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Safety and Effectiveness of Naproxen 220 mg + Paracetamol 300 mg + Pamabrom 25 mg Fixed Dose Combination in Women with Premenstrual Syndrome: A Post-Marketing, Open-Label, Uncontrolled, Prospective, Multicenter, Observational Study

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Abstract: Premenstrual syndrome is characterized by pain and related symptoms that negatively affect women's quality of life. Our aim was to evaluate the safety and effectiveness of a specific oral fixed dose combination of naproxen 220 mg + paracetamol 300 mg + pamabrom 25 mg in tablet form. A prospective, open-label, multicenter, uncontrolled, observational post-marketing study was conducted from December 2017 to December 2019 consisting of 270 women over 18. The primary outcome was the number and severity of adverse effects. Secondary outcomes were pain intensity, number and intensity of other premenstrual symptoms, and the proportion of patients with a pain score reduction of at least 50%. The mean age of participants was 28.9 ± 8.8 years. We found that 8 women (3%) experienced adverse events, namely headache (5/8), gastritis (2/8) dyspepsia (1/8), diarrhea (1/8), and nausea (1/8). In three of the eight women, the study was discontinued due to adverse effects. Pain intensity was reduced (−4.5, 95%CI; −5, −4, $p < 0.001$). The proportion of patients with pain reduction of at least 50% was 70.7%. The study results suggest that the combination of drugs used in this formulation is safe and effective for premenstrual symptoms.

Keywords: pain; nonsteroidal anti-inflammatory drugs; dysmenorrhea; edema; inflammation; over-the-counter drugs

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1. Introduction

Premenstrual syndrome (PMS) consists of multiple psychological and physical symptoms that many women experience during the luteal phase of the menstrual cycle [1]. Dysmenorrhea (lower abdominal cramps) is one of the most prevalent of these symptoms. Others are abdominal bloating, peripheral edema, labile mood, lethargy, irritability, fatigue, breast-tenderness, anxiety, and headache. These symptoms are often of sufficient severity to interfere with interpersonal relationships and daily function. The prevalence of dysmenorrhea among women is significantly high and is not related to economic status [2]. In 2010, the prevalence rate of primary dysmenorrhea in young women was reported to be in the range 43–91% [3]. Some studies have shown that an estimated 90% of females during the reproductive age are affected by PMS [4]. Data from Mexico suggest that dysmenorrhea

occurs in approximately 64% of women [5]. PMS can negatively affect school performance and productivity at work. In a recent study by Sima and colleagues [6], dysmenorrhea showed a high prevalence among medical students (78.4%, n = 1720), undermining their ability to function. Many participants in this study felt agitated or nervous (72.7), tired (66.9%), with little energy for daily activities (75.9%), experiencing high stress (57.9%), and inability to eat a normal diet (30.0%). Academic performance (49.4%), social life (34.5%), and couple relationships (29.6%) suffered, along with relationships with family (21.4%) and friends (15.4%).

Pharmacological intervention is directed toward reducing symptoms and their impact on function and relationships, thus improving women´s quality of life [7]. Many over-the-counter (OTC) medicines containing mild diuretics, analgesics, prostaglandin inhibitors, or antihistamines are used by patients. Guidelines also suggest the use of selective serotonin reuptake inhibitors (SSRIs), diuretics, androgens, and/or gonadotropin-releasing hormone drugs in patients with premenstrual dysphoric disorder, a severe form of PMS [8,9]. Fixed-dose combination (FDC) drugs have shown an advantage in the management of PMS [10]. In Mexico, the oral FDC of naproxen 220 mg + paracetamol 300 mg + pamabrom 25 mg tablet is commercially available as an OTC medicine. The efficacy and safety of this combination has previously been evaluated in a randomized controlled clinical trial, which included 200 patients with primary dysmenorrhea [11]. This study demonstrated that naproxen 220 mg + paracetamol 300 mg + pamabrom 25 mg significantly reduced pain intensity ($p < 0.01$). Furthermore, the proportion of patients who reported a pain reduction of at least 50% was 80.6 (70/98). The combination was shown to be safe and was well tolerated. Only 4 (4.0%) women experienced adverse events: somnolence (1), headache (2), dizziness (1), increased thirst (1) and diarrhea (1). No serious adverse events were reported. With respect to the use of nonsteroidal anti-inflammatory drugs (NSAIDs), however, including single and fixed dose combinations, numerous side effects have been reported. These include irritation of gastric mucosa, stomach ulcers, nausea, vomiting, and nervous system disorders [10].

