Official Study Title: PHASE III, RANDOMIZED, ACTIVE-COMPARATOR CONTROLLED CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF NIFEDIPINE 30MG EXTENDED-RELEASE IN ADULT PATIENTS DIAGNOSED WITH MILD OR MODERATE HYPERTENSION IN COLOMBIA.

Protocol Number: NIF30-0120
Protocol Version: Version 3
Document Date: 23-Aug-2023
NCT Number: To be confirmed

Date: 26th february 2026

Dear ClinicalTrials.gov Registration Team,

Please find attached the study protocol titled “PHASE III, RANDOMIZED, ACTIVE-COMPARATOR CONTROLLED CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF NIFEDIPINE 30MG EXTENDED-RELEASE IN ADULT PATIENTS DIAGNOSED WITH MILD OR MODERATE HYPERTENSION IN COLOMBIA”, Protocol NIF30-0120, Version 3, dated 23-Aug-2023, submitted for registration purposes.

The NCT number is currently pending confirmation and will be provided once available.

Should you require any additional information or documentation, please do not hesitate to contact me.

Sincerely,

Trinidad Plata B.
MSL Laboratorios Richmond Colombia
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Product: 910002

Cover

Protocol title: Phase III randomized, active-controlled clinical trial to evaluate the efficacy and safety of Nifedipine 30 mg extended-release in adult patients diagnosed with mild to moderate hypertension in Colombia.

Protocol number: NIF30-0120

Compound number: 910002

Sponsor name and registered legal address:

Regulatory Agency Identification Number(s):

EudraCT number: 2020-004732-16

Approval date: 05/13/2021

CONFIDENTIALITY:

The information contained in this document is private and confidential. The purpose of this protocol is to support corresponding requests to institutional review boards (IRBs) and independent ethics committees (IECs) in order to endorse the proposed clinical trial. Therefore, it may not be copied, distributed, or disclosed to other persons without the prior written approval of Caimed or its designated representatives.

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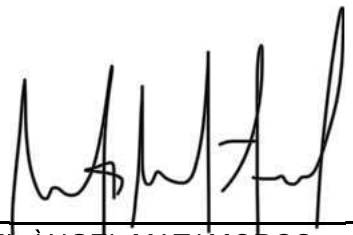


10-10-2024

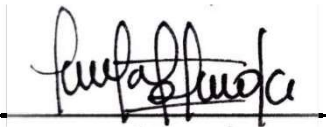
MIGUEL ÀNGEL MATAMOROS Date:

Position: General Manager

The Sponsor's contact details specific to this protocol are provided in the Investigator's Study Folder.

Investigator Signature

I agree to conduct this clinical study in accordance with the design described in the protocol and to comply with all provisions of this protocol.



10-10-2024

Paula Marcela Ochoa Castañeda: Date

Position: Principal Investigator

DOCUMENT HISTORY

Document	Date of Publication	General justification
NIF30-0120 V0	12/15/20	Original protocol submitted to the EC
NIF30-0120 V1	May 13, 2021	Approved with the following changes: It is clarified that all activities related to the reception, storage, dispensing, and inventory control of investigational products are carried out in the defined area of the institution's pharmaceutical service.
NIF30-0120 V2	10-11-2021	Request to adjust to CE, footnote this Protocol NIF30-0120V0 Changes to this were approved, so it would be V1 6.4.1 vials They are boxes 8.2.8 Change vial to box and temperature to below 30 degrees, point 11. Participant identification card, leave Name of the investigating physician Claudia Inés Birchenall Jiménez, leave 24-hour telephone number: +5715600520, 5.2. Exclusion criteria for concomitant medications are included. 13. Schedule of activities remains unchanged. In the event of participant absence, activities must be rescheduled within the following 5 days according to the schedule.
NIF30-0120 V3	08-23-2023	The EC is requested to change the version of the protocol. Due to the changes made to this protocol, it is changed from V2 to V3 as shown in the footer: NIF30-0120V3. human [HIV] e.g. Ritonavir, 1. Synopsis: Treatment group. Group II was modified 4.4.3 Basis for use of

		comparator adjustment is made 5.1 Inclusion criteria: Adjusted 5.2 Exclusion criteria: Modified 6.1 Administrative treatments: Modified Explanatory note regarding the availability and origin of the drug is removed Figure 2. Removed 8.2.5 Review of previous and concomitant medications: Adjusted Table 3 General variables of studies parameterized in CRF: Adjusted 13 Schedule of activities: Modified 15.6 Appendix 6 Protocol for the delivery of samples of Nifedipine 30 mg Extended Release for Safety and Efficacy Study. Sample Identification. Deleted: As well as the samples subject to the claim. Adjusted in accordance with the Clinical Research Medication and Supply Guide Code ASS-RSA-GU045 Number of Samples to be Delivered: according to current medical formulation The number of samples to be delivered is adjusted according to the actual number. [DCCR1]

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1 Synopsis

Protocol title: Phase III, randomized, active comparator-controlled clinical trial to evaluate the efficacy and safety of Nifedipine 30mg Extended Release in adult patients diagnosed with mild or moderate hypertension in Colombia.

Abbreviated title: Efficacy and safety of Nifedipine 30 mg Extended Release in adult patients diagnosed with mild or moderate hypertension.

Objectives/hypotheses and endpoints:

Objective	Evaluation criteria
Primary	
- To evaluate the efficacy of Nifedipine 30mg Extended Release Richmond versus Nifedipine 30mg Extended Release currently registered in Colombia, measured by the proportion of patients with blood pressure control in adult patients diagnosed with mild or moderate hypertension moderate hypertension at week 8 of follow-up	- Blood pressure control (SBP/DBP) at 8 weeks of follow-up
Secondary	
- Evaluate the efficacy of Nifedipine 30 mg Extended Release Richmond versus Nifedipine 30 mg Extended Release currently registered in Colombia, measured by the proportion of patients with blood pressure control in adult patients diagnosed with mild or moderate hypertension at week 4 of follow-up	- Blood pressure control (SBP/DBP) at 4 weeks of follow-up
- Evaluate the safety of Nifedipine 30 mg Extended Release Richmond versus active comparator, measured by the proportion of adverse events identified during follow-up.	- Cumulative safety data
- Evaluate the safety of Nifedipine 30mg Extended Release Richmond versus active comparator as measured by the proportion of serious adverse events identified during follow-up.	- Cumulative safety data

General design:

Study phase	III
Clinical indication	Pharmacological management of essential hypertension
Population	Adults diagnosed with mild to moderate hypertension Mild to moderate

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Type of study	Intervention
Type of control	Active control
Study masking	Double-blind
Estimated study duration	The study is estimated to take 30 weeks from the time the first participant signs the informed consent form to the last study-related visit/call for the last participant. participant

Number of participants:
It is proposed to recruit 50 volunteers

Treatment groups and duration:

Treatment groups	GROUP I: Administration of 30 mg extended-release Nifedipine Richmond for 8 weeks, followed by a change in treatment to comparator Nifedipine "according to the current medical formula" for 10 weeks (including 2 weeks of statistical silence). GROUP II: Administration of Nifedipine 30mg Extended Release Richmond for 8 weeks, followed by a switch to comparator Nifedipine "according to the current medical formula" for 10 weeks (including 2 weeks of statistical silence).
Duration of participation	Each volunteer will participate in the study for 20 weeks from the signing of the informed consent form for inclusion in the study until the final contact. The selection of patients who meet the selection criteria will be carried out during a 6-month enrollment period until the minimum sample size of 50 pairs, a total of 100 subjects in a crossover design (one patient = two study subjects), is reached. -*Expected study start date:* 2nd quarter of 2021 -*Expected completion date* *:* 4th quarter of 2021. During their participation, participants will receive antihypertensive medications (both nifedipine [comparator and study] and antihypertensive combination [unmodified]), a digital blood pressure monitor for home measurements, and a diary for recording medication intake and blood pressure readings.

2 Introduction

2.1 Rationale for the study

Hypertension is an established risk factor for the development of cardiovascular (CV) disease(1). According to the World Health Organization, the global prevalence of hypertension is increasing and is estimated to cause approximately 7 million premature deaths per year(2). Clinical evidence supports lowering blood pressure (BP) to achieve defined BP targets in order to reduce the risk of CV outcomes(3,4). Achieving adequate BP control through the selection of appropriate treatment is therefore of great concern to both physicians and patients(5).

Systemic arterial hypertension is characterized by the chronic persistence of elevated blood pressure in the circulatory system(6). It is one of the diseases that most affects the world population and is considered one of the most important risk factors for the development of acute myocardial infarction, stroke, chronic kidney disease, and other types of vascular diseases (7,8). It is considered the most important modifiable risk factor for coronary heart disease (the leading cause of death in North America), stroke (the third leading cause of death in North America), congestive heart failure, peripheral vascular disease, and end-stage renal disease (8).

With regard to the etiology of the disease, high blood pressure is classified as primary (essential) or secondary. Ninety to ninety-five percent of patients have primary or essential high blood pressure of multifactorial origin, involving both genetic and environmental factors(6). Primary high blood pressure occurs in the absence of a specific disease considered to cause hypertension. Some of the causes associated with the onset of secondary hypertension include renovascular disease, parenchymal kidney disease, primary aldosteronism, obstructive sleep apnea, Cushing's syndrome, pheochromocytoma, hypothyroidism, hyperthyroidism, and aortic coarctation, among others(9,10).

With regard to the epidemiology of the disease, it is estimated that 972 million people worldwide have hypertension, representing approximately 26% of the global population, and this prevalence is expected to increase to 29% by 2025 (11). With regard to the prevalence of the disease by sex, up to the age of 45, it is more common in men. Between the ages of 45 and 64, the prevalence by sex is balanced, and after the age of 64, a higher percentage of women have the disease compared to men (6,7).

Blood pressure is documented based on the relationship between systolic blood pressure, which measures the pressure exerted by blood on the arterial walls when the heart contracts, and diastolic blood pressure, which generally occurs when the heart is relaxed(6).

It is difficult to define the blood pressure readings that constitute hypertension, given that there are currently several clinical practice guidelines that attempt to standardize these measurements. According to the ESC/ESH guidelines, the following classification is defined:

Table 1. Classification of blood pressure in the doctor's office [a] and definitions of hypertension [b] (12)

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120-129	and/or	80–84
High normal	130-139	and/or	85–89
Grade 1 hypertension	140-159	and/or	90–99
Grade 2 hypertension	160-179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension [b]	≥140	and	<90

BP: blood pressure; SBP: systolic blood pressure.
[a] The BP category is defined according to the BP readings taken in the doctor's office with the patient seated and the highest BP value, whether systolic or diastolic.
[b]Isolated systolic hypertension is classified as grade 1, 2, or 3 according to the SBP values in the indicated ranges. The same classification is used for all ages 16 years and older.

Hypertension is considered to be present when two or more measurements taken at two or more different times show abnormal values(7).

In addition to taking blood pressure in accordance with AHA recommendations, a complete medical history should be taken, accompanied by an adequate physical examination and fasting glucose, complete blood count, lipid profile, serum creatinine, electrolytes (sodium, potassium, calcium), TSH, urinalysis, and electrocardiogram. A comprehensive medical history will allow for a more comprehensive approach to the patient (10). Regarding the management of the disease, a combination of pharmacological and non-pharmacological measures is essential. In normotensive patients, the recommendation is to promote healthy lifestyles and reassess in one year. For patients with high blood pressure, stricter non-pharmacological measures should be initiated and reassessed in 3 to 6 months (10).

In patients with stage 1 hypertension, the 10-year risk of stroke or acute coronary disease should be established, for which the ASCVD risk estimator is recommended (10).

In terms of pharmacological management, in general, for all hypertensive patients under 60 years of age, it is recommended to start treatment with antihypertensive drugs when the diagnosis is confirmed

and the patient has blood pressure readings above 130/80 mmHg. For initial management, the use of two or more antihypertensive drugs is recommended to achieve the therapeutic goal of <130/80 mmHg (8,13). In patients over 60 years of age, it is recommended to start pharmacological management when blood pressure readings are above 150/90 mmHg, and the goal is to maintain blood pressure below 150/90 mmHg, reducing the risk of stroke, heart disease, and death(8,13).

