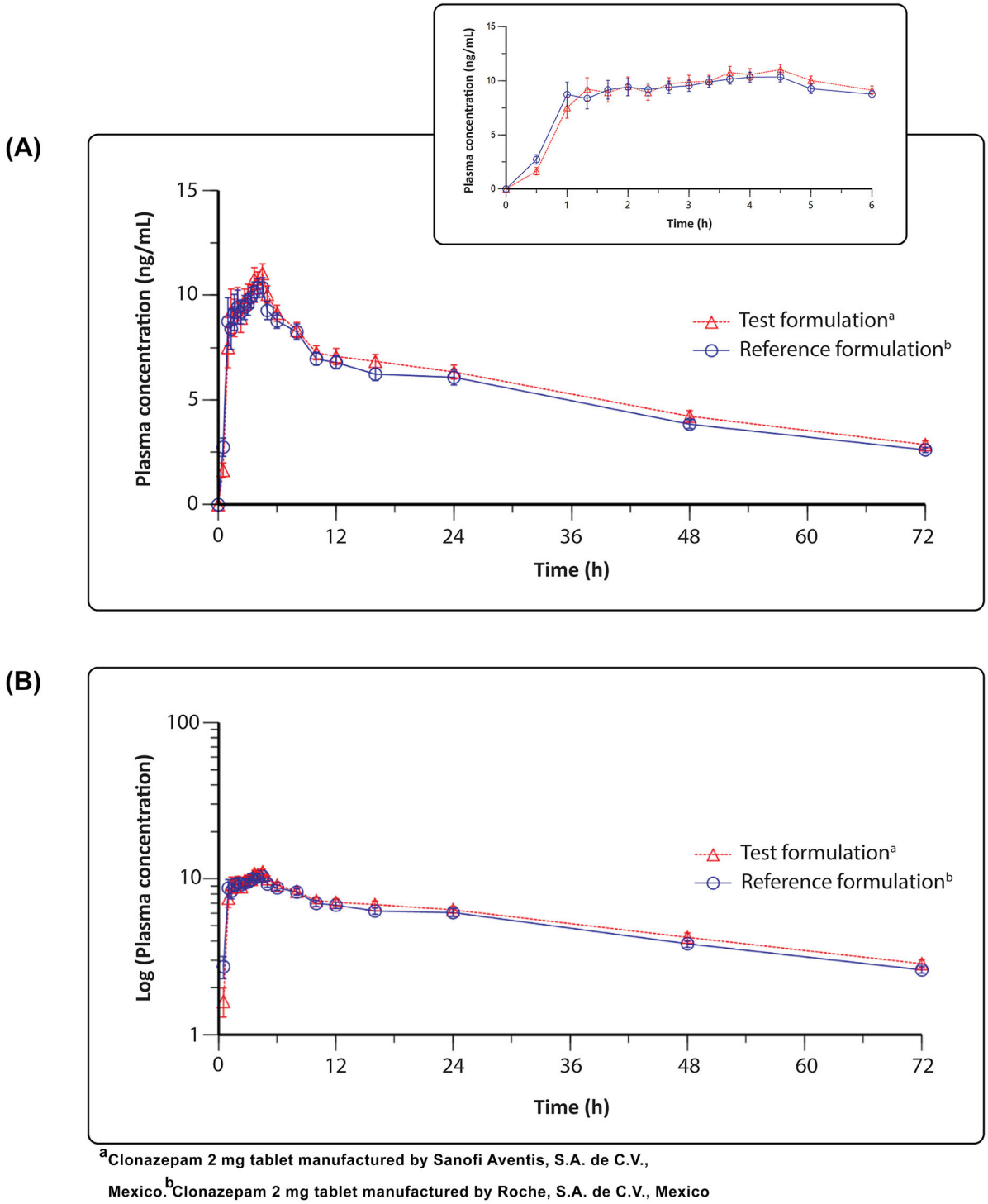

Fig. 2 **A** Mean plasma concentration of clonazepam versus time profiles for test and reference formulations of clonazepam 2 mg tablet. **B** log-transformed mean plasma concentration of clonazepam versus time for each formulation. The inset shows 0–6 h on an expanded time scale