The present study was aimed to re-evaluate the post-marketing safety and effectiveness of naproxen 220 mg + paracetamol 300 mg + pamabrom 25 mg tablets in Mexican women with PMS.

2. Results

A total of two hundred and seventy patients (mean age 28.9 ± 8.8 years) were included. The study population was characterized by a previous history of daily activities limitation (63.0%), school or work absence (51.5%), and hospitalization due to PMS symptoms (2.2%) (Table 1). The CONSORT diagram represents the distribution in the study population (Figure 1).

Intention-to-treat (ITT) safety and effectiveness analyses were performed. During the study, eight (3%) patients experienced adverse events. These were headache (5/8), gastritis (2/8) dyspepsia (1/8), diarrhea (1/8), and nausea (1/8). The investigators classified 6/10 adverse events as treatment-associated and 3/8 patients were consequently discontinued from the study. All adverse events were coded with the preferred terms and classified by system organ class (SOC) as recommended by MedDRA (version 22.0) (Table 2).

Pain intensity was measured by NRS and showed a reduction as follow: 3.6 ± 2.6 (day 1; n = 270), 2.5 ± 2.4 (day 2; n = 185), 2.9 ± 2.1 (day 3; n = 69), and 2.0 ± 2.3 (day 4; n = 44). The median difference in pain intensity (−4.5, 95%CI; −5, −4) demonstrated that the naproxen 220 mg + paracetamol 300 mg + pamabrom 25 mg tablet significantly reduced pain intensity through time ($p < 0.001$). Figure 2 shows the mean of pain intensity vs. time profile. In addition, we determined the proportion of patients who reported a pain reduction of at least 50% at the end of the treatment. This proportion was 70.7% (95%CI; 64.9%, 76.1%).

Table 1. Baseline characteristics.

	Study Population (n = 270)
Age, years (mean ± S.D.)	28.9 ± 8.8
BMI, kg/m^2 (mean ± S.D.)	28.1 ± 1.4
Students (n, %)	93, 34.4
Workers (n, %)	148, 54.8
Presence of comorbidities (n, %)	12, 4.4
Diabetes (type 2)	1
Allergic rhinitis	2
Epilepsy	1
Atopic dermatitis	1
Anemia	1
Obesity	4
Asthma	1
Polycystic ovarian syndrome	1
Daily activities limitation (n, %)	170, 63.0
School or work absence	51.50%
Daily activities limitation	60.00%
Hospitalization	2.20%

S.D.: standard deviation, BMI: body mass index (weight in kg/height in m^2).

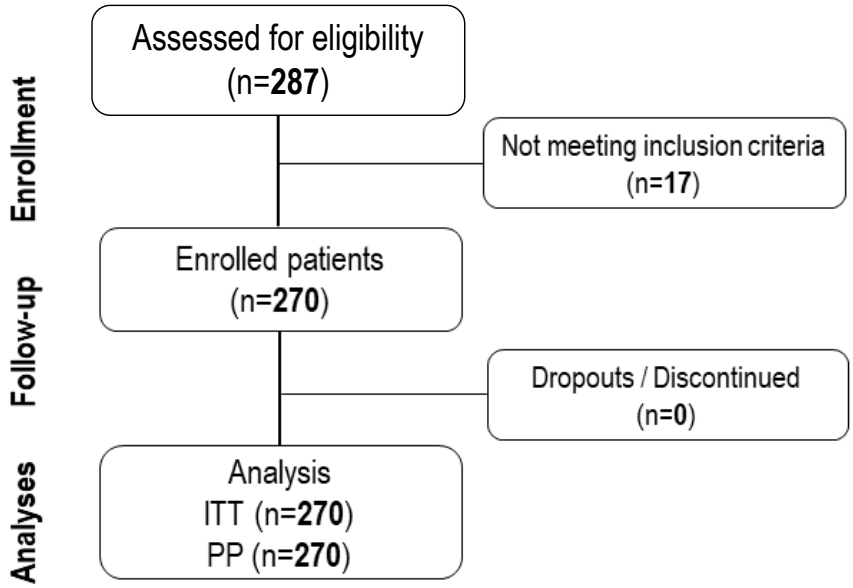

Figure 1. CONSORT diagram. The figure shows the sample distribution and population for data analysis. ITT: intention to treat population; PP: per protocol population.

