A comparative bioavailability study of two formulations of pregabalin in healthy Chilean volunteers

Ther Adv Chronic Dis
(2010) 1(4) 141–148
DOI: 10.1177/2040622310379932

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Abstract

Objective: The aim of this study was to compare the pharmacokinetic parameters between two brands of pregabalin in healthy Chilean volunteers.

Methods: A randomized, single-dose, two-period, two-sequence, crossover study design with a 2-week washout period was conducted in healthy Chilean males. Plasma samples were collected over a 12-hour period after administration of 150 mg pregabalin in each period. A validated ultra-performance liquid chromatography with positive ionization mass spectrometric detection method was used to analyze pregabalin concentration in plasma. Pharmacokinetic parameters were determined using a noncompartmental method. Bioequivalence between the test and reference products was determined when the ratio for the 90% confidence intervals (CIs) of the difference in the means of the log-transformed area under the curve $(AUC)_{0-t}$, $AUC_{0-\infty}$, and maximum concentration (C_{max}) of the two products were within 0.80 and 1.25.

Results: The study was carried out on 22 healthy Chilean volunteers. The mean (SD) C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of the test formulation (Pregobin™) of pregabalin were 2.10 (0.56) μg/ml, 10.35 (2.00) μgxh/ml and 13.92 (2.74) μgxh/ml, respectively. The mean (SD) C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of the reference formulation (Lyrica™) of pregabalin were 2.15 (0.52) μg/ml, 10.31 (1.85) μgxh/ml and 13.78 (2.25) μgxh/ml, respectively. The parametric 90% CIs for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 0.97–1.13, 1.01–1.04, and 0.98–1.02, respectively.

Conclusions: These results suggest that both products are bioequivalent and can be used as interchangeable options in the clinical setting.

Keywords: bioavailability, bioequivalence, gabapentin, pharmacokinetics, pregabalin

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Introduction

Pregabalin (PGB), (S)-3-(aminomethyl)-5-methylhexanoic acid, is an anticonvulsant drug structurally related to the inhibitory neurotransmitter of the central nervous system, γ-aminobutyric acid (GABA). PGB is used in combination with other anticonvulsant agents in the management of partial seizures in adult patients presenting postherpetic neuralgia (PHN), pain associated with diabetic peripheral neuropathy (DPN), and in generalized anxiety disorder [Shneker and McAuley, 2005; Zareba, 2005]. It was designed as a more potent successor to gabapentin (GBP) and was first marketed by Pfizer under the trade name Lyrica®. Recent studies have shown that PGB is also effective in treating chronic pain in disorders such as fibromyalgia [Crofford *et al.* 2005] and spinal cord injury [Siddall *et al.* 2006].

Although this active pharmaceutical ingredient was developed as a GABA analog it does not bind GABA or benzodiazepine receptors; therefore, it does not increase GABA-like responses nor its uptake or degradation. However, it can increase the GABA transporter protein. Like GBP, PGB binds to the α2δ subunit of the voltage-dependent calcium channel [Rogawski and Taylor, 2006] in the central nervous system. However, the exact mechanism of action is still

unknown. *In vitro*, PGB reduces calcium-dependent release of several neurotransmitters, e.g. glutamate, norepinephrine and substance P, probably due to modulation of calcium channels [Fink *et al.* 2002; Dooley *et al.* 2000a, 2000b].

PGB does not bind to proteins in plasma and it is not substantially metabolized in humans. Its only N-methylated metabolite is found in urine at 0.9% of the dose. Bioavailability studies with PGB single doses in healthy volunteers showed proportional values of maximum concentration (C_{max}) and area under the curve (AUC), a time to maximum concentration (T_{max}) of about 1 hour, a half life ($t_{1/2}$) of about 5–7 hours, and an oral bioavailability of 90%, with an apparent volume of distribution following oral administration of approximately 0.5 l/kg [Busch *et al.* 1998]. Although the mechanism of PGB absorption is unknown, it has been proposed that, as for GBP, PGB should be a substrate for the L-aminoacid transport system [Stewart *et al.* 1993].