Table 3 Pharmacokinetic parameters after a single-dose of test and reference formulations of clonazepam 2 mg tablet

Pharmacokinetic parameters*	Test formulation[a]	Reference formulation[b]
C_{max} (ng/mL)		
Arithmetic mean	13.93	13.23
Geometric mean	13.40	12.57
SD	3.99	4.65
CV (%)	29	35
AUC_{0-t} (ng h/mL)		
Arithmetic mean	387.58	364.77
Geometric mean	374.33	355.37
SD	105.91	85.02
CV (%)	27	23
$AUC_{0-\infty}$ (ng h/mL)		
Arithmetic mean	572.40	540.88
Geometric mean	548.04	523.86
SD	178.88	138.79
CV (%)	31	26
T_{max} (h)		
Arithmetic mean	2.94	3.33
Geometric mean	2.55	2.90
SD	1.43	1.60
CV (%)	49	48
$t_{1/2}$ (h)		
Arithmetic mean	43.49	44.16
Geometric mean	42.85	43.09
SD	7.61	10.18
CV (%)	18	23

AUC_{0-t} = area under the plasma concentration–time curve from time 0 to last measurable concentration (72 h), $AUC_{0-\infty}$ = area under the plasma concentration–time curve from time 0 to infinity, C_{max} = maximum plasma concentration, CV = coefficient of variation, SD = standard deviation, T_{max} = time to reach maximum plasma concentration, $t_{1/2}$ = half-life

*29 subjects were included in the pharmacokinetic analysis

[a]Clonazepam 2 mg tablet manufactured by Sanofi Aventis, S.A. de C.V., Mexico

[b]Clonazepam 2 mg tablet manufactured by Roche, S.A. de C.V., Mexico

Table 4 Bioequivalence analysis (90% CIs) of clonazepam 2 mg test and reference formulations

Parameter	GMR test[a]/reference[b] (%)	90% CI		Intra-subject, CV (%)	Power
		Lower	Upper		
ln C_{max}	106.9	99.2	115.3	16.90	0.9988
ln AUC_{0-t}	105.5	100.6	110.6	10.67	1.0000
ln $AUC_{0-\infty}$	104.9	98.5	111.6	14.00	0.9999

The GMR and 90% CI for AUC_{0-t} and $AUC_{0-\infty}$ parameters were calculated using LOQ = 0, but the original data submitted to the Mexican health authorities considered the values below LOQ = "missing". This statistical consideration does not have any impact on the results since the difference is minimal after the point

AUC_{0-t} = area under the plasma concentration–time curve from time 0 to last measurable concentration (72 h), $AUC_{0-\infty}$ = area under the plasma concentration–time curve from time 0 to infinity, CI = confidence interval, C_{max} = maximum plasma concentration, GMR = geometric mean ratio, CV = coefficient of variation, ln = logarithm, LOQ = limit of quantitation

[a]Clonazepam 2 mg tablet manufactured by Sanofi Aventis, S.A. de C.V., Mexico

[b]Clonazepam 2 mg tablet manufactured by Roche, S.A. de C.V., Mexico

perform the pharmacokinetic and statistical analyses.

RESULTS

Subject Disposition and Baseline Characteristics

A total of 30 healthy volunteers, including 20 males and 10 females, were enrolled in the study from November 2021 to December 2021. They were randomized to each of the two treatment sequences of clonazepam 2 mg tablet. Of these, 29 subjects completed the study; 1 subject withdrew for undisclosed personal reasons in the first period. Therefore, 29 subjects were included in the pharmacokinetic analysis, whereas all 30 subjects were included for safety evaluation. The baseline characteristics of study subjects are described in Table 2. The mean age was 29.80 (± 8.97 SD) years; the mean body weight was 63.87 (± 10.94 SD) kg; and the mean BMI was 23.06 (± 2.44 SD) kg/m^2.