We also evaluated the effect of the naproxen 220 mg + paracetamol 300 mg + pamabrom 25 mg tablet on PMS symptoms. The mean scores from the PMS questionnaire through time are shown in Table 3. Figure 3 shows the proportion of patients who reported a reduction in PMS symptoms score of at least 50%. These results indicate that this combination of naproxen 220 mg + paracetamol 300 mg + pamabrom 25 mg alleviated PMS symptoms in more than 50% of the women who received at least one dose.

Table 2. Adverse events.

Adverse Event by SOC and PT	n (%)	Severity	Treatment Related
Gastrointestinal disorders			
Dyspepsia	1 (0.4)	Moderate	Yes
Gastritis	2 (0.7)	Mild (1) Moderate (1)	Yes Yes
Nausea	1 (0.4)	Mild	Yes
Diarrhea	1 (0.4)	Moderate	No
Nervous system disorders			
Headache	5 (1.9)	Mild (4) Moderate (1)	Yes (2) No (3)

The adverse events were coded with the preferred terms (PT) and classified by system organ class (SOC) using MedDRA (version 22.0).

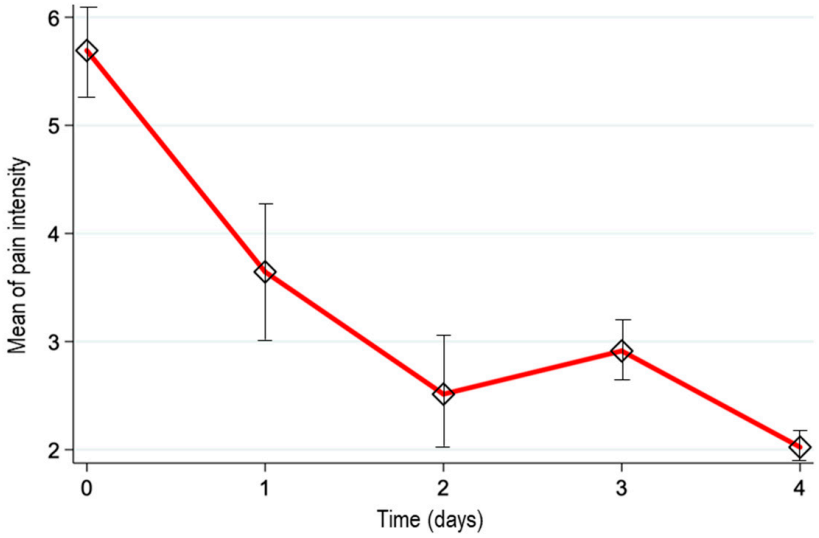

Figure 2. Pain intensity through time. The plot shows the mean (±SD) of the pain intensity score as determined by the numeric rate scale.

Table 3. Mean scores from the PMS questionnaire.

Dimension of the PMS Questionnaire	Time (Days)	Mean ± SD	N
PMS-A	0	6.3 ± 3.1	269
	1	4.3 ± 3.4	269
	2	3.8 ± 2.5	140
	3	3.5 ± 2.5	60
	4	3.2 ± 1.8	37
PMS-C	0	5.5 ± 3.4	269
	1	3.8 ± 3.4	269
	2	3.8 ± 2.9	120
	3	3.3 ± 3.0	64
	4	3.2 ± 2.4	44
PMS-D	0	4.7 ± 3.9	270
	1	3.2 ± 3.8	269
	2	4.3 ± 3.0	91
	3	4.0 ± 2.4	38
	4	4.0 ± 2.0	26

Table 3. *Cont.*

Dimension of the PMS Questionnaire	Time (Days)	Mean ± SD	N
PMS-H	0	8.2 ± 4.2	270
	1	5.3 ± 4.6	269
	2	4.9 ± 3.6	128
	3	4.3 ± 3.2	65
	4	4.1 ± 2.4	40
PMS—other symptoms	0	5.5 ± 4.0	269
	1	3.6 ± 3.9	269
	2	5.0 ± 3.5	97
	3	4.2 ± 3.4	47
	4	4.7 ± 3.2	33
PMS—symptoms during study period	0	3.8 ± 2.4	270
	1	2.6 ± 2.1	269
	2	2.5 ± 1.5	106
	3	2.2 ± 1.1	53
	4	1.6 ± 1.4	40

PMS: premenstrual syndrome; PMS-A: anxiety, irritability, and nervous tension; PMS-C: headaches, increased appetite, desire for sweets, fatigue, palpitations, and tremors; PMS-D: depression, insomnia, tearfulness, forgetfulness, and confusion; PMS-H: includes water retention, swelling, breast tenderness, bloating, and weight gain (all related to edema). Values represent the mean ± standard deviation of the sum of PMS symptoms.