For initial antihypertensive management in non-black patients, the following antihypertensive drugs are recommended at low doses: calcium channel blockers, thiazide diuretics, renin-angiotensin-aldosterone system (RAAS) inhibitors, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs). For black patients, the recommendation is to start with a thiazide diuretic or a calcium channel blocker (13). On the other hand, it is important to remember that the simultaneous use of ACEIs, ARBs, and/or renin inhibitors is contraindicated as they can be potentially harmful (6,10,13).

The guidelines of the European Society of Hypertension (ESH)/European Society of Cardiology (ESC) recognize that most patients with high BP will need a combination of two or more antihypertensive drugs to achieve their BP target (14). The combination of a calcium channel blocker (CCB) such as nifedipine with beta-blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin II receptor blockers (ARBs) has been shown to be beneficial(15), and guidelines recommend these CCB combinations as a first-line treatment option(14,16).

Nifedipine is a dihydropyridine calcium channel blocker, whose short-acting formulation has been associated with reflex activation of the sympathetic nervous system (SNS) leading to flushing, tachycardia, worsening myocardial ischemia, and cerebrovascular ischemia; therefore, only longer-acting formulations should be used(17). Numerous extended-release formulations are available worldwide and have been shown to be equally effective compared to other antihypertensive agents such as ARBs, beta-blockers, and diuretics in the treatment of hypertension (18–20).

Nifedipine has been directly compared with other antihypertensive agents, particularly when the extended-release formulation was launched. In a 10-week, double-blind, multicenter study of 102 participants, patients received 30 or 60 mg of modified-release nifedipine daily, 25 or 50 mg of hydrochlorothiazide (HCTZ) daily, or placebo (21). Most patients in the active treatment groups completed the study on 50 mg of HCTZ or 60 mg of nifedipine. Both treatments were significantly better than placebo in lowering SBP and DBP, with 71% of the HCTZ group and 67% of the nifedipine group achieving a seated DBP <90 mmHg. The authors concluded that monotherapy with modified-release nifedipine reduces BP with similar efficacy to HCTZ(21).

In another double-blind study, patients received modified-release nifedipine or

sustained-release propranolol for 8 weeks, which could be adjusted to an optimal dose if DBP remained >90 mmHg (18). The primary objective of the trial was to evaluate the change in BP from baseline, as well as the proportion of patients whose BP decreased to the target. Most patients in the nifedipine and propranolol groups completed the trial on 90 mg and 240 mg daily, respectively. In this study, SBP was reduced by a mean of 15.9 mmHg in the nifedipine group compared with 5.7 mmHg in the propranolol group ($p < 0.001$). DBP was reduced by an average of 10 mmHg in the nifedipine group versus 6.1 mmHg in the propranolol group ($p <0.018$). SBP was also reduced to a greater extent in the nifedipine group ($p <0.005$). The proportion of patients receiving nifedipine who achieved a decrease in BP in the sitting and standing positions was 61% and 52%, respectively, compared with 25% and 28% in the propranolol group. This study showed that modified-release nifedipine is more effective than sustained-release propranolol in reducing sitting SBP and DBP, as well as standing SBP (18).

Nifedipine has also been compared with other dihydropyridine CCBs, such as amlodipine. One study in particular randomly assigned patients to nifedipine GITS 30 mg or amlodipine 5 mg for 21 weeks to evaluate the effect on DBP and quality of life(22). The primary objectives of the study were to evaluate the change in SBP and DBP, as well as the change in health-related quality of life. The study showed no significant differences between the treatment arms with regard to SBP or DBP. The mean decrease in SBP was 18.8 mmHg with nifedipine and 19.7 mmHg with amlodipine, while the mean reduction in DBP was 15.5 mmHg with nifedipine and 15.7 mmHg with amlodipine ($p>0.55$ for SBP and DBP)(22).

As mentioned above, ACE inhibitors are recommended as first-line antihypertensive drugs in patients with different comorbid conditions. One study compared the efficacy of modified-release nifedipine 30 to 60 mg once daily with that of enalapril 5 to 10 mg daily over the course of 8 weeks by measuring BP and HR at each visit, as well as using ambulatory BP monitoring (ABPM)(23). At the end of the treatment period, DBP and SBP decreased significantly from baseline in both groups ($p <0.001$ for DBP in both treatments). More patients in the nifedipine group remained on a low-dose regimen compared to the enalapril group ($p <0.05$). Twenty-four-hour SBP decreased from 141 ± 15 mmHg to 134 ± 14 mmHg in the nifedipine group compared with enalapril, where SBP decreased from 140 ± 15 mmHg to 131 ± 15 mmHg. DBP was 86 ± 9 mmHg for both groups at baseline and decreased to 82 ± 9 mmHg in the nifedipine group and 80 ± 8 mmHg in the enalapril group. This trial demonstrated that modified-release nifedipine and enalapril are equally effective for the treatment of hypertension(23).

ARBs are a standard first-line therapy and an alternative to ACE inhibitors in the treatment of hypertension, particularly in patients with indications such as diabetes, chronic kidney disease, and heart failure(3). One trial compared the effects of modified-release nifedipine 30 mg, 60 mg, or 90 mg with losartan 50 mg as monotherapy or with HCTZ 12.5 mg or 25 mg on mean seated DBP after 12 weeks(19). Two hundred twenty-three patients were treated, and BP decreases

were similar in both groups. Patients with higher baseline DBP (106–115 mmHg) showed a significantly greater benefit in seated DBP at the end of therapy when treated with losartan compared with modified-release nifedipine (-16.2 ± 7.1 mmHg, p = 0.03). There were no significant differences in SBP, the percentage of patients who had a seated DBP <90 mmHg at the end of treatment, heart rate, quality of life, or adverse events between the two groups. The authors concluded that losartan is equally effective as modified-release nifedipine in the treatment of hypertension, but with greater tolerability, particularly with regard to edema.

Finally, observational studies can provide important information on the efficacy and safety of antihypertensive agents in the real-world clinical setting. For example, AdADOSE was an observational study to evaluate the efficacy of modified-release nifedipine in combination with other antihypertensive agents conducted in 10 countries(5). The study recruited 4,497 patients (n = 4,477, safety population; n = 3,430, efficacy population). The mean baseline systolic/diastolic BP (SBP/DBP) was 166.4/99.7 mmHg; 85.2% of patients had received previous antihypertensive treatment, and 90.6% had ≥1 concomitant disease. After combination therapy with modified-release nifedipine, 64.8% of patients without concomitant diseases achieved target BP, as did 56.5%, 32.3%, and 22.6% of patients with 1, 2–3, and >3 concomitant diseases, respectively. The proportion of patients who achieved target BP was 51.5% in previously untreated patients and 33.7% in previously treated patients. Combination therapy with modified-release nifedipine resulted in mean SBP/DBP changes of -36.1/-18.8 mmHg in all patients, -40.2/-21.5 mmHg in previously untreated patients, and -35.6/-18.4 mmHg in previously treated patients, with similar BP reductions regardless of the number of concomitant diseases, thus confirming its effectiveness in real life(5).

2.2 Benefit/risk assessment

Clinical studies are designed to provide information about the safety and efficacy of the investigational drug, so no direct benefit to participants is guaranteed. However, benefits derived from the study are identified, such as continuity of treatment, follow-up and support, and therapeutic education.

The aim is to minimize the risks associated with the drug. Patients with a body mass index below 18.5, previous liver disorders, heart failure, a history of allergies, coronary heart disease, aortic stenosis, or angina pectoris will not be accepted. In addition, the introduction of a safe drug to the Colombian market will increase its availability.

The investigator's manual and informed consent document provide additional detailed information on the risks and benefits for participants in this clinical study.

3 Objectives/hypotheses and evaluation criteria

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3.1 Primary objective

- To evaluate the efficacy of Richmond Extended-Release Nifedipine 30 mg versus Extended-Release Nifedipine 30 mg, a comparator currently registered in Colombia, as measured by the proportion of patients with blood pressure control in adult patients diagnosed with mild or moderate hypertension at week 8 of follow-up.

Endpoint: Blood pressure control (SBP/DBP) at 8 weeks of follow-up

3.2 Secondary objectives

- To evaluate the efficacy of Nifedipine 30 mg Extended Release Richmond versus Nifedipine 30 mg Extended Release comparator with current registration in Colombia, measured by the proportion of patients with blood pressure control in adult patients diagnosed with mild or moderate hypertension at week 4 of follow-up

Endpoint: Blood pressure control (SBP/DBP) at 4 weeks of follow-up

- Evaluate the safety of Nifedipine 30mg Extended Release Richmond versus active comparator measured by the proportion of adverse events identified during follow-up.

Endpoint: Cumulative safety data

- Evaluate the safety of Nifedipine 30mg Extended Release Richmond versus active comparator measured by the proportion of serious adverse events identified during follow-up.

Endpoint: Cumulative safety data

4 Study design

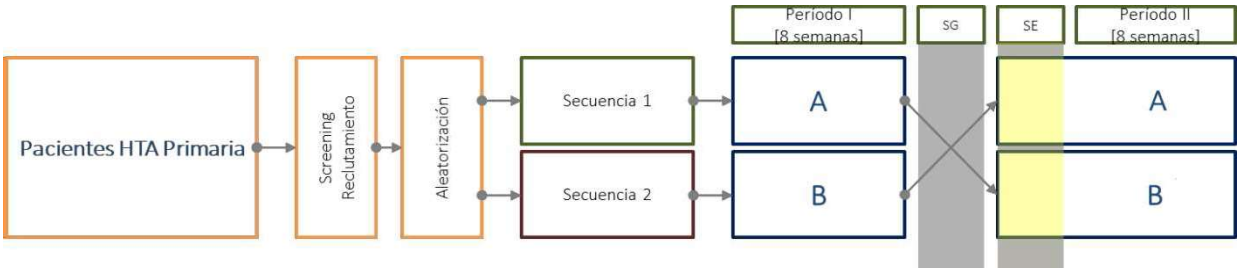
- Randomized, controlled, 2x2 crossover, phase III, non-inferiority clinical trial to evaluate the efficacy and safety of Nifedipine 30mg extended release Richmond via oral administration VS. Comparator via oral administration, in patients with primary hypertension, at a referral clinic in the city of Bogotá.

Target population: Patients with hypertension with normal blood pressure readings (SBP < 140 mmHg or DBP < 90 mmHg)

Source of subjects: Subjects participating in the study will be selected in doctors' offices, medication delivery points, and the community at large. After explaining the study to be conducted, its risks and benefits, verifying the inclusion and exclusion criteria, performing a medical evaluation, reviewing the results of screening studies, and obtaining informed consent.

4.1 Study diagram

Figure 1. 2x2x2 crossover design, two formulations, two periods, and two sequences.



GS: Group Switch, SS: Statistical Silence

4.2 Sample

4.2.1 Design

Random assignment of subjects taken consecutively or sequentially from patients who meet the selection criteria, with an enrollment period of 6 months, to achieve the minimum adequate sample size

Sample size.

The sample size was estimated for the non-inferiority crossover study.
When comparing Richmond oral VS. oral comparator, in patients diagnosed with mild or moderate hypertension, who entered the study baseline with controlled blood pressure readings (SBP < 140 or DBP < 90 mmHg), where a maximum change of 3.0 mmHg was taken as the maximum level of change between the two treatments in SBP and DBP, for the hypothesis of non-inferiority in blood pressure control, to an alternative tail taking a 2.5% significance level with 90% power, with a standard deviation of the difference in means of 6 mmHg, the sample size is n=44 pairs (88 subjects in 44 patients) and with a 10% loss adjustment of 50 pairs (100 subjects in 50 patients), with a 1:1 ratio.

4.3 Definition of study start and end

The overall study begins when the first participant signs the informed consent form and ends when the last participant completes the last study-related visit and/or phone call, withdraws from the study, or is lost to follow-up (investigator is unable to contact the research volunteer).

4.3.1 Clinical criteria for early termination of the study

Based on the recommendations, the study will be terminated early when serious adverse effects such as arrhythmias, angina pectoris, palpitations, pulmonary edema, allergic hepatitis, aplastic anemia, Steven-Johnson syndrome, pemphigus, or phototoxicity occur (see Investigator's Manual).