Pharmacokinetic Analysis

The mean plasma concentration–time curves of clonazepam from the test and reference formulations under fasting conditions are shown in Fig. 2. Results of the pharmacokinetic analysis after single-dose oral administration of clonazepam 2 mg tablet (test and reference) formulations are summarized in Table 3. No significant differences were found among the pharmacokinetic parameters of clonazepam between test and reference formulations. The mean C_{max} was ≈ 13 ng/mL and AUC_{0-t} was ≈ 360 ng h/mL, measured at 72 h after dosing. The maximum plasma level (T_{max}) was reached within 3 h and eliminated with a half-life ($t_{1/2}$) of about 43 h.

Bioequivalence

The results from ANOVA for ln-transformed pharmacokinetic parameters (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) revealed that there was no significant effect of the variation due to sequence or formulation ($P \geq 0.05$). However, the effect of period was significant for C_{max} ($P = 0.0337$), but neither for AUC_{0-t} nor for $AUC_{0-\infty}$ ($P > 0.05$). The GMRs of test/reference formulations were 106.9%, 105.5%, and 104.9% for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, respectively, and were within the acceptable bioequivalence range (80–125%). The intra-subject variability was less than 20% for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ (Table 4).

Safety

No serious, severe, or unexpected AEs were observed during the study, and no subject discontinued as a result of any AE. In total, seven AEs were recorded among the 30 enrolled healthy volunteers after drug administration. Among this, one case of dizziness (3.3%) was observed in the first period. Six cases of asymptomatic hypotension (20%) were observed in the second period, three of which were related to test formulation and the remaining three were related to reference formulation. In addition to asymptomatic hypotension, one subject also experienced dizziness in the second period. The hypotension appeared 1.5–2.5 h after drug administration and no medication was given to treat the subjects. Furthermore, the study did not reveal any clinically significant abnormalities in the laboratory tests, vital signs, or electrocardiography findings.

DISCUSSION

Comparative pharmacokinetic or bioequivalence studies are essential to demonstrate similarities in the rate and extent of absorption from two formulations of the same drug. To the best of authors' knowledge, this is one of the few studies evaluating the bioequivalence of two oral tablet formulations (test and reference) of clonazepam 2 mg in healthy Mexican volunteers under fasting conditions. There is no report of interaction of food on the absorption of clonazepam [18]. The National Health Service (NHS) in England recommends taking clonazepam tablet formulations with or without food [19]. However, this study was performed under fasting conditions in accordance with the local guidance and as reported in previous studies [6, 11, 14, 17] to demonstrate the interchangeability of the test and reference formulations of clonazepam 2 mg tablet. In bioequivalence studies, use of a truncated AUC method is recommended for drugs with a long elimination half-life, such as clonazepam, and limiting the sample collection period to 72 h is a reasonable approach for its accuracy and sensitivity [20]. Therefore, in this study, a truncated AUC ($AUC_{0–72}$) approach was employed and samples were collected up to 72 h.

The pharmacokinetic analysis revealed a similar pharmacokinetic (C_{max}, $AUC_{0–t}$, $AUC_{0–\infty}$, T_{max}, and $t_{1/2}$) behavior of clonazepam between test and reference formulations. The plasma concentration of clonazepam was similar following a single-dose administration of each formulation in each period. The absorption of clonazepam was fast ($\approx$ 3 h) indicating a rapid onset of action. The 90% CI for the estimate of bioavailability was greater than 98%, suggesting complete absorption of clonazepam (Table 4). Even though clonazepam is prescribed daily in multiple doses [21], the longer $t_{1/2}$ of clonazepam might reduce the frequency of dosing to once or twice daily, which would aid in treatment adherence and compliance [22, 23]. The elimination of clonazepam was slow ($t_{1/2}$ $\approx$ 40 h), indicating longer-acting effects of clonazepam than the short-acting benzodiazepines, such as alprazolam and lorazepam [6], and it provides benefits by reducing the severity of withdrawal syndrome and rebound anxiety [22, 23]. Overall, the results indicate similar absorption, distribution, and elimination profiles for both formulations of clonazepam under fasting conditions. The results of this study are comparable with previous bioequivalence studies of clonazepam 2 mg conducted in healthy volunteers from different geographical regions following a single-dose administration [6, 11, 14].