The simultaneous consumption of food with PGB can reduce C_{max} by 25–30%, and increase the T_{max} to 3 hours [Blommel and Blommel, 2007]. The serum concentrations for healthy volunteers obtained with a single dose of 200 mg of PGB was 5.96 µg/ml [Bockbrader *et al.* 2010]. The drug does not bind to proteins and is not expected to be an inducer of liver enzymes [Kwan, 2006].

On the other hand, the use of generic antiepileptic drugs has increased in Chile as well as globally during the past few years. Although these less-expensive products may represent an important alternative for many patients, it is not clear at this point whether the generic forms are comparable with the standards of their more expensive counterparts. The Chilean medical community has shown concerns about this issue indicating the need for new data and tight application of regulations. In this context, the main goal of this study was to evaluate bioavailability of two sources of PGB in healthy males and females Chilean volunteers. The goal was to determine bioequivalence of a test formulation of 150 mg (capsules) of PGB, Pregobin™ (Drugtech-Recalcine S.A., Santiago, Chile) and another commercial formulation of 150 mg (capsules) of PGB, Lyrica™ (Pfizer GMBH, Freiburg, Germany, imported to Chile by Pfizer Chile S.A.) used as a reference formulation.

Subjects, materials and methods

Subjects

Twenty-two healthy adult male and female volunteers between 21 and 50 years old with normal body mass indexes were selected. All subjects were considered healthy as determined by screening tests including medical history, physical examination, and laboratory analyses (Table 1).

Before enrollment and at the end of the study, each subject underwent a physical examination and clinical laboratory testing (blood chemistry, hematology, and urinalysis). Baseline clinical

Table 1. Demographic characteristics and baseline data of hematological and biochemical parameters of healthy Chilean volunteers subjects ($n = 22$).

	Mean	SD	Normal range
Age (years)	28.5	8.26	NA
Weight (kg)	69.38	13.24	NA
Height (cm)	169.04	9.43	NA
BMI (kg/m^2)	24.27	3.51	19–27
Creatinine (mg/dl)	0.88	0.14	0.8–1.5
Alkaline phosphatase (UI)	70.40	16.91	38.0–126.0
Glucose (mg/dl)	85.13	9.08	60.0–100.0
Uremia (mg/dl)	27.81	8.66	0.0–50.0
AST (UI)	20.40	6.17	5.0–40.0
ALT (UI)	23.18	10.76	7.0–56.0
Hematocrit	40.03	6.55	40.0–54.0
Leukocytes (x µL)	6226.36	1433.19	5000–10,000
Hemoglobin (mg/dl)	13.94	1.27	13.0–16.0
Total bilirubin (mg/dl)	0.75	0.34	0.2–1.3

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; NA, not applicable; SD, standard deviation.

laboratory tests were also performed before drug administration.

The enrollment criteria excluded subjects who had taken any prescription drug within 2 weeks prior to entering the study, those with clinical history of drug hypersensitivity, pregnant women or those presently using steroidal contraception and postmenopausal women.

The experimental protocol was designed in accordance with the general ethical principles outlined in the Declaration of Helsinki and under US Food and Drug Administration and World Health Organization guidelines [Food and Drug Administration, 2003; World Health Organization, 1998; Nuremberg Doctors' Trial, 1964]. The protocol for this study, as well as the protocol amendments, and the informed consent documents were reviewed and approved by the Ethics Committee of the Faculty of Medicine of the University of Chile (protocol ID PREG-03-2007, approved with number 2435 on 2006/12/15).

Study design

The study was conducted in a double-blind, randomized, single-dose, two-period, crossover design with a 1-week washout period between doses. A single dose of 150 mg PGB of either formulation was administered after overnight fasting. After dosing, serial blood samples were collected during a period of 12 hours. Blood samples (5 ml) were drawn at 0, 0.08, 0.16, 0.30, 0.50, 1.0, 1.5, 2.0, 2.5, 4.0, 6.0, 8.0, and 12 hours after administration. The subjects were housed for 14 hours postdose and were monitored for safety and adverse effects throughout the study. There was an interval of 2 weeks between two clinical phases: the first period was 15 January 2007; the second period was 29 January 2007.

Pregabalin sources

The commercially available test product, Pregobin^{TM} (Drugtech-Recalcine S.A.) from batch number 100106 (expiry date September 2008), and the innovator product, Lyrica^{TM} (Pfizer) from batch number 0175125 (expiry date November 2008), contained 150 mg of PGB per capsule and were characterized with regard to content and *in vitro* solubility profile.