These conditions will be identified as clinical endpoints in which the benefit/risk ratio for the study population is unacceptable.

4.4 Endpoints

4.4.1 Efficacy endpoints

- Percentage of patients with controlled blood pressure (SBP ≤ 140 mmHg / DBP ≤ 90 mmHg) from baseline to 4 and 8 weeks
- Distribution of changes in HTN classification, from baseline to 4 and 8 months
- Changes in PAS, PAD, and PAM from baseline to weeks 4 and 8 between Richmond 30 mg extended-release nifedipine administered orally vs. comparator administered orally

4.4.2 Safety endpoints

- Proportion of patients experiencing serious adverse events overall and by type of serious adverse event [time frame: 4 and 8 weeks]
- Proportion of patients experiencing non-serious events overall and by type of non-serious adverse event [time frame: 4 and 8 weeks]

Safety will be assessed by monitoring adverse events and laboratory tests. Subjects will be asked about any unexpected symptoms or occurrences during the study. All adverse events, regardless of severity or relationship to the study drug, will be recorded on case report forms.
The safety and tolerability of the drug will be evaluated through clinical assessment of AEs and verification of other parameters, including vital signs, physical examination, electrocardiogram, and clinical laboratory results at defined follow-up times, according to the study's SoA activity schedule.

Adverse events are evaluated and recorded according to a defined institutional procedure (P-INV-02: Adverse Events in Clinical Research). Participants may be asked to attend unscheduled visits for additional safety monitoring.

4.4.3 Rationale for use of comparator

Given the notification of shortage reported by the manufacturer of the *gold* standard reference product (ADALAT OROS®), the nifedipine product with a similar galenic form that has a valid INVIMA health registration in this case, Nifedipine 30mg Extended Release, will be used as a comparator.

4.5 Justification of the dose

The clinical study will evaluate the use of extended-release nifedipine at a daily dose of 30mg, established by the treating physician's clinical criteria, as monotherapy or in combination with another antihypertensive agent.

5 Study population

5.1 Inclusion criteria

- Men or women aged 18 years or older
- Confirmed diagnosis of mild-moderate primary hypertension according to the ESC/ESH Guidelines(12), WITH BLOOD PRESSURE READINGS OF SBP < 140 OR DBP < 90 mmHg
- Patients with blood pressure control during the last 4 weeks of inclusion, verified by medical history, according to ESC/ESH Guidelines(12) criteria.
- Use of nifedipine as preferred monotherapy or in combination therapy according to clinical criteria (maintaining the combination during the study without changing the dose of nifedipine or the concomitant medications with which the patient is already being treated)
- Voluntary participation by providing written informed consent.

5.2 Exclusion criteria

- Contraindication for the use of nifedipine according to the safety profile established in the literature (Investigator's Manual).
-
- History of hypertensive encephalopathy documented in medical records.

- Evidence of secondary hypertension such as aortic coarctation, pheochromocytoma, hyperaldosteronism, except for controlled hypothyroidism-hyperthyroidism and obstructive sleep apnea
- History of a diagnosis or condition that, in the investigator's opinion, may affect patient safety.
- History of severe allergies to any drug
- Subject with heart failure, New York Heart Association (NYHA) class III or IV
- Severe coronary artery disease manifested by a history of myocardial infarction or unstable angina in the last 6 months prior to visit 1.
- Heart valve disease "Valvular heart disease with symptoms (dyspnea, syncope, or precordial pain) documented by current medical history."
- History of malignancy in the last 5 years, excluding skin or basal cell cancer
- Surgical or medical conditions that may alter the metabolism, excretion, distribution, or absorption of any drug.
    - Gastrointestinal disease or surgery that may result in malabsorption.
    - Severe narrowing of the gastrointestinal tract; Kock's pouch (ileostomy after proctocolectomy)
    - Cholestasis or biliary obstruction or history of pancreatic injury or clinically significant increase in lipase, amylase, or bilirubin.
    - Transaminase levels (AST and ALT) > 3 x ULN
    - Renal failure, defined as eGFR <30 mL/min (calculated using the Cockroft-Gault formula) or on hemodialysis

- Participation in another research trial
- Pregnant women
- Subjects with an aortic aneurysm who, in the opinion of the investigator, are not suitable for inclusion in the study.
- Considered by the investigator for any reason to be unsuitable for participation in a clinical study
- : such as everolimus and pimozide. History of noncompliance, alcoholism, or drug abuse that, in the investigator's opinion, will compromise the successful completion of the study.
- Use and indication of the following medications: alosetron, cisapride, anti-obesity preparations (fenfluramide, dexfenfluramide, phentermine), troglitazone, systemic anabolics, coagulation factors, doxazosin, terbinafine, isotretinoin, itraconazole, celecoxib, phenytoin, centrally acting sympathomimetic drugs, mefloquine, phenylpropanolamine.

5.3 Lifestyle restrictions

No lifestyle restrictions are required for the study procedures.

5.3.1 Meals and dietary restrictions

Participants should avoid consuming grapefruit, including juices and foods containing grapefruit, due to the interaction between its components and nifedipine (see Investigator's Manual).

5.4 Participants who were not selected

Participants who do not pass the selection phase are defined as participants who give their informed consent to undergo screening but are not included in the study. Minimal information is required on these cases to ensure transparent reporting of the study stages in compliance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines (24) and regulatory authority inquiries. Information on this group includes demographic data and criteria for non-inclusion in the study.

5.5 Participant replacement strategy

Participants who discontinue their participation in the study will not be replaced.

6 Treatment

Treatment in the study is defined as any investigational treatment, marketed product, or placebo intended to be administered to a study participant according to the study protocol.

6.1 Treatments administered

Product: 910002
The study treatments to be used in this trial will be provided by the sponsor and are described below:

- Richmond 30 mg extended-release nifedipine, administered orally

Either as monotherapy or in combination with another antihypertensive agent according to the pharmacotherapeutic management established by the treating physician in accordance with the clinical history and blood pressure readings. No changes will be made to treatments within the framework of the research, and the antihypertensive combination will be maintained throughout the study period.

- Nifedipine 30 mg extended release Comparator orally

o As monotherapy or in combination with another antihypertensive agent according to the pharmacotherapeutic management established by the treating physician based on clinical history and blood pressure readings. No changes will be made to treatments within the framework of the investigation, and the antihypertensive combination will be maintained throughout the study period.

6.2 Treatment allocation method

Randomization/treatment assignment will be performed in permuted blocks at the research center by a person assigned and qualified for this activity who is not involved in the clinical evaluation of the participant, according to the following procedure (Figure 1):

- **Group A:** 8 weeks of treatment with Nifedipine Richmond New Formulation —-
  -- 8 weeks of treatment with reference product (the first 2 weeks will be included for statistical silence).

- **Group B:** 8 weeks of treatment with reference product[1] ----------8 weeks of treatment with Nifedipine Richmond (the first 2 weeks will be included for statistical silence).

The random assignment method is by permuted blocks, where the random sequence will be taken between study groups A and B. The sequence will be carried out taking into account permutations 1. AB and 2. BA.

The random selection will use the random function (RANDOM: uniform distribution between 0 and 1) and the randomly selected sequence will be obtained using the equation RANDOM*2+1, taking the integer part; in the EXCEL Office 365 program.

Table 2. Random sequence list

Patient	Random	Randomx2+1	Sequence selected	Assigned sequence
1	0.67511186	2.350223724	2	BA
2	0.63655793	2.273115864	2	BA
3	0.82005771	2.640115417	2	BA

Product: 910002

4	0.75238537	2.504770731	2	BA
5	0.27060773	1.541215464	1	AB
6	0.13509461	1.27018922	1	AB
7	0.0059008	1.011801603	1	AB
8	0.00522046	1.01044092	1	AB
9	0.57459303	2.149186066	2	BA
10	0.13413163	1.268263257	1	AB
11	0.46855475	1.937109506	1	AB
12	0.43792582	1.875851646	1	AB
13	0.92905912	2.858118233	2	BA
14	0.76263057	2.525261134	2	BA
15	0.59039799	2.180795977	2	BA
16	0.67106409	2.342128183	2	BA
17	0.57513717	2.150274349	2	BA
18	0.95687127	2.91374253	2	BA
19	0.87915414	2.758308274	2	BA
20	0.51677593	2.033551866	2	BA
21	0.37768148	1.755362968	1	AB
22	0.13192216	1.263844313	1	AB
23	0.42201985	1.84403969	1	AB
24	0.20962522	1.419250439	1	AB
25	0.20456967	1.409139347	1	AB
26	0.65660156	2.313203122	2	BA
27	0.54821573	2.096431466	2	BA
28	0.91311981	2.826239619	2	BA
29	0.09187709	1.183754176	1	AB
30	0.66954146	2.339082914	2	BA
31	0.56996805	2.139936106	2	BA
32	0.35135826	1.702716511	1	AB
33	0.31718197	1.634363941	1	AB
34	0.42369607	1.84739214	1	AB
35	0.82200106	2.644002116	2	BA
36	0.50705857	2.014117148	2	BA
37	0.05075322	1.101506442	1	AB
38	0.03452872	1.069057445	1	AB
39	0.5778017	2.155603408	2	BA
40	0.74539157	2.490783148	2	BA
41	0.4633266	1.926653207	1	AB
42	0.6429415	2.285882992	2	BA
43	0.58347941	2.166958827	2	BA
44	0.80208274	2.604165476	2	BA
45	0.73496442	2.469928848	2	BA
46	0.37694131	1.753882624	1	AB

Product: 910002

47	0.98503347	2.970066934	2	BA
48	0.64999045	2.299980891	2	BA
49	0.38904254	1.778085075	1	AB
50	0.37535928	1.750718554	1	AB

The Principal Investigator or a member of the research team who is trained, authorized, and supervised by the PI is responsible for ensuring that randomization instructions at the research center are carried out correctly in accordance with the protocol. The investigator must follow the randomization procedures in accordance with the protocol and the randomization allocation system and must ensure that the code is only opened in accordance with the protocol. Likewise, they must keep a record of the randomization procedure, which must be recorded in the medical record, in the Investigator's File, and in the Research File (I-INV-07: Randomization of Patients for Clinical Research at Méderi).

6.3 Blinding

Double-blind masking will be performed. Oral formulations will be packaged identically so that treatment masking is maintained; thus, the patient volunteer, the investigator, and the personnel involved in the clinical evaluation of the participants will not know the group assignments. The research pharmacist will have information about the coding and identification of the test and reference drugs according to the protocol for delivery of 30 mg extended-release nifedipine samples for safety and efficacy study (Appendix 6).

6.4 Preparation/handling/storage/accounting

6.4.1 Dose preparation

Participants will receive blinded boxes of Nifedipine 30 mg for the study period (F-FAR-35: Research Product Dispensing).

Additionally, participants will receive the usual complementary antihypertensive management in case combination therapy is required. The dispensing of this medication will be guaranteed without modifications so as not to introduce bias into the study due to changes in the manufacturer's laboratory or administrative issues that prevent the continuity of the prescribed treatment.

Both nifedipine 30 mg [study and comparator] and concomitant antihypertensive medications will be provided by the sponsor for the conduct of the study.

6.4.2 Handling, storage, and accounting

The investigator or designated person must ensure that

of appropriate temperature and humidity during the handling of all study treatments received, and any discrepancies shall be reported and resolved prior to use.

Only participants included in the research may receive the study treatment, which may only be administered by personnel authorized by the research center. All treatments shall be stored in a secure area with restricted access and with the respective humidity and temperature controls recorded in accordance with the specific conditions required by the product, according to the procedures indicated in the quality document established by the research center (P-FAR-20: Receipt, Storage, Dispensing, and Inventory Control of Investigational Products). Additionally, the investigator and the research center will be responsible for accounting, reconciliation, and maintenance of study treatment records (receipt, reconciliation, and final destination registration) reported in the corresponding documentation.

The research center is responsible for the technical receipt of research products, ensuring compliance with quality requirements and recording the batch number, manufacturer, and date of all products purchased in accordance with local regulatory guidelines. It should be noted that all activities related to the receipt, storage, dispensing, and inventory control of research products are carried out in the designated area of the institution's pharmaceutical service.