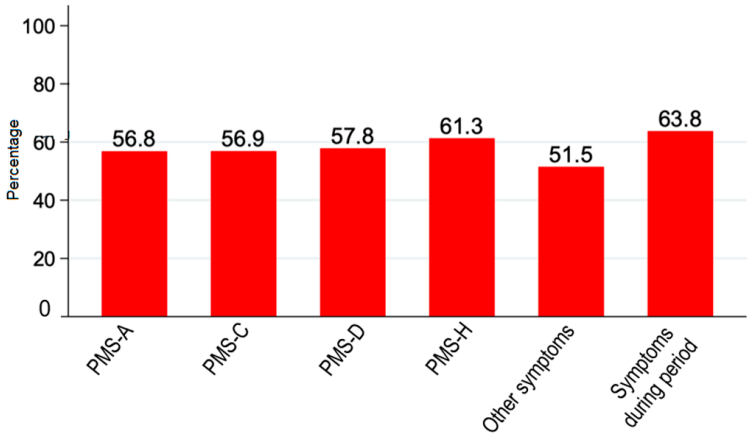

Figure 3. Proportion of patients with a reduction in PMS symptoms score by at least 50%. The pain intensity was measured using the NRS scale. This proportion was 70.7% (95%CI; 64.9%, 76.1%).

3. Discussion

The management of PMS currently consists of nonpharmacological interventions as well as analgesic, hormonal, and/or antidepressant therapy. NSAIDs have been used as a first line of pharmacological treatment in patients with primary dysmenorrhea associated with PMS. The indication is supported by the key role played by prostaglandins in the pathogenesis of primary dysmenorrhea and other premenstrual symptoms [12,13]. Physicians have categorized PMS into four groups: PMS-A, PMS-C, PMS-D, and PMS-H. Group A is predominantly related to anxiety, irritability, and nervous tension; Group C with headaches, and also increased appetite, desire for sweets, fatigue, palpitations, and tremors; Group D with depression, insomnia, tearfulness, forgetfulness, and confusion, and Group H with water retention, swelling, breast tenderness, bloating, weight gain, and peripheral edema [14]. Many therapies have been tried. These include analgesic, anti-inflammatory, and diuretics, along with hormonal treatment inhibitors or precursors of prostaglandins, nutritional supplements, and psychotropic medications [15]. Our approach was to combine drugs with different mechanisms of action in order to achieve a multimodal effect, yielding measurable effectiveness with a minimum of adverse effects.

The results of the present study showed an adverse events incidence of 3.0% (8/270 patients). The adverse events were similar in nature and intensity to previously reports. Mild to moderate adverse events in patients treated with naproxen 220 mg + paracetamol 300 mg + pamabrom 25 mg, e.g., nausea, dyspepsia, headache, gastritis, and diarrhea, have been reported by others [11]. However, the 3% incidence is lower than that reported in previous studies [11,16]. A meta-analysis, aimed to determine the effectiveness and safety of NSAIDs in the treatment of primary dysmenorrhea, included 25 studies of 2133 women (1272 in cross-over studies and 861 in parallel-group studies). They compared the following NSAIDs versus placebo: naproxen (ten studies); piroxicam (five studies); diclofenac, ibuprofen, ketoprofen (three studies each); celecoxib, fenoprofen (two studies each); aceclofenac, aspirin, dexketoprofen, etodolac, etoricoxib, niflumic acid, and nimesulide (one study each). Although there were no evident differences between any individual NSAID with placebo, the pooled results showed that NSAIDs were more likely to cause an adverse effect than placebo (OR 1.29, 95%CI 1.11 to 1.51, 25 studies, I2 = 0%). The most reported adverse effects were mild neurological and gastrointestinal symptoms [17]. The results of our study also showed mild gastrointestinal effects as the main adverse events reported by patients. Other adverse effects of these drugs reported in the literature are diuresis, nausea, vomiting, epigastric pain, jaundice, leukopenia, anemia, liver and/or kidney damage, headache, gastrointestinal bleeding and perforation, thrombocytopenia, vasculitis, toxic epidermolysis (Stevens–Johnson Syndrome), and seizure. None of these were reported in the present study.