Analytical method

Ultra-performance liquid chromatography (UPLC) with positive ionization mass spectrometric detection was used to determine PGB plasma concentrations. This method was a modified version of that developed by Ji and colleagues [Ji *et al.* 2006] and was validated (for specificity, sensitivity, linearity, recovery, precision, and accuracy) in our laboratory. GBP was used in this study as an internal standard (Merck AG).

Chromatographic and MS/MS conditions. For LC/MS/MS analysis, the chromatographic system consisted of an UPLC Acquity unit (Waters Corporation), a Quatro Micro API detector ESCI Multimode-Ionization. The separation was performed on an Acquity UPLC BEH-Hilic column 1.7 μm, 2.1 mm × 50 mm (Waters Corporation), using a mobile phase of acetonitrile/ammonium formate 100 mM pH 3.0 (85/15 v/v) with a flow rate of 0.4 ml/min. The total injected volume was 5 μl of each sample.

The temperatures of the column and autosampler tray were 30°C and 4°C, respectively. The optimum collision energy was 15 eV for both, using argon as the collision gas and multiple-reaction monitoring (MRM) mode was used for the quantification m/z 160.3→97.3 for PGB and m/z 172.4→154.3 for GBP. Peak areas were integrated using Masslynx version 4.1 software (Micromass, UK).

Blood sample preparation. Sample preparation involved a simple protein precipitation with acetonitrile. The plasma samples were filtered through 0.22 μM Millex-GV Millipore filters, then to 10 μl of plasma was added 10 μl of internal standard (1 μg/ml in methanol) and 100 μl of acetonitrile. The mixture was vortex mixed for 30 s and centrifuged at 8000 rpm for 5 min at 4°C. Finally, 5 μl of supernatant was injected into the UPLC/MS/MS system.

Validation procedure. Standard stock solutions of PGB and GBP (IS) were prepared in methanol to 1 μg/ml and stored at 4°C. Working standard solutions for calibration and controls were prepared from the stock solution by adequate dilution using acetonitrile. A calibration curve includes the following concentration points: 0.1, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, and 8.0 μg/ml.

The quality control samples (QC) were prepared with human plasma and appropriate amounts of drug to obtain concentrations of 0.5, 1.0, and

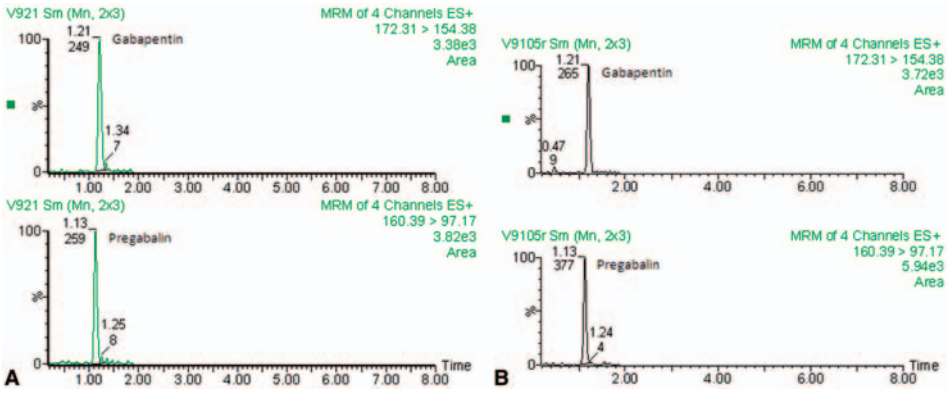

Figure 1. Representative chromatographic profiles from one volunteer for A (Pregobin™) and B (Lyrica™) formulations.

4.0 μg/ml. The retention time was 1.05 min for PGB and 1.12 min for GBP. Standard plots of the ratio of PGB/GBP concentrations *versus* PGB plasma concentration were linear over a range of 0.1–8.0 μg/ml ($r = 0.99916$). Accuracy from QC samples at 0.5, 1.0, and 4.0 μg/ml concentrations were 3.8%, 4.5%, and 1.8%, respectively. The intra-assay coefficient of variation was 4.7%, 6.1%, and 4.1%, respectively, and the inter-assay coefficient of variation was 1.1%, 0.7%, and 2.0%, respectively. No significant degradation of PGB during storage and processing conditions was noted. A representative chromatogram is presented in Figure 1.