The investigator is responsible for taking the necessary measures to maintain adequate records and ensure that the supply, storage, handling, distribution, and use of study treatments are appropriate in accordance with the protocol and applicable regulations.

6.5 Treatment compliance

The investigator or assigned staff will train the participant in the use of the medication, blood pressure monitor, and medication and blood pressure log. The participant will be instructed to record the number of study treatment capsules and/or tablets and antihypertensive combination therapy tablets taken during the study period.

At follow-up visits, participants will be instructed to return any unused treatment, and the accuracy of the medication diary will be verified by comparing the data entered with the amounts of study treatment returned. If any discrepancies are noted, the investigator/coordinator should discuss the discrepancy with the participant and document the detailed explanation in the study records.

6.6 Concomitant treatment

The investigator should review each medication (prescribed or not) that the participant is receiving before starting the study and at each follow-up visit. Verification will be performed by asking the participant about any current or new medications they are using, and a respective interaction analysis will be performed so that the necessary actions can be taken to minimize the risk of response modification due to concomitant use with other medications. The investigator will inform the participant of the

Importance of reporting new therapies or modifications in the use of current drugs for the proper conduct of research.

During the screening procedure, the patient's pharmacotherapy will be verified in order to identify drugs whose concomitant use may generate an interaction (defined in the Investigator's Manual) and which are defined as exclusion criteria.

6.7 Treatment after completion of the study

No specific treatment is defined for after the end of the study. The investigator will inform the participant of the need to continue with their usual drug management as recommended by their treating physician.

7 Criteria for discontinuation of treatment/withdrawal of the participant

Patients have the right to withdraw from the study at any time during its course and for any reason.

They may also be withdrawn from the study at the investigator's discretion for the following reasons:

- Adverse events that the investigator determines are possibly or probably related to the study treatment.
- Failure to comply with the administration of the dose, evaluations, and other requirements defined by the study.
- Confirmation of pregnancy
- Personal circumstances of the participant which, in the opinion of the investigator and/or sponsor, make continued participation in the study a necessary risk for the participant, or do not allow the participant to comply with the requirements of the protocol.

Once the participant's definitive withdrawal has been determined, they will be removed from the study and will not be allowed to re-enter.

7.1 Loss of contact with the participant during follow-up

If the participant does not attend the research center for the required visits according to the schedule, the institutional instructions (I-INV-22: Follow-up of Lost Subjects in Clinical Research Studies) will be followed and the following activities will be carried out:

- The researcher/coordinator should attempt to contact the participant and schedule a missed visit. During contact with the participant, they should be advised on compliance with the instructions and controls required to ensure the proper conduct of the study.
- The investigator/coordinator should record the different strategies and attempts to contact the participant in the corresponding medical record.
- Evaluate the participant's withdrawal based on loss of contact and the participant's willingness to comply with the procedures defined in the protocol.

8 Study evaluations and procedures

8.1 General phases of execution

There are five phases for the execution of the clinical trial. The study procedures and the timing of their implementation are summarized in item 10 (Schedule of activities) and in Figure 2.

- **Recruitment:** Process of inviting volunteers to participate in clinical studies in areas where potential participants are concentrated (drug distribution centers, healthcare centers, etc.), identified among partner entities for the prioritization of strategies. The use of communication tools is proposed for the dissemination of the protocol, adherence tools or material, and the requirements for the recruitment of potential participants, which includes the selection criteria endorsed by the IRB according to institutional procedure (P-INV-24: Strategy for Recruitment, Selection, and Adherence of Volunteers for Clinical Research).

- **Screening:** Potential volunteers are identified and an initial approach is made. If a favorable response is obtained, the informed consent process for this phase is carried out, a participant identification card is issued, and medical assessment procedures, BMI, and sample collection for clinical laboratory analysis are performed.

- **Selection:** Based on the analysis of screening results, volunteers who meet the selection criteria established in this protocol will be identified and contacted. The first visit will be made, during which the researcher will talk to the potential participant, explaining the nature of the study, the requirements, and/or restrictions. Subsequently, the informed consent process for inclusion in the clinical study will be carried out, followed by the recording of general data and medical evaluation with initial recording of variables: sex, age, BMI, cardiovascular risk factors (family history of heart disease, hyperlipidemia, diabetes mellitus, abdominal obesity, smoking), comorbidities, previous treatment for HTN, concomitant medications, and laboratory results. At this stage, randomization is performed to define the study arm and corresponding medication dispensing according to sequence and delivery of follow-up items (digital blood pressure monitor, educational material, and daily log).

- **Follow-up of research volunteers:** The follow-up process will be carried out through visits every 4 weeks per medication studied (according to sequence 2 x 2). At visit 2 at the end of week 8, the study medication will be changed (group switch), and weeks 9 and 10 are identified as a statistical silence period. At the end of week 10, follow-up visit 3 will be carried out, in which the baseline conditions for medication B will be identified according to sequence, and follow-up visits 4 and 5 will then be carried out. During the follow-up visits, the schedule will be followed, with assessment by medicine, verification of adherence through counting of remaining medication units

of medication remaining, verification of blood pressure readings, exploration of adverse events according to medical evaluation, and verification of laboratory results (Appendix 2). All information obtained during the visits will be recorded in the study CRF. Adverse event reports will follow the established institutional route for reporting to the Research Ethics Committee (REC) and relevant institutions, as appropriate.

- **Home monitoring:** Using the digital blood pressure monitor provided by the study (sponsor) and the recording material (diaries), the patient will take daily blood pressure measurements in the morning according to the procedure given by the doctor during the initial visit and reinforced during follow-up visits. The research volunteer will be instructed on the need to comply with recommendations regarding daily blood pressure measurements and recording them on the form designed for this purpose. In addition, warning signs will be reinforced for reporting and contacting the investigator during all visits. Reminder strategies will be implemented to ensure adherence to drug treatment and pharmacovigilance follow-up, such as messages and/or calls by the study coordinator on a weekly basis.
- **Study completion visit:** During weeks 19 and 20, study closure visits will be conducted, during which a final medical assessment will be performed.

During the study, the investigator is responsible for ensuring that procedures are performed by qualified and trained study personnel. The delegation of responsibilities of the study site personnel will be documented in the investigator's study folder.

All activities carried out during the selection process will be reviewed and recorded in the appropriate format to confirm compliance with eligibility criteria and documentation of basic information and reasons for non-selection.

The investigator may consider performing additional tests or evaluations for patient safety reasons, to be carried out in accordance with current regulations under good clinical practice criteria.

8.2 General procedures

8.2.1 Informed consent

The researcher or designated person (qualified and trained) will carry out the informed consent process, obtaining the documented consent of each potential participant prior to their participation in the study, in accordance with institutional procedure P-INV-03: Informed Consent for Clinical Research.

Consent will be documented on a specific research form, in a version approved by the Research Ethics Committee (REC), dated and signed by the participant,

witnesses, and the person in charge of the consent process. A copy of the document will be given to the participant.

In the event of any modification or additional information, the new version will be submitted for verification and endorsement by the IRB. If this information is relevant to the participant's decision to continue in the study, it must be communicated to them in a timely manner. The process will be documented using a modified informed consent form, a copy of which will be given to the participant.

The delivery of the copy of the form will be documented in an institutional document (F-INV-05: Proof of Delivery of Informed Consent) in which the study identification, research participant data, and signature of receipt of the consent copy will be recorded.

Two moments are defined for the informed consent process: a consent document for the screening process and another for the participant's effective inclusion in the research.

8.2.2 Verification of inclusion/exclusion criteria

The investigator or designated qualified and trained person will review the selection criteria to ensure that the participant meets the inclusion criteria and does not meet any of the exclusion criteria so that the participant can be included in the study and proceed with randomization and the initial visit.

8.2.3 Participant identification card

All participants will receive a "Participant Identification Card" document that will identify them as participants in the research study. This document will contain:

- Research Center Information
- Unique treatment number (included after randomization)

The investigator or designated person will provide instructions for using the card, which must be carried by the participant at all times and presented in case of an emergency or health service requirement.

8.2.4 Medical history assessment

During the selection process, the investigator or designated person qualified and trained in research must obtain and record medical history for evaluation and analysis.

8.2.5 Review of previous and concomitant medications

The investigator or designated person qualified and trained in the research will verify the use of medications (prescribed or not) used during the 30 days preceding

randomization. All medications that the participant is using at the time of selection will also be recorded.

8.2.6 Assignment of selection number

All participants who have given their written informed consent for the screening process will be assigned a unique selection number that will be used to identify them during the procedures to be performed prior to randomization. These numbers are unique and will not be reused for other participants during the study.

8.2.7 Treatment number assignment/randomization

After the screening phase and following the assignment of selection numbers, the centralized randomization process will be carried out by the person assigned by the research center, trained and qualified for this purpose, and the randomization number will be delivered and treatment assignment will be carried out.

8.2.8 Treatment administration

During the initial visit, the research pharmacist will deliver a masked box according to the participant's treatment assignment. The first study dose, corresponding to day 1, will be administered at the research center, at which time instructions will be given for home use for the following days, during which the participant will self-administer the medications.

The instructions given during the initial and follow-up visits, based on the information provided by the research pharmacist, will focus on three items:

- **Schedules**: Medications should be taken at approximately the same time every day (each participant's medication-taking habits will be evaluated so that the instructions encourage adherence to treatment based on lifestyle). Medications should not be chewed, crushed, or divided; they should preferably be taken with water and on an empty stomach.

- **Missed doses**: If the participant misses/forgets a dose of medication, despite reminder strategies, they should take the missed dose as soon as possible on the same day. If more than 12 hours have passed since the scheduled time, they should wait until the next dose and take a regular dose. They should not take extra medication to make up for the missed dose.

- **Storage**: Medications should be stored in a cool, dry place (below 30°C), protected from direct light, and kept in a tightly closed container.

8.3 Blood pressure measurement

Blood pressure readings will be taken by the researcher or a designated person qualified and trained in the study during the initial, follow-up, and final visits defined in the research schedule. DBP and SBP will be taken during each visit, with the patient seated, on the left arm, following WHO recommendations and using Korotkoff sounds.

Participants will be asked to measure and record their blood pressure at home during the study period using the calibrated digital blood pressure monitor provided by the researcher, following these recommendations for taking measurements:

- Take measurements on the left arm with the blood pressure monitor provided by the researcher.
- Sit in a comfortable chair for three to five minutes with the upper arm at heart level before taking a measurement.
- Do not exercise or engage in any other activity that requires cardiovascular effort prior to taking the measurement.
- Do not eat immediately before the reading, avoid consuming energy drinks such as coffee, tea, or soda.
- Take three readings at intervals of 1 to 2 minutes.
- Take the measurement once a day, at a time when you are not under stress, preferably when you wake up.
- Record the measurements in the blood pressure diary provided by the study.

8.4 Follow-up visits

The follow-up process will be carried out through visits every 4 weeks for each drug studied (according to the 2x2 sequence). At visit 2, at the end of week 8, the study drug will be switched (group switch) and weeks 9 and 10 will be identified as a statistical silence period. At the end of week 10, follow-up visit 3 will be conducted, in which the baseline conditions for medication B will be identified according to sequence, and follow-up visits 4 and 5 will then be conducted.

During these visits, efficacy and safety will be evaluated based on physical assessment, laboratory results, and safety reports identified and/or followed up during the consultation.

To encourage adherence to the clinical study, the sponsor will offer gifts to participants, such as notebooks, pens, cups, thermal blankets, briefcases, gym vouchers, healthy cooking courses, and lifestyle courses.

8.4.1 Withdrawal/discontinuation

If the participant decides to discontinue treatment and withdraw from the study, the investigator must carry out all activities required for the early discontinuation visit, performing the corresponding medical assessment and follow-up of all adverse events present at the time of withdrawal. All activities will be documented

by the principal investigator in the research medical record and corresponding CRF. In addition, the event reporting process will be followed as appropriate (P-INV-02 Reporting of Adverse Events and Serious Adverse Events in Research).