A prior study demonstrated the efficacy of a fixed dose combination containing naproxen 220 mg + paracetamol 300 mg + pamabrom 25 mg in PMS [11]. Naproxen and paracetamol are analgesic and anti-inflammatory drugs, respectively, that are commonly used for treating painful conditions such as primary dysmenorrhea [18,19]. The anti-inflammatory and analgesic properties of naproxen have been attributed to the inhibition of cyclooxygenase and the consequent inhibition of prostaglandin synthesis [20]. Paracetamol exerts an antinociceptive effect through interference with serotonergic descending pain pathways. It may also inhibit prostaglandin synthesis or influence cannabinoid receptors through an active metabolite [21]. A meta-analysis previously demonstrated the efficacy of naproxen in primary dysmenorrhea (OR 3.99, 95%CI, 2.18 to 7.30) [19]. Marjoribanks et al. [17] published a meta-analysis comparing NSAIDs used in the treatment of primary dysmenorrhea. They found that naproxen was significantly more effective than placebo in producing moderate to excellent relief of pain (OR 3.67, 95%CI, 2.94 to 4.58). Fixed dose combinations of paracetamol with NSAIDs also resulted in significant pain relief in women with primary dysmenorrhea [22]. A systematic literature review suggests that a combination of paracetamol and an NSAID may offer superior analgesia for acute pain than either drug alone [23]. Other studies have demonstrated that an NSAID plus pamabrom combination is effective in the control of pain and edema in patients with primary dysmenorrhea [16,24]. The present study is in line with previous reports. It shows the effectiveness of naproxen 220 mg + paracetamol 300 mg + pamabrom 25 mg since at day 3 more than 50% discontinued the treatment due to symptom control, while the proportion of patients with symptom control was higher than 80% at day 4.

One limitation of this study is that safety and effectiveness results apply only to the drug formulation used and may not apply to other combinations of the same active ingredients. Another limitation is that patients were recruited and treated by their own physicians, which may have introduced a bias in reporting.

Nevertheless, the present work contributes to knowledge about the safety profile of this fixed-dose OTC formulation of naproxen 220 mg + paracetamol 300 mg + pamabrom 25 mg in the management of PMS. The monitoring of therapeutics in the real-world post-marketing phase is of vital importance for patients, health professionals, sponsors, and regulatory authorities.

In summary, the present post-marketing study demonstrated that the naproxen 220 mg + paracetamol 300 mg + pamabrom 25 mg formulation resulted in a low frequency of

adverse events over a 5-day duration. No serious or unexpected adverse events were reported, and the major adverse event was mild gastrointestinal upset. The fixed dose combination drug used in this study improved PMS symptoms, effectively reducing the intensity of pain and edema. We conclude that this treatment for PMS is safe and effective.

4. Materials and Methods

4.1. Study Design and Patients

This was designed as a prospective, open-label, noninterventional, uncontrolled, multicenter, observational post-marketing study, and was conducted from December 2017 to December 2019 in the following centers in Mexico: (1) American British Cowdray Medical Center (Mexico City), (2) Hospital San Angel Inn (México City), (3) Clinical Trials México S.A. de C.V. (Hidalgo), and (4) ICARO Investigaciones en Medicina, S.A. de C.V. (Chihuahua). Data were collected via questionnaire from 270 consenting female outpatients over age 18 and with a clinical diagnosis of PMS. Patients were excluded if they had received nonsteroidal anti-inflammatory drugs (NSAIDs) or were on hormonal contraceptives. In addition, women with a previous history of hypersensitivity to the treatment drugs, cardiovascular diseases, active sex life without contraceptives, pregnant or lactating, or meeting criteria for asthma, nasal polyps, angioedema, urticaria, hepatic or renal dysfunction, granulocytopenia or agranulocytosis, coagulation disorders, gastrointestinal disorders, current anticoagulant use, or alcohol/drug abuse were excluded from the study. The study protocol (LIO-04-15) and unidentified subjects´ data were registered in the Mexican data base of clinical trials. The protocol and main data are available on the Mexican public registry for clinical trials: http://siipris03.cofepris.gob.mx/Resoluciones/Consultas/ConWebRegEnsayosClinicos.asp (protocol number LIO-04-15) (accessed on 14 November 2023).