Pharmacokinetic and statistical analyses

The sample size (n) was calculated on the basis of a crossover design with log-transformed data, considering an intra-individual variation coefficient of 20%, a power of 80% and a significance level of 5%, according to Chow and Wang [2001]. Under these conditions, the calculated sample size was 18 volunteers; thus, taking into consideration potential withdrawals and dropouts we enrolled 24 volunteers. PGB has no reported intra-individual variation coefficient; however, because it is a high solubility/high permeability drug with low hepatic metabolism we can conclude it should have very low variability.

Plasma concentrations of PGB *versus* time were evaluated by standard noncompartmental analysis methods. The highest plasma concentration observed and the corresponding time was defined as the C_{max} and T_{max} values, respectively. The elimination rate constant (K_{el}) was obtained by linear regression from the best-fit slope of the terminal log-linear decline in plasma concentrations *versus* time profile. The half-life ($t_{1/2}$) was obtained as $0.693/K_{el}$. The area under the plasma concentration curve to the last quantifiable concentration (C_t) at time t (AUC_{0-t}) was determined by linear trapezoidal integration. The AUC extrapolated to infinity ($AUC_{0-\infty}$) was calculated as $AUC_{0-t} + C_t/K_{el}$. The apparent total body clearance after oral administration (Cl/F) was estimated as dose/$AUC_{0-\infty}$. It was assumed that the terminal $t_{1/2}$ was the elimination half life, thus the apparent volume of distribution after oral dosing (V/F) was calculated as $(Cl/F)/K_{el}$. The area under the first moment of the plasma concentration *versus* time curve ($AUMC_{0-\infty}$) was obtained by applying the linear trapezoidal method to the product of concentration × time *versus* time up to time t and adding the extrapolated area of $C_t \times t/K_{el} + C_t/(K_{el})^2$. Mean residence time (MRT), reflecting the average time that a molecule remains in the body, was calculated from $AUMC_{0-\infty}/AUC_{0-\infty}$. The pharmacokinetic parameters were generated using the software AUC-RPP [Ritschel, 1986].

Bioequivalence analysis

STATA 10.0 and SPSS 11 were used to generate statistical outputs. STATA *pk* command was used to evaluate average bioequivalence, specifically *pkcross* and *pkequiv*, with the former performing a crossover analysis using an analysis of variance (ANOVA) model considering sequence, period, treatment effects and using a 90% confidence interval (CI), the latter using different approaches to evaluate bioequivalence. In this study we use a standard classic CI and two one-sided Schuirmann hypothesis test [Schuirmann, 1987; Ritschel, 1986].

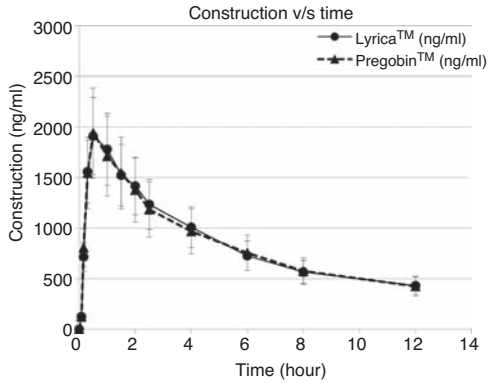

Figure 2. Changes in pregabalin concentrations in plasma (mean ± SD) after ingestion of 150 mg of either Pregobin™ or Lyrica™ formulations.

Results

Two of the 24 selected volunteers did not complete the study due to their absence at the first session, while the remaining 22 individuals participated in the study.

Table 1 provides the anthropometric and biochemical characteristics and the identification of the 22 volunteers finally included in this study. Mean age of the group was 28.5 ± 8.26 years; mean body weight was 69.38 ± 13.24 kg; mean height was 169.04 ± 9.43 cm and mean of body mass index was 24.27 ± 3.51 kg/m^2. The values for glycemia, uremia, creatinine, bilirubin, hematocrit, hemoglobin, leukocytes, alkaline phosphatase, and aminotransferases ranged between normal values for all volunteers; thus verifying their healthy condition.