8.4.2 Unblinding in clinical research

In the event of an emergency situation in which the investigator or delegate needs to identify the treatment assigned to the participant, the established institutional procedure will be followed (P-INV-12: Unblinding). The treating physician may request immediate medical information about the patient in the event of a medical emergency in order to optimize clinical management. The investigator will review the physician's request and, if the clinical decision takes a different course of action based on the results, unblinding will be permitted.

The principal investigator will immediately notify the sponsor and proceed with communicating with the person responsible for randomization at the research center to perform the unblinding.

The entire process will be documented in the corresponding medical record, describing the circumstances surrounding the unblinding (date, reason, and person requesting and performing the unblinding), and notification of the report will be sent to the Ethics Committee by the principal investigator or study coordinator.

8.5 Efficacy assessments

Blood pressure control will be assessed at all visits from selection to the final visit. To assess the efficacy of the medication, blood pressure will be measured using a control criterion of SBP/DBP below 140/90 mmHg.

At each check-up, blood pressure and vital signs, weight, and height will be assessed, and laboratory tests will be requested at the beginning of the study and at the end of each cycle, in accordance with guidelines for monitoring patients diagnosed with high blood pressure.

8.5.1 Physical examination

A complete physical examination will be performed at the initial, follow-up, and final medical visits (inspection, palpation, auscultation, and percussion). The investigator may request a specific physical examination if the participant presents any symptoms.

8.5.2 Weight and height assessment

The patient's weight and height should be assessed at the start of the study and at the end of each cycle.

8.5.3 Vital signs

Vital signs will be checked at the initial, follow-up, and final visits. These include measurement of heart rate , respiratory rate , body body

(preferably oral).

8.5.4 Electrocardiogram

Twelve-lead ECGs will be performed at the start and end of each cycle. They will be interpreted at the research center by the investigator.

8.5.5 Adverse event monitoring

Adverse event monitoring will include the collection of all AEs and SAEs identified from the signing of the informed consent form until the closing visit.

8.5.6 Clinical laboratory evaluation

Clinical laboratory tests will be performed during screening and at the baseline, follow-up at the end of each cycle, and closing visits (see Appendix 2).

The investigator will review the results, record the data, and document all clinically significant changes identified. All laboratory tests will be performed according to the institution's defined operating procedures.

If laboratory results with abnormal values considered clinically significant are identified, the necessary repetitions must be performed to follow up until normalization or return to baseline values.

8.6 Treatment of overdose (25,26)

8.6.1 Symptoms

Symptoms associated with severe nifedipine poisoning are defined as: Altered consciousness to the point of coma, decreased blood pressure, tachycardia, bradycardia, hyperglycemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary edema.

8.6.2 Treatment

Priority should be given to eliminating nifedipine and restoring stable cardiovascular conditions. Elimination should be as complete as possible, including from the small intestine, to prevent further absorption of the active ingredient.

The following indications should be considered:

i. Use of activated charcoal (50 g for adults) if the patient presents within one hour of ingesting a potentially toxic amount. Although it may seem reasonable to assume that delayed administration of activated charcoal may be beneficial for sustained-release (SR, MR) preparations, there is no evidence to support this.

ii. Alternatively, consider gastric lavage in adults within one hour of a potentially fatal overdose.

iii. Consider additional doses of activated charcoal every 4 hours if a clinically significant amount of a sustained-release preparation with a single dose of an osmotic laxative has been ingested.

iv. Asymptomatic patients should be observed for at least 4 hours after ingestion and for 12 hours if a sustained-release preparation has been taken.

Hypotension resulting from cardiogenic shock and arterial vasodilation may be treated with calcium (10-20 mL of a 10% calcium gluconate solution administered intravenously over 5-10 minutes). If the effects are inadequate, treatment may be continued with ECG monitoring. If an insufficient increase in blood pressure is achieved with calcium, vasoconstrictive sympathomimetics such as dopamine or norepinephrine should be administered. The dose of these drugs should be determined by the patient's response.

Symptomatic bradycardia may be treated with atropine, beta-sympathomimetics, or a temporary cardiac pacemaker, as necessary.

Additional fluids should be administered with caution to avoid cardiac overload.

8.6.3 Adverse events, serious adverse events, and other safety events requiring notification

AEs, SAEs, and other safety events requiring notification shall be reported by the participant to the investigator and/or designated, qualified, and trained personnel during medical visits and/or follow-up calls. The investigator and designated personnel are responsible for detecting, evaluating, documenting, and reporting events that meet the definitions of AEs, SAEs, and other safety events requiring reporting.

The definitions of adverse event (AE) and serious adverse event (SAE), as well as the processes and formats for recording and reporting, are described in Appendix 3. All serious and non-serious adverse events are defined as events of clinical interest (ECI).

8.6.4 Time period, frequency, and method for obtaining information on AEs, SAEs, and other safety events that require notification and follow-up

I. The collection of information on AEs, SAEs, and other reportable safety events is defined from the signing of the informed consent form and assignment of treatment to the closing visit and will be reported by the investigator.

II. The preferred method for obtaining information on AEs is oral questioning of the participant, using open-ended, non-leading questions to avoid any bias in the detection of AEs/SAEs/other safety events.

III. Once the initial notification of AE/SAE/other safety events has been made, the

investigator will be responsible for following up with each participant through visits and phone calls. Safety events requiring notification must be followed up until resolution, stabilization, or identification of another explanation. It is essential that the investigator follow up on all events to determine their outcome.

8.6.5 Regulatory reporting requirements for SAEs

Legal and ethical obligations will be fulfilled by IMMEDIATE notification of SAEs (within 24 hours) by the investigator to the sponsor.

The sponsor has a legal responsibility to notify the relevant local regulatory authority of safety events related to the study treatment.

All adverse events will be reported to the regulatory authority, IRB, and investigators following the guidelines established in applicable legislation and regulations (E6[R1]-ICH; F-INV-22: Reporting and Follow-up of Adverse Events in Clinical Research).

Unexpected serious adverse reactions must be reported in a safety report prepared by the investigator in accordance with regulatory requirements and sponsor policy.

8.6.6 Events related to the disease and/or disease-related outcomes not classifiable as AEs or SAEs

Events that cannot be classified as AEs or SAEs should be collected throughout the study period. Events that constitute efficacy evaluation criteria will be evaluated by determining severity and causality.

8.6.7 Pregnancy and exposure during breastfeeding

Pregnancy and breastfeeding are not considered adverse events; however, they are grounds for exclusion from the study. Upon spontaneous communication to the investigator or identification of pregnancy by a test performed during follow-up, the sponsor shall be notified.

Reported cases will be followed up until completion, identifying the outcome (full-term pregnancy, termination, etc.).

9 Statistical analysis plan

The statistical analysis procedures and strategies proposed for the research protocol are presented below. Any modifications related to the evaluation criteria or analysis methods proposed during the course of the study and before unblinding will be submitted as an amendment to the protocol for approval by the IRB. If the modification is proposed after the study has been completed and before unblinding, it will be mentioned in the clinical study report identified as a complementary statistical analysis.

9.1 Summary of statistical analysis plan

Product: 910002

Design	Phase III, randomized, active-controlled clinical trial to evaluate the efficacy and safety of Nifedipine 30 mg extended-release in adult patients diagnosed with mild or moderate hypertension in Colombia.
Randomization	Permuted blocks, 1:1 ratio
Blinding	Double-blind
Analysis population	Efficacy assessment: Intention-to-treat (ITT) analysis Safety assessment: Analysis of patients treated (ASaT)
Criteria for Primary	Criteria
Secondary of assessment	Proportion of patients achieving the blood pressure control target (<140/90 mmHg) at week 4 of follow-up. Proportion of patients experiencing serious and non-serious adverse events at week 8 of follow-up.
Statistical methods for for efficacy analysis	Difference in mean SBP and DBP from baseline to weeks 4 and 8 Significance value and 95% CI for difference in mean SBP and DBP from baseline to 4 and 8 weeks between the two treatments (repeated measures ANOVA). p-value or significance value and 95% CI for differences between the proportions of normal blood pressure readings (<140/90 mmHg) at 4 and 8 weeks between treatments using McNemar's chi-square test for differences in proportions with and without continuity correction or Fisher's exact test for paired designs (expected values < 5).
Statistical methods for for safety analysis	Percentage of serious and non-serious adverse events between treatments and percentage by type of adverse event for each treatment (descriptive).
Size and power of the sample	A sample size of 50 patients is defined, each patient = 2 study subjects.

	For a maximum change of 3 mmHg between the two treatments, with 90% power, 95% reliability, and 10% losses, a 1:1 ratio, and a sample size of 50:50 (1 patient = 2 study subjects).

9.2 Responsibility for analysis/internal blinding

The statistical analysis proposed for this study will be the responsibility of the center's research biostatistician. Blinding will be maintained until the data have been declared final and complete, i.e., after medical/scientific evaluation and identification of protocol deviations.

9.3 Endpoints for analysis

9.3.1 Efficacy evaluation criteria

The primary efficacy endpoint will be the proportion of participants who achieve blood pressure control, i.e., below the threshold of 140/90 mmHg at week 8 of follow-up.

9.3.2 Safety evaluation criteria

The following are defined as safety evaluation criteria:

- Proportion of participants who experience a drug-related adverse event during the study period
- Proportion of participants who experience a SERIOUS adverse event related to the drug during the study period
- Proportion of participants experiencing an adverse event
- Proportion of participants experiencing a SERIOUS adverse event

Adverse events will be recorded until the final visit in weeks 19-20 of the study.

9.4 Populations for analysis

9.4.1 Population for efficacy analysis

The total randomized population will be analyzed for the efficacy analysis (Intention-to-Treat-ITT). Additionally, a per-protocol (PP) analysis is proposed as a complementary analysis, in which the population is analyzed excluding participants with identified significant protocol deviations that could significantly affect the efficacy assessment, specifically, non-compliance in drug administration (non-adherence to treatment identified in follow-up visits by counting units and recording in a diary).

9.4.2 Population for safety analysis

The total randomized population that received at least one dose of study treatment (*All-Subjects-as-Treated* - AsaT) will be analyzed.

9.5 Statistical methods

9.5.1 Statistical methods for efficacy analysis

9.5.1.1 Primary efficacy analysis

The difference in means and **95% CI** for **SBP and DBP** between the two treatments will be evaluated before and after the intervention at 4 and 8 months, using a fixed-effects repeated measures ANOVA and a Grizzle mixed linear model ANOVA for two crossover periods to adjust for possible carryover effects. The normality of SBP and DBP will be evaluated beforehand at baseline and at 4 and 8 weeks using the Shapiro-Wilk normality test.

The differences in the proportions of subjects with normal blood pressure readings (SBP < 140 or DBP < 90) at 4 and 8 weeks will be evaluated using McNemar's chi-square test for differences in proportions with and without continuity correction or Fisher's exact test for paired designs (expected values < 5).

9.5.1.2 Secondary efficacy analysis

The percentage of serious and non-serious adverse events and the type of event will be measured for each treatment (descriptive).

Handling of missing data

Two types of missing data are defined:

- Intermittent losses (IL): resulting from missed visits that have no bearing on the primary efficacy endpoint.

- Monotonic losses (ML): due to early withdrawal of the participant.

The analysis of missing data to be used as the main method will be Observed Failure (in the case of IL, the data will be excluded; in the case of ML, it will be considered without failure). The method of identifying failure as a participant who did not complete follow-up will be used as a backup method for secondary analysis.

9.5.2 Statistical methods for safety analysis

Safety will be evaluated using inferential analysis to determine the statistical significance of comparisons between treatment groups, indicating p-values and 95% CIs for the evaluation of the proportion of patients who experienced an AE or SAE related or unrelated to the study drug.

9.5.3 Summaries of baseline characteristics, demographics, and other analyses

Relevant characteristics will be evaluated by treatment group using descriptive statistics, presenting the number and percentage of participants.

The selected, randomized population and the main reasons for non-compliance for selection and reasons for discontinuation/withdrawal will be indicated.

Demographic variables such as age and sex, baseline characteristics, previous and concomitant treatments will be summarized using descriptive statistics for continuous or categorical variables, as appropriate.