The Mexican ministry of Health and the US FDA guidance suggest considering ln-transformed pharmacokinetic parameters (C_{max}, $AUC_{0–t}$, or $AUC_{0–\infty}$) to obtain desired confidence interval (80–125%). In this study, the 90% CIs of the ln-transformed GMRs (test/reference) of C_{max}, $AUC_{0–t}$, and $AUC_{0–\infty}$ were within the acceptable bioequivalence range of 80–125%. This indicates that the two formulations were bioequivalent with respect to their rates and extent of absorption. The intra-subject variability for pharmacokinetic parameters was less than 20%, suggesting that clonazepam exhibited lower variability among the Mexican population under fasting conditions. Several

factors are attributable to the intra-subject variability which include (1) physicochemical and PK characteristics of the drug such as its solubility, stability in the gastrointestinal tract, gastric emptying, absorption levels, and first-pass effects; (2) formulation characteristics such as dosage forms, rate of drug release from the dosage form, and mechanisms of drug release control. However, the effects of these combined factors on intra-subject variability have not been elucidated [24]. Since this was a crossover bioequivalence study, each subject received both the test and the reference formulation and thereby served as its own control. Therefore, the impact of intra-subject variability on the PK parameter was reduced. Moreover, to minimize the variability due to sample extraction, processing, or analysis, voriconazole was used as an internal standard to improve the efficiency, precision, and accuracy of the analytical method, and the method validation demonstrated to be appropriate for the intended purpose of the study.

The study predominantly included male volunteers (66.7%); however, no influence of sex (gender) was observed on the pharmacokinetics of clonazepam under fasting conditions. The results of ANOVA demonstrated that there was no significant influence of sequence effect, formulation effect, or period effect on the study outcomes. Interestingly, the effect of period was significant for C_{max} only ($P < 0.05$). Since the two formulations are bioequivalent, access to clonazepam medication may be increased by introduction of the test formulation among the Mexican patients.

During the study, no serious or severe AEs that could lead to study discontinuation were reported. Mild AEs, such as dizziness and hypotension, occurred, and have also been reported earlier [22, 25]; however, no treatment was required. There were no limitations associated with this bioequivalence study.

CONCLUSIONS

The study demonstrated that the test and reference formulations of clonazepam 2 mg tablet were bioequivalent in healthy adult Mexican volunteers under fasting conditions. Both formulations exhibit similar pharmacokinetic behavior with a consistent safety and tolerability profile.

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Author Contributions. Both authors (Luis Genis-Najera and Maria Elena Sañudo-Maury) met the authorship criteria as defined by the International Committee of Medical Journal Editors (ICMJE). They made a substantial contribution to the study design and performed statistical analysis and data interpretation. The authors have full access to the study data and take complete responsibility for data accuracy and integrity. They critically reviewed the manuscript and provided their feedback on each revised draft of the manuscript. The final version of the manuscript was reviewed and approved by the authors for submission to publication.

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Data Availability. The datasets generated and/or analyzed during the current study are available from the corresponding author on

reasonable request. The privacy of clinical trial participants is protected by anonymizing individual patient-level data and redacting study documents. Sanofi has established guidelines and procedures for sharing de-identified data with qualified researchers, which can be found at https://vivli.org/.

Declarations

Conflict of Interest. Luis Genis-Najera and Maria Elena Sañudo-Maury are employees of Sanofi and may own shares and/or stocks in the company. The authors declare no other conflicts of interest relevant to this study.

Ethical Approval. This study was performed in compliance with the principles of the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice, the Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS – Federal Committee for Protection from Sanitary Risks) regulatory requirements, the Mexican guidance NOM 177-SSA1-2013 that establishes the requirements for bioequivalence studies, and the Mexican Regulation of the General Health Law Regarding Health Research. The study protocol (213301410B0051) was approved by the Research Ethics Committee of DEBBIOM (April 13, 2021). An informed consent form was signed by all volunteers before their participation in this study.

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