Figure 2 (average plasmatic concentrations of PGB *versus* time), shows that plasma concentration diminished in a multiexponential mode after the peak concentration time.

Table 2 shows the pharmacokinetic profiles for Pregobin™ and Lyrica™. The 90% CIs for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were 96.76–112.90%, 100.38–103.69% and 97.22–102.22%, respectively (Table 3). Other pharmacokinetic parameters, not considered for determining bioequivalence t_{max}, $t_{1/2}$, and MRT and clearance (Cl) were also analyzed (Table 2).

ANOVA analysis is shown in Table 4. For intersubjects, there was evidence of variability to C_{max} and AUC. On the other hand, there were not sequence effects in pharmacokinetic parameters.

Table 2. Pharmacokinetic parameters of test and reference 150 mg pregabalin capsules of two different pharmaceutical forms after single-dose administration in healthy Chilean volunteers.

Parameters	Pregobin™	Lyrica™
$AUC_{0\to t}$ (μg/ml × h$^{-1)}$)		
Mean (SD)	10.35 (2.0)	10.31 (1.85)
%CV	19.32	17.94
$AUC_{0\to\infty}$ (μg/ml × h^{-1})		
Mean (SD)	13.92 (2.74)	13.78 (2.25)
%CV	19.68	16.33
C_{max} (μg/ml)		
Mean (SD)	2.10 (0.56)	2.15 (0.52)
%CV	26.67	24.19
T_{max} (h)		
Mean (SD)	0.75 (0.43)	0.63 (0.4)
%CV	57.33	63.49
$t_{1/2}$, (h)		
Mean (SD)	5.67 (1.12)	5.56 (0.98)
%CV	19.75	17.63
MRT (h)		
Mean (SD)	8.60 (1.77)	8.49 (1.55)
%CV	20.58	18.26
Cl_{tot}/F (ml/min)		
Mean (SD)	185.77 (34.1)	186.92 (35.87)
%CV	18.36	19.19
Vd_{beta}/F (l/kg)		
Mean (SD)	1.30 (0.24)	1.29 (0.22)
%CV	18.46	17.05

AUC, area under the curve; Cl_{tot}/F, apparent total body clearance; C_{max}, maximum concentration; CV, coefficient of variation; MRT, mean residence time; SD, standard deviation; $t_{1/2}$, half life; T_{max}, time to maximum concentrations; Vd_{beta}/F, apparent terminal volume of distribution.

Moreover, for intrasubjects no significant variability was observed, with the exception of AUC_{0-t} ($p = 0.0462$).

Following administration of the PGB capsules, four of the subjects reported mild or moderate adverse effects; the most frequent were somnolence (two volunteers), nausea (one volunteer) and xerostomia (one volunteer). There were no serious adverse effects observed throughout the study. During the study there were no significant changes in clinical laboratory values, vital signs, physical findings, or other observations related to safety.

Discussion

This study was designed to measure all relevant aspects underlying the pharmacokinetics of PGB that may be used to establish the degree of similarity between the two formulations indicated above. Almost perfectly overlapped curves of drug concentration and time were observed

Table 3. Classic confidence interval for bioequivalence and Schuirmann's test to compare Lyrica™ (reference) and Pregobin™ (test) parameters in healthy volunteers.

	Classic confidence interval for bioequivalence						Schuirmann's test	
	Equivalence limits reference (%)		Test limits (%)		Bioequivalence probability (%)*	Two one-side test		*p*-value
Ln C_{max}								
difference	−0.141	0.141	−0.023	0.091	96.00	Upper side	−3.243	0.004
Ratio	80	120	96.791	112.905		Lower side	5.319	<0.0001
Ln $AUC_{0\rightarrow t}$								
difference	−0.463	0.463	−0.039	0.037	100.00	Upper side	−1.141	<0.0001
ratio	80	120	100.384	103.686		Lower side	21.077	<0.0001
Ln$AUC_{0\rightarrow\infty}$								
difference	−0.523	0.523	−0.073	0.058	100.00	Upper side	−13.997	<0.0001
ratio	80	120	97.222	102.220		Lower side	−13.612	<0.0001

AUC, area under the curve; C_{max}, maximum concentration; Ln, log normal.
*Probability test limits are within equivalence limits.