9.6 Sample size calculation and sample power

The primary endpoint is defined as a maximum change of 3 mmHg between the two treatments, with a power of 90%, reliability of 95%, and losses of 10%, a 1:1 ratio, and a sample size of 50:50 (1 patient = 2 study subjects).

9.7 Subgroup analysis

To determine whether the treatment effect is consistent across different subgroups, the treatment effect estimate between groups for the primary efficacy endpoint will be analyzed according to:

- Age category (≤60 vs. >60 years)
- Gender (female, male)

Other clinically important variables may be identified for which other subgroup analyses may be performed. If the subgroup category contains fewer than 15 participants in any of the treatment groups, only descriptive statistics will be presented.

9.8 Compliance (Compliance with medication administration)

Compliance will be defined for each participant as the ratio of the number of days on treatment (on which the participant actually took the dose as reported in the diary and verified by counting at the follow-up visit) to the number of days from randomization to the last scheduled day according to the study or the last day of medication intake in case of interruption.

Compliance rates will be presented for each treatment group in a descriptive manner.

10 Information collection tools

All information derived from the screening and selection processes will be recorded in the participant's research medical record. This data, together with the reports made by the participant in the medication log and blood pressure readings, will be recorded

in the study CRF. Table 2 summarizes the variables to be recorded in the CRF.

Table 3. General study variables parameterized in the CRF.

Type	Variable	Description
ID	ID	Participant identification number in study
Demographics[1]	Gender	Female, Male
	Date of birth	Date of birth
	Age	Age measured in years reported at the time of inclusion
Background[1]	Reported diagnoses	Diabetes, Hypertension, Kidney Disease, Obesity Medications (prescription/non-prescription)
Selection criteria[2]	Record of verification of inclusion and exclusion criteria exclusion criteria	According to criteria defined in protocol
Clinical evaluation[3]	Date of care	Date of visits (according to research schedule)
	Weight	Weight measured in kilograms
	Height	Height measured in centimeters
	Waist diameter	Waist circumference measured in centimeters
	BMI	Body mass index
	Heart rate	Heart rate value
	Respiratory rate	Respiratory rate value
	Contraceptives	1. Yes 2. No
	Plasma BUN	BUN value
	Serum Creatinine	Creatinine value
	Blood Glucose	Blood glucose value
	Glycosylated Hb	Glycosylated hemoglobin value
	White blood cells	Leukocyte count
	Hematocrit	Hematocrit value
	Hemoglobin	Hemoglobin value
	Platelets	Platelet count
	Potassium	Potassium level
	SGOT	Transaminase
	SGPT	Transaminase
	Urinalysis	Description of urinalysis
	Gonadotropin qualitative	
	Total bilirubin	
	Sodium	
	TSH	
	Free T4	

	Alkaline phosphatase	
	Potassium	
	Hepatitis B	
	Chloride	
	Urea nitrogen	
	Electrocardiogram	Description of the electrocardiogram
Medication adherence[3]	Adherence report during study	Identified according to the procedure for counting units and reviewing the logbook by participant
Efficacy assessment criteria[4]	Blood Pressure Systolic	Systolic blood pressure measured in mm Hg
	Blood Pressure Diastolic	Diastolic blood pressure measured in mm Hg
Safety evaluation criteria[5]	Adverse events	Report of adverse event (serious/non-serious), type, causality analysis and severity, date of report, follow-ups, outcomes.

[1]Information obtained during the screening and selection process
[2] Parameterization of each selection criterion in order to identify the reasons for inclusion or exclusion from the study.
[3]Variables identified and recorded for each visit: start, follow-up, and closure
[4] Record of measurements broken down by source: doctor's visit [recorded in research medical history] and self-measurement by the patient [daily report record].
[4] Record of safety events identified during medical visits and weekly follow-up calls by the study coordinator.

11 Participant identification card

Clinical trial identification card

Keep this confidential document with you at all times while you are participating in the study.

Dear participant,

Show this card to doctors and/or nurses in the following cases:

- If you visit any other department or medical center other than the study center.
- If you are

hospitalized Dear Doctor,

This subject is currently enrolled in a study. Please contact the study physician if the subject experiences any adverse events, is hospitalized, or has questions about the subject's participation in the study.

Clinical trial identification card

Keep this confidential document with you at all times while you are participating in the study.

The bearer of this card is participating in a clinical research study.

Participant name: _____

Product: 910002
Product number: _____

Protocol number: _____

Evaluation number: _____

Randomization number: _____

Clinical trial identification card

Keep this confidential document with you at all times while you are participating in the study

In case of emergency, contact:

Research Center: Medical Care and Research Center - CAIMED Name of the research

physician: Paula Marcela Ochoa Castañeda

Phone number during business hours: 3175131016 24-hour

phone number: 3175131016

FOR HEALTHCARE PROVIDERS ONLY (When the investigating physician is unavailable): Backup phone number: 3175131016

Call center information

Your call will be answered by the principal investigator of the study or by a designated person trained to respond and provide assistance. This may take a few minutes, so please do not hang up.

12 Budget

13 Schedule of Activities (SoA)

Activity	ST	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14	S15	S16	S17	S18	S19	S20	Notes	
General procedures																							
Informed consent	X																						
Patient identification card	X																						
Selection criteria (inclusion/exclusion)	X																						
Medical history	X																						
Review of pharmacotherapeutic profile (history/concomitant medications)	X																						
Participant inclusion		X																					
Randomization/Treatment assignment		X																					
Informed dispensing of medication		X				X				X						X				X		Performed by a pharmaceutical research chemist	
Verification of adherence						X				X	X					X				X		Verification of adherence to antihypertensive treatment will be carried out by counting the units returned by the participant at the follow-up visit.	
Reminder strategies		X	X			X				X						X				X		Text messages and/or phone calls will be used to encourage adherence to antihypertensive treatment, blood pressure measurement, and the respective study journal entry.	

Product: 910002

Activity	ST	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14	S15	S16	S17	S18	S19	S20	Notes
Procedures Effectiveness*																						
Verification of voltage figures		X				X				X						X				X		The efficacy of the drug will be evaluated by measuring blood pressure readings. During the initial, follow-up, and final visits, the investigator will take the corresponding measurements according to the established protocol.
Safety procedures*																						
Medical evaluation	X	X				X				X						X				X		
Reading of paraclinical tests		X					X				X		X				X				X	
Pregnancy test	X	X				X				X		X				X				X		
Verification of signs and symptoms	X	X				X				X						X				X		
Clinical laboratories	X					X				X		X				X				X		
Electrocardiogram	X					X				X						X				X		
Adverse event monitoring			X			X		X		X	X					X	X	X		X		
TA logbook						X				X						X				X		
Closing																					X	

*Follow-up visits for efficacy and safety assessment procedures should be scheduled according to protocol guidelines. In case of participant non-attendance, these should be rescheduled within +-5 days according to the schedule.

Screening week (SW): identification of recruitment sites, communications logistics, selection criteria (inclusion/exclusion), medical history, review of pharmacotherapeutic profile (history/concomitant medications), Identification and approach to patients with Nifedipine, presentation of research protocol, verification of selection criteria, informed consent process, medical evolution, verification of signs and symptoms, clinical laboratory and electrocardiogram.

S1: Initial visit, participant inclusion, medical assessment, BP verification, therapeutic education, medical education, reading of paraclinical tests, pregnancy test (2), monitoring of adverse events. A pregnancy test is taken during the screening week and prior to administration of the medication due to possible hormonal changes.

S2: Reminder strategy, monitoring of adverse events by telephone call from the CAIMED study team within a 5-day window.

S5: Visit 1, corresponding to four weeks after dispensing the medication, medical assessment, BP check, therapeutic education, clinical laboratory tests, pregnancy test, electrocardiogram, monitoring of adverse events, dispensing of medication, monitoring of adverse events, and BP logbook. Verification of adherence

S6: During this week, the paraclinical tests taken in week five will be verified. If the patient shows any abnormalities, the study physician will contact the patient.

S9: Visit 2, corresponding to four weeks after dispensing the medication, medical assessment, BP check, therapeutic education, clinical laboratory tests, pregnancy test, electrocardiogram, monitoring of adverse events, dispensing of medication, monitoring of adverse events, and BP logbook. Verification of adherence

S10: Reminder strategy, monitoring of adverse events by telephone call from the CAIMED study team within a 5-day window. During that week, the paraclinical tests taken in week nine will be verified, and if the patient shows any abnormalities, the study physician will contact the patient.

S11: Visit 3: Follow-up visit 3 will be conducted to verify the baseline conditions for medication B according to the sequence. During this visit, a medical assessment, BP check, therapeutic education, clinical laboratory tests, pregnancy test, electrocardiogram, monitoring of adverse events, BP logbook, and adherence verification will be performed.

S12: During this week, the paraclinical tests taken in week five will be verified. If the patient presents any abnormalities, the study physician will contact the patient.

S15: Visit 4: corresponds to four weeks after dispensing medication B, medical assessment, BP check, therapeutic education, clinical laboratory tests, pregnancy test, electrocardiogram, monitoring of adverse events, medication dispensing, monitoring of adverse events, and BP logbook. Adherence check

S16: During this week, the paraclinical tests taken in week five will be verified. If the patient shows any abnormalities, the study physician will contact the patient.

S19: Visit 5: medical assessment, BP check, therapeutic education, clinical laboratory tests, pregnancy test, electrocardiogram, monitoring of adverse events, adherence check

S20: During this week, the paraclinical tests taken in week five will be verified. If the patient presents any abnormalities, the study physician will contact the patient. CLOSING

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15 Appendices

15.1 **Appendix 1:** Abbreviations

ALT Alanine aminotransferase
AsaT All-Subjects-as-Treated
AST Aspartate aminotransferase
BUN Blood urea nitrogen
REC Research Ethics Committee
CPK Creatine phosphokinase
IRB Institutional Review Board
CYP3A4 Cytochrome P450 3A4
AE Adverse event
SAE Serious Adverse Event
ACE Angiotensin-Converting Enzyme
ICF Informed Consent Form
CRF Clinical Record Form (e:electronic)
WBC White blood cells
RBC Red blood cells
hs-CRP High-sensitivity C-reactive protein
ICH International Council for Harmonization
IL interleukin
BMI Body mass index
ITT Intention to treat
LDH Lactate dehydrogenase
SOP Standard operating procedures
RAAS Renin-angiotensin-aldosterone system
SUSAR Suspected serious unexpected adverse reaction
eGFR Estimated glomerular filtration rate

15.2 **Appendix 2:** List of assessment and follow-up examinations for patients included in the clinical trial.

Assessment and follow-up examinations
Electrocardiogram
Complete blood count
Hepatitis B surface antigen [ag has]
Urea nitrogen
Creatinine in serum or other fluids
Glutamic-pyruvic transaminase or alanine aminotransferase
Glutamic oxaloacetic transaminase or aspartate aminotransferase
Alkaline phosphatase
Free T4
TSH
Blood glucose
Sodium

Potassium
Chloride
Total bilirubin
Urine analysis
Gonadotropin qualitative

15.3 **Appendix 3:** Adverse events: definitions and procedures for recording, evaluating, monitoring, and reporting

15.3.1 Definition AE

Information regarding AEs will be collected from the first dose of the study drug until the last visit inclusive. All AEs prior to randomization will be recorded in the medical history and retained in the patients' medical records.
Any sign or symptom defined in the protocol as a lack of efficacy or as an efficacy parameter (endpoint) will be entered as an AE in the CRF.

15.3.2 Definition of SAE

Serious adverse events (SAEs) are those that meet any of the following criteria of the International Council for Harmonization (ICH):

- It is fatal or immediately life-threatening;
- It results in persistent or significant disability/incapacity;
- Requires or prolongs hospitalization;
- Is an overdose (intentional or accidental);
- Is considered medically significant.

Medically important events may not immediately endanger the patient's life or cause death or hospitalization, but they may endanger the patient or require intervention to prevent one of the outcomes listed in the above definition.
If an AEFI occurs, study treatment may be interrupted or discontinued at the investigator's discretion. If an acute medical emergency occurs, the investigator should make every effort to verify the health event before breaking the randomization code.
The investigator will review the physician's request, and if the clinical decision takes a different course of action based on the results, unblinding will be permitted.