4.2. Ethics

The study was conducted in accordance with the Declaration of Helsinki, the Good Clinical Practices (ICH E6), and local regulations. The protocol (LIO-04-15) and the informed consent forms were reviewed and approved by the local ethics committee (LIO-04-15/28022018, CECYC Pharma, S.A. de C.V., Morelos, México). Patients were included only after signing consent on a form in which the risks, benefits, and patient rights were thoroughly explained. Investigators were compensated for their time by the study's sponsor, Laboratorios Liomont, S.A. de C.V. Participants were recruited and followed throughout the study by their own physicians.

4.3. Study Medication

Naproxen 220 mg + paracetamol 300 mg + pamabrom 25 mg tablet (Analgen Fem®, Cuajimalpa de Morelos, Ciudad de México, México) was prescribed in compliance with the recommendations of the prescribing information (one or two tablets every 8 h for five days maximum during the PMS period, to be discontinued once symptoms were controlled).

4.4. Safety and Effectiveness Variables

The primary safety measure was the proportion of patients who experienced an adverse event during the study; all adverse events, associated or not with the study medication, were recorded. The effectiveness measures were:

(a) Pain intensity determined by a numerical rating scale (NRS) [12], where 0 = no pain at all, 1–3 = mild, 4–6 = moderate, and 7–10 = severe.
(b) The proportion of patients with a baseline pain score reduction of at least 50%.
(c) The premenstrual questionnaire (PMSQ) as applied to determine the presence of the following symptoms: PMS-A (anxiety, irritability, and nervous tension); PMS-C (headaches, increased appetite, desire for sweets, fatigue, palpitations, and tremors); PMS-D (depression, insomnia, tearfulness, forgetfulness, and confusion); PMS-H (water retention, swelling, breast tenderness, bloating, and weight gain). Patients

were asked to evaluate their symptoms as follows (Barboza et al., 2014): 0 = symptom was absent; 1 = symptom was barely noticeable; 2 = symptom inhibited activities; 3 = symptom altered my lifestyle.

4.5. Statistical Analyses

The required sample size was calculated based on previous work (Moore et al., 2015 [16]). A sample size of 187 patients was estimated considering a type I error of 5% ($\alpha = 0.05$), a confidence interval 95%, statistical power of 80%, 14.5% as adverse events proportion. Assuming a 45% dropout rate, the final sample was 270 subjects. The analysis of safety and effectiveness was performed on all the enrolled patients who received at least one dose of study medication. The significance level was set at 5% (type I error, $\alpha = 0.05$) or 2.5% (type I error, $\alpha = 0.025$). Stata 15 (StataCorp LLC, College Station, TX, USA), NCSS 20 (NCSS, LLC, Kaysville, UT, USA) and East 6 (Cytel Inc., Waltham, MA, USA) software were used for analysis.

Author Contributions: L.D.-R., M.G.-d.l.-P. and Á.E.P.-J.: substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work. Á.E.P.-J., O.B.-A. and M.G.-d.l.-P.: drafting the work or revising it critically for important intellectual content. J.E.V., O.B.-A., Á.E.P.-J., M.G.-d.l.-P. and L.D.-R.: provided approval for publication of the content. J.E.V., O.B.-A., Á.E.P.-J., M.G.-d.l.-P. and L.D.-R.: agreed to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: All patients were consented before any study activity was performed. The informed consent for was previously revised and approved by the Ethics Committees.

Data Availability Statement: The data sets generated and analyzed for this study can be found in the study protocol (LIO-04-15) and unidentified subjects' data for sharing were registered in the Mexican data base of clinical trials and in the data on file owned by Laboratorios Liomont, S.A. de C.V. Website: http://siipris03.cofepris.gob.mx/Resoluciones/Consultas/ConWebRegEnsayosClinicos.asp (please register the study number LIO-04-15 to display information) (accessed on 14 November 2023).

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Conflicts of Interest: Livan Delgado-Roche is an employee of Laboratorios Liomont, S.A. de C.V. Jesús E. Villegas is an employee of ICARO; Mario González-de la-Parra is an employee of Biokinetics. The other authors declare no conflicts of interest.

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