Table 4. Analysis of variance (ANOVA) for maximum concentration C_{max}, area under the curve $(AUC)_{0\rightarrow t}$ and $AUC_{0\rightarrow\infty}$ (after logarithmic transformation) for parallel group design and two-treatment, two-period crossover design to pregabalin formulations.

Sources of variation	Sum of squares	Degree of freedom	Mean sum of squares	Fisher statistics	*p*-value
C_{max}					
Intersubjects					
Sequence effect	0.33	1	0.33	2.78	0.1112
Residuals	2.35	20	0.12	9.91	<0.0001
Intrasubjects					
Treatment effect	0.00	1	0.00	0.00	0.9455
Period effect	0.01	1	0.01	1.08	0.3118
Residuals	0.24	20	0.01		
$AUC_{0\rightarrow t}$					
Intersubjects					
Sequence effect	0.04	1	0.04	0.46	0.5047
Residuals	1.55	20	0.08	14.62	<0.0001
Intrasubjects					
Treatment effect	0.02	1	0.02	4.52	0.0462
Period effect	0.00	1	0.00	0.00	0.9748
Residuals	0.11	20	0.01		
$AUC_{0\rightarrow\infty}$					
Intersubjects					
Sequence effect	0.00	1	0.00	0.07	0.7960
Residuals	1.01	20	0.05	3.20	0.0062
Intrasubjects					
Treatment effect	0.07	1	0.07	4.13	0.0555
Period effect	0.00	1	0.00	0.04	0.8491
Residuals	0.32	20	0.02		

(Figure 1; the arithmetic differences are irrelevant due to the 90% CI). The clinical implications of these results allow us to have an anticonvulsant objective point of reference to choose an anticonvulsant medication.

In general terms, the magnitude of the absorption of a drug is reflected in the value of the parameter AUC related to the time postadministration. In the present study, the AUC between 0 and 12 hours ($AUC_{0\rightarrow t}$) and between zero and infinite time ($AUC_{0\rightarrow\infty}$) were analyzed. For these periods of time, reliable measurements of the bioavailability of the drug were obtained from each individual.

Here, the pharmacokinetics results showed conclusive data with regards to therapeutic equivalence. The comparison between the test (formulation A) and the reference (formulation B) of C_{max}, T_{max}, $AUC_{0\rightarrow t}$ and $AUC_{0\rightarrow\infty}$, showed percentages that fall in the rank of

equivalence (according to the FDA and ISP, Chile) (Table 3).

The similar pharmacokinetic profile of both formulations is also reflected in the MRT with a ratio of 1.013 between Lyrica™ and Pregobin™. This should not mean a bigger difference with respect to Lyrica™ due to the similar behavior of Pregobin™ in the body reflected in $AUC_{0\rightarrow t}$ and $AUC_{0\rightarrow\infty}$.

The pharmacokinetic values are similar to those reported in scientific literature [Blommel and Blommel, 2007]. The results indicate similarity regarding pharmacokinetics of the drug in the body for both formulations.

According to the biopharmaceutical classification system (BCS) of the FDA, PGB has a high solubility/high permeability profile; thus, it is a class 1 drug which can be bioexempted for *in vivo* bioequivalence studies. However, it is highly convenient to make *in vivo* studies which reflect, in a better way, the bioavailability profiles.

In summary, according to the analyses of results, we conclude that both formulations of PGB are bioequivalent. Therefore, following FDA guidelines and Chilean ISP criteria, we recommend that, for clinical usage, Pregobin™ 150 mg be used as interchangeable with Lyrica™ 150 mg.

Acknowledgements

This manuscript is dedicated to the memory of Dr Mario Escala Zanolli, an excellent physician who left us unexpectedly. The authors wish to thank to Dr Hernán Vásquez for reviewing this manuscript, Mrs Magdalena Orellana, Ms Jeannette Hermosilla, Mr Héctor Valenzuela, Mr Ramiro Pérez, Mr Santiago Leyton and Mr Juan Rojas for their excellent technical support. We also thank Biohealth LLC Clinical Research for their collaboration.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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