The principal investigator will immediately notify the sponsor and proceed with communicating with the person responsible for randomization at the research center to perform the unblinding.

The entire process will be documented in the corresponding medical record, describing the circumstances surrounding the unblinding (date, reason, and person requesting and performing the unblinding), and notification of the report will be sent to the Ethics Committee by the principal investigator or study coordinator.

15.3.3 AE and SAE Reporting and Notification to the Sponsor of AEs, SAEs, and other safety events requiring notification

I. If an AE or SAE is identified, the activities described in the institutional procedure (F-INV-22: Reporting and Follow-up of Adverse Events in Clinical Research) will be carried out. It is the investigator's responsibility to review all documentation related to the event and record the relevant information on the established forms. The investigator will make a diagnosis of the underlying event of the AE/SAE based on signs and symptoms.

II. In addition, the severity of the event will be assessed and classified as mild, moderate, or severe (the latter should not be confused with an SAE).

III. The investigator will perform a causality analysis of the event to determine the probability that the sponsor's product caused the AE based on criteria of exposure, temporal evolution, probable cause, interruption of exposure and re-exposure, and consistency with the safety profile of the study drug.

IV. The investigator is required to perform/arrange for additional evaluations to elucidate the nature or causality.

V. All AE/SAE follow-up processes will be recorded in the CRF.

VI. Notification to the sponsor is defined in institutional procedure F-INV-22: Reporting and Follow-up of Adverse Events in Clinical Research. SAEs must be reported immediately to both the sponsor and the IRB.

15.4 App**endix 4:** Study management considerations

15.4.1 Data protection

Each participant will be assigned a unique study number. All participant data sets or records sent to the sponsor, under security mechanisms established between the parties, will contain only this identification number. No data that could identify the participant, such as name, ID number, etc., will be sent.

15.4.2 Confidentiality of information

By signing this protocol, the researcher agrees to maintain confidentiality and that the information contained herein will be shared only after a confidentiality agreement has been signed with entities such as the Research Ethics Committee, affiliated institutions, or similar bodies.

15.4.3 Confidentiality of participant records

By signing this protocol, the researcher agrees to handle all participant information in accordance with current guidelines, rules, and regulations. The sponsor, the IRB, and/or regulatory authorities may request access to the records under the access guidelines required for the protection of information.

15.4.4 Data quality assurance

All participant data related to the study will be recorded in CRF (printed or electronic). The investigator or designated qualified person will be responsible for verifying that the data included is accurate and correct, confirming the evaluation with their signature. The recorded data will be supported by accurate documentation (source documents). Audit/monitoring/evaluation procedures may be carried out by bodies such as the IRB, regulatory authorities, and/or the Sponsor. The investigator will provide access to source documents for the proper conduct of these procedures.

15.4.5 Source documents

Source documents constitute proof of the participant's existence and support the integrity of the data obtained and procedures performed. These documents shall be filed at the research center, where the procedures required for their safekeeping shall be carried out (F-INV-32: Control of Access to the Research Archive; I-INV-02: Chain of Custody of Research Records). The information recorded in the CRF must match the source documents.

15.4.6 Study and site closure

The study will be closed in accordance with procedure P-INV-04: Approval, Conduct, and Closure of Clinical Research Studies and instruction I-INV-03: Handling of Information at the Closure of a Study.

The Sponsor or designated person may terminate the study for medical, regulatory, administrative, or compliance reasons.

15.5 **Appendix 5:** Sponsor Code of Conduct

Laboratorios Richmond Colombia SAS Code of Ethics and Conduct in Research CECI

Bogotá, October 29, 2020

Author
Laura Victoria Mejia Moncada,
MD, Epidemiologist
Reviewed by Gustavo Ramírez Ballesteros
Law Degree

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1. INTRODUCTION

Laboratorios Richmond Colombia SAS (hereinafter Richmond) is a Colombian pharmaceutical company whose main shareholder is currently Laboratorios Richmond S.A.C.I.F. of Argentina, founded in 1935 and committed, both at its headquarters and in its subsidiaries, to excellence and continuous improvement, developing and producing quality medicines with added human value.

The business group is made up of a staff of more than 400 (four hundred) people at the regional level, most of whom are professionals, of which around 50% work in the areas of research and development, quality control, production, and engineering.

The company participates in numerous national and international conferences (ASCO, IAS, AAOC, SNA, SAC, IPGA, CPhI, ACIN, ACINVIR, REVIVA, PRIMED, FAI, ACF, etc.), demonstrating active and outstanding participation in these events. It also has several agreements with public institutions, universities, and foundations, whether in the training of advanced students, the development of special studies, or the preparation of joint research protocols.

Richmond continues its ambitious expansion plan nationally and internationally, constantly expanding its product lines and entering new markets. We currently have a presence through representatives in more than 20 countries in Central and South America, Africa, Asia, and the Middle East. In Latin America, we have our own offices in Argentina, Chile, Colombia, Peru, Paraguay, and soon Mexico.

In 2016, Richmond Argentina acquired a 51% stake in Laboratorios Expofarma S.A. in Colombia with the aim of expanding technological development and extending the operations of both organizations. In 2019, it acquired the remaining shares and completed its 100% stake in the company, allowing the company to take on a new name and corporate form, becoming Laboratorio Richmond Colombia S.A.S.

In 2017, our parent company, Laboratorios Richmond S.A.C.I.F., began trading on the Argentine Stock Exchange (capital market), providing an interesting diversification opportunity for local investors and new capital for the company to finance new technologies and penetrate more markets.

Richmond's goal is to contribute to the development of the community's well-being, assuming, like any organization dedicated to the preservation of human health, an untransferable social responsibility, offering its employees job opportunities and scientific and professional development, where economic gains come from activities that benefit society as a whole.

Richmond has two production plants located in the El Pilar Industrial Park in the city of Buenos Aires, one plant with 5,600 square meters and the other with 2,000 square meters

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square meters, designed according to energy sustainability criteria with certifications such as:

- Quality system certified by the Organization for Standardization (ISO 9001:2008) and MERCOSUR.
- The Environmental Management System was certified according to ISO 14001 standards in October 2016 and renewed in 2018.
- Good Manufacturing Practices and Control issued by MERCOSUR
- Good Manufacturing Practices by INVIMA.

In Colombia, it has a production plant located in the Barrios Unidos district, with around 120 direct contract employees and 50 indirect contracts. This plant manufactures or packages generic drugs covered by the Health Benefits Plan (PBS) of Colombian legislation. In Colombia, we have:

- Certificate of Good Manufacturing Practices by INVIMA
- ASINFAR members
- Members of the Pharmaceutical Cluster of the Bogotá Chamber of Commerce
- Members of the Colombian Pharmacovigilance Association

2. PURPOSE

When Richmond conducts a clinical study, it will be referred to as the Sponsor, which is defined in INS Resolution 2378 of 2008 as "an individual, company, institution, or organization responsible for initiating, administering/controlling, and/or financing a clinical study. This role may be performed by a corporation or agency external to the institution or by the investigator or hospital institution."

According to Resolutions 2378 of 2008 and 3823 of 1997, sponsors are required to submit protocols for drug research conducted in Colombia for approval by INVIMA (Directorate of Medicines and Biological Products), which are evaluated by the Specialized Chamber of Medicines and Biological Products of the Review Commission (SEMPB) in the first instance and by the Good Clinical Practices Group. Approval of the protocol will be sent to the sponsor in the form of written authorization.

As sponsors, we establish agreements with institutions endorsed by the competent authorities to conduct clinical studies in Colombia and define our behavior, ethical activities, and conduct in this document, Richmond Laboratories Code of Ethics and Conduct in Research, hereinafter CECI, which recognizes clinical research in humans as a way of generating knowledge framed by respect for the individual and their right to self-determination and the right to make informed decisions. As promulgated in the Declaration of Helsinki, which is the most important document in terms of ethics.

3. MISSION, VISION, AND VALUES

Vision

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We share the vision of a world where health is not a privilege. That is why we want to contribute to improving, protecting, and caring for people's health.

Mission

To be a competitive, flexible, and technologically innovative pharmaceutical laboratory with sustained growth in the local and international markets.

To build a team whose efforts and professional expertise are focused on providing excellent, high-quality products and services.

Contribute to the development of our community by being a profitable and responsible company.

Values

We are a team for whom health comes before business. Our commitment to quality and service improves patient well-being and provides peace of mind to doctors and institutions.

Our professional and individual development goes hand in hand with the development of our company. The development of our company contributes to the improvement of our community.

Our profits come from activities that benefit society.

We are proud of what we do. While we change to improve, our values remain unchanged.

4. REGULATIONS

Richmond complies with current local regulations and consults international documents and treaties in order to carry out research on human subjects, which are summarized below:

Table 1: Research Regulations

Regulations/Organization	Name	Country	Subject	Scope Richmond
RESOLUTION NUMBER 8430 OF 1993	Scientific standards, techniques and administrative for research center in health.	Colombia	ARTICLE 13. It responsibility of the institution research or sponsor, provide medical care to the subject who suffers any harm, if it is	The following shall be established agreements with the center of research where provide health care to the subject

			directly related to the investigation, without prejudice to the compensation to which they are legally entitled.	
			ARTICLE 46 c) That the investigating institution and the sponsors are responsible for the medical treatment of the damage caused and, where appropriate, for the compensation that legally corresponds for the harmful consequences harmful consequences of the research.	Agreements shall be established with the research center where medical treatment and compensation fairly due as a result of the research shall be provided.
RESOLUTION NUMBER 2378 OF 2008	Good Clinical Practices	Colombia	Institutions approved to conduct research on humans must comply with Good Practices	Richmond will contract research centers endorsed by Invima.
PROCEDURE GHP-035	Code of Ethics and Conduct Lab. Richmond	Richmond Colombia	Framework for action that helps guide employees' good judgment and integrity	Limits the scope of issues such as conflicts of interest, confidentiality of information and intellectual property.
Internal Document	CONFIDENTIALITY AND DUTY AGREEMENT	Richmond Colombia	Article 4, paragraph h) of Statutory Law 1581	Agreement between Richmond and employee for

			of 2012, Personal Data Protection LEPD, all persons involved in the processing of personal data that is not public in nature are obliged to guarantee the confidentiality of the information, even after the end of their relationship with any of the tasks involved in the processing, and may only supply or communicate personal data when this corresponds to the development of the activities authorized in the aforementioned law and under the terms provided for therein.	limiting confidential information
The Nuremberg Code	Germany (1947)	International	Principles governing experimentation on human subjects	Clinical research and its protocols, respect, autonomy, and self-determination of the individual
Declaration of Geneva	WMA, 1948)	International	Updates the Hippocratic Oath, constituting the fundamental pillars	

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			of this process
Universal Declaration of Human Rights	UN 1948	International	Fundamental human rights that must be protected throughout the world.
The Declaration of Helsinki	1964 World Medical Association	International	The most important document in terms of research ethics. The basic principle is respect for the individual and their right to self-determination and the right to make informed decisions (informed consent

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6. SCIENTIFIC CONSIDERATIONS

Research studies

Richmond collaborates with phase 4 clinical studies and therapeutic equivalence (bioavailability-bioequivalence) with its own drugs in Argentina, especially in infectious diseases such as HIV, complying with current ANMAT (National Administration of Medicines, Food, and Medical Technology) regulations. Bioequivalence studies are mandatory in Argentina in order to obtain marketing authorization. These studies have been published in several conferences and are available to the medical community. Some of them are listed below:

Table 2. Clinical studies related to Richmond

Name/objective	Author	Published	Contribution of Richmond
Andes—evaluate the safety, tolerability, and antiviral efficacy of DRV/r and 3TC versus DRV/r therapy with 3TC and Tenofovir or FTC and TDF in HIV-1 infected subjects without prior treatment in adults	Huésped-Pedro Cahn Foundation	(Conference on Retroviruses and Opportunistic Infections) 2018, Boston	140 Darunavir/Ritonavir 800/100mg treatments

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Study of Comparative bioavailability of darunavir 800 mg in the presence ritonavir in healthy volunteers	CRO Clínica F.P. Clinical Pharma S.R.L.	2014 study, for marketing in Argentina	Funded by Richmond Argentina
Comparative bioavailability study of darunavir 600 mg in the presence of ritonavir in healthy volunteers	Clinical CRO F.P. Clinical Pharma S.R.L.	2014 study, for marketing in Argentina	Funded by Richmond Argentina
Bioequivalence study of two formulations containing the combination of Efavirenz 600 mg, Emtricitabine 200 mg, and Tenofovir Disoproxil Fumarate 300 mg, single oral dose in healthy volunteers.	Center of the Mutual Association of Professionals of the Italian Hospital	2017 study, for marketing in Argentina	Funded by Richmond Argentina
Single-dose bioequivalence study of Previd® / Vyvalto® in healthy volunteers	CRO Clínica F.P. Clinical Pharma S.R.L. at CIAREC Clinic	2018 study, for marketing in Argentina	Funded by Richmond Argentina
Dual therapy with fixed dose combination of Darunavir/Ritonavir plus	Helios Salud, Buenos Aires, Argentina F. Rombini, D.M. Cecchini, A.	Published in EACS 2019 – Annual Meeting of the European AIDS Clinical Society	Darunavir/Ritonavir 800/100mg treatments

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Raltegravir in HIV-infected patients in Argentina	Urueña, C. Vecchio, M. Huberman, I. Cassetti.		

Information available from the Medical Affairs Department

Selection of research centers

In Colombia, Richmond will hire research centers that meet the highest standards in their field, are approved by Invima, and comply with national and international regulations to carry out experimental therapeutic studies.

At Richmond, we have appointed the following members to select the research center:

Position	Country
Richmond General Manager	Colombia
Operations Manager and Technical Director	Colombia
Scientific Liaison Physician	Colombia
Medical Affairs Manager	Argentina supports Colombia
Director of Scientific and Technical Affairs	Argentina supports Colombia

The Medical Affairs Department at Richmond Argentina prepares a summary presentation, sufficiently substantiated, of the project or preliminary draft to be presented to the Research Centers, which is selected according to:

1. A proposal that can answer the research question
2. The deadlines for the project are met.
3. Compliance with Richmond's budget.

Clinical Trial Monitor

When required, Richmond, as sponsor, will hire a clinical study monitor who will be responsible for supervising and controlling the quality of the data arising from the trials, who will be responsible for the sponsor's interaction with the site where the research is conducted, and who will be part of the research team. This person must have experience in conducting clinical studies or trials, be a healthcare professional, and have completed courses in Good Clinical Practices and other studies required for this purpose. They must also demonstrate teamwork skills, commitment, organization, and planning abilities.

Authorship and Intellectual Property

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For all intents and purposes, the authorship and, therefore, the moral rights of the research requested by Richmond shall belong to the Research Center and the researchers it designates to carry it out. In each publication or reference made to the study, it shall be indicated that the study was conducted on behalf of the Research Center, regardless of whether Richmond makes the corresponding citation. The economic rights of the research shall belong to Richmond in its capacity as sponsor.

7. PROTECTION OF SUBJECTS

Characteristics of participating subjects

People who are tested to get results on compounds or products being studied by research centers doing studies for Richmond should always do it voluntarily and freely. They shall be selected by the respective research center according to the needs of the study, ensuring, in all cases, optimal safety conditions and conducting prior health checks to establish the best possible safety conditions for each participant.

Informed Consent

Each participant must sign a document containing a clear explanation of the studies to which they will be subjected and their characteristics, indicating any possible consequences that may arise from their completion, the insurance mechanisms, the manner in which any anomalies that may arise must be communicated to the research center, clearly and expressly indicating that they consent to participate in the study, for the time and under the conditions required by the study, freely and spontaneously, for which they have received sufficient and clear information necessary to express their acceptance.

To this end, the research center will carry out all necessary activities and procedures to provide each participant with all the information they need to participate in the study, and this will be reported in the document mentioned in the preceding paragraph.

Confidentiality

The Informed Consent form that is signed will also set out the unconditional commitment undertaken by the research center and Richmond to maintain the confidentiality of the clinical and medical information obtained from each participant as a result of the study, in accordance with the provisions in force in relation to the confidentiality and handling of medical records applicable in the country.

Likewise, the participant shall undertake to maintain confidentiality with respect to any confidential information to which they may have access as a result of the study in relation to the research center, Richmond, its activities, policies, methods, and other information that has been expressly determined by them to be subject to confidentiality of any kind.

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General information on participating subjects derived from studies conducted by Richmond and a Research Center will be treated in accordance with current regulations, as described in Table No. 1.

Richmond Laboratories aims to use its Corporate Code of Conduct and Ethics and Confidentiality Agreement to promote good judgment and integrity among its employees and protect the personal data to which it has access, under penalty of incurring liability in accordance with applicable regulations.

When a study or research project is conducted, Richmond, as the project sponsor, will appoint a representative with the appropriate training to carry out the study.

7. FINANCIAL CONSIDERATIONS

In carrying out the manufacturing, technical, and commercial activities of LABORATORIOS RICHMOND COLOMBIA S.A.S., the company obtains the resources that first cover its costs and expenses, meet the company's tax obligations, and subsequently contribute a surplus for the recognition of any dividends that may be paid to shareholders.

As part of these activities and to promote the improvement of the quality of its products, the effectiveness of its services, and the safety of its end consumers, all under conditions of efficiency and sustainable profitability for the company, LABORATORIOS RICHMOND COLOMBIA S.A.S. allocates part of the resources obtained from its activity to the development of studies, analyses, and research that allow it to access the improvements required by the various areas of the company, especially with regard to refining its technical knowledge aimed at optimizing its products and providing the public with the best quality within its economic means.

It is therefore a matter of having its own resources for research, analysis, and development within the framework of the highest standards of ethics and commitment to patient health, providing them with safe, affordable, effective, and state-of-the-art medicines, objectives that are achieved by allocating enormous resources obtained in the daily exercise of its activity to research and studies based on the high principles and standards described in this document.

It should be noted that for LABORATORIOS RICHMOND COLOMBIA S.A.S. and its shareholders, it is vital that in the relationships it establishes with its business partners, public officials, the general public, and other stakeholders, they can trust the accuracy and integrity of the financial and other information we publish. Internally, it is also essential to have reliable information so that we can make informed decisions and comply with the objectives set out, with the corresponding legislation, respecting the obligations regarding the publication of information.

Our books and records accurately and clearly reflect our transactions, with a reasonable level of detail and in accordance with our accounting practices and policies.

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Some employees have specific responsibilities in this area, although we all contribute to the process of recording business results and maintaining records, and all employees are responsible, to the extent of their competencies, for helping to ensure that the information we record is accurate, timely, complete, and maintained in a manner consistent with our internal control system.

In addition, we exercise special care with regard to money laundering, which is a huge global problem with serious consequences. The set of mechanisms or procedures aimed at giving the appearance of legitimacy or legality to goods or assets of uncertain origin would undermine our integrity, damage our reputation, and could expose RICHMOND and its employees to serious financial and criminal penalties. Therefore, it is vital in the performance of our activities that, when faced with situations that may arise, we take special precautions that we adhere to strictly at all times.

8. CONTACT INFORMATION

Laboratorios Richmond has appointed the Scientific Liaison Physician as the representative in the research study and the Operations Management and Technical Management as the alternate. Both positions have the training and qualifications to conduct clinical research and make decisions when required.

Position	Name	Profession	Contact
Scientific Liaison Physician	Edwin Garay Jaramillo	General Practitioner Specialist in Health Services Management Master's Degree in Public Health	Calle 71C N° 29B-07 Bogotá, Telephone (01) 4378200 Mobile 3208127672 farmacovigilanciacolombia@richmondlab.com egaray@richmondlab.com
Operations Management and Technical Direction	David Calixto Carmona Rudas	Pharmaceutical Chemist	71C Street No. 29B-07 Bogotá, Telephone (01) 4378200- Ext 200 Cell phone 3153929114 dcarmona@richmondlab.com

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15.6 **Appendix 6:** Protocol for delivery of samples of extended-release nifedipine 30 mg for safety and efficacy study

PROTOCOL FOR DELIVERY OF EXTENDED-RELEASE NIFEDIPINE 30 mg SAMPLES FOR SAFETY AND EFFICACY STUDY

LABORATORIOS RICHMOND COLOMBIA S.A.S.

OBJECTIVE

To define the masking technique for the delivery of the extended-release Nifedipine 30 mg sample necessary for the development of the safety and efficacy study on this product, sponsored by Laboratorios Richmond Colombia S.A.S.

DEFINITIONS

Blinding

It is a recognized fact that the expectations of both trial participants and investigators can influence the assessment of the response to the intervention, thus influencing the results, as they carry a risk of classification bias. This is why masking or blinding techniques are used(27).

Blinding therefore prevents the researchers' preferred intervention from being favored in the assessment(28). Even if the researcher is impartial, the initial results obtained may influence expectations for subsequent results. In addition, participants also assess the effects, whether beneficial or adverse, differently if they know which intervention group they have been assigned to. Furthermore, if a subject knows that they are assigned to the placebo group, they may modify their behavior because they "feel unprotected," a phenomenon called decontamination, which is a significant problem, especially in lifestyle studies(27).

In this way, blinding is complemented by randomization to try to ensure the objectivity and impartiality of researchers and trial participants. These masking techniques can be performed at different levels, which we describe below(27).

Open-label or non-blinded trial

Sometimes, the nature of the intervention makes it impossible to conceal it from participants. Consider, for example, a surgical intervention or treatment with a drug that has obvious or recognizable toxicity. Another example where masking can sometimes be difficult is in the case of non-pharmacological interventions, although there are strategies that help to solve the problem. On other occasions, it is unethical to mask, such as when invasive placebos are required (e.g., parenteral injections in children). In these cases, what is called an open-label, non-blind study is conducted, but we can always resort to blinding other participants, such as those who collect the data or those who perform the statistical analysis. This is called a blinded evaluator(29).

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Simple blind

In this case, the researchers or, more commonly, the participants are unaware of the intervention each one is receiving(27).

Double-blind

Both the participants and the researchers in the trial do not know which group each of the trial participants has been assigned to(27).

The study will be conducted using double-blind masking. The Nifedipine Comparator and Nifedipine Richmond products will be packaged identically so that treatment masking is maintained. Thus, the volunteer, the investigator, and the staff involved in the clinical evaluation of the participants will not know the group assignments.

Triple-blind

In this case, in addition to those already mentioned, the person analyzing the data or responsible for monitoring and suspending the study is also unaware of which group each participant has been assigned to. An extended variant of this masking, called "quadruple-blind," is also described, in which even the study sponsor does not know whether the intervention being promoted is successful until the results are published(27). It should be noted that when masking is used, protocols must be established in advance to allow the blind to be broken in the event of serious adverse effects and to facilitate the interruption of the trial for safety reasons, if necessary.

According to RESOLUTION 2378 OF 2008, which adopts Good Clinical Practices for institutions conducting research with drugs in humans, this protocol complies with its guidelines:

Ensure that study personnel are familiar with and properly handle the investigational product through the following actions:

a) Training of persons responsible for handling and dispensing the product.

b) Written delivery of procedures and instructions for handling and storing the study drug, specifying: 1. Procedure for proper and safe receipt of drugs. 2. Storage conditions. 3. Method of delivery to participants.
4. Final disposal of medication not used in the study Review of accounting records for the investigational product.

Availability of safety and efficacy data from previous clinical or preclinical studies to support its administration in humans. a) Route of administration b) Dosage c) Time period d) Study population e) Adverse reactions f) Contraindications Investigator's protocol and manual.

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ASPECTS RELATED TO THE SPONSOR

The sponsor must obtain and document approval for the use of the study product from INVIMA (INIVIMA project approval certificate).

The sponsor must ensure control of the distribution and return of the investigational product during the study. These measures include:

a) Supplying the investigational product

b) Maintaining records documenting the shipment, receipt, return, and destruction of the product involved in the study Delivery and return letters for the investigational product.

Description

The masking of samples of the product Nifedipine 30 mg Extended Release Capsules from Laboratorios Richmond Colombia S.A.S will be carried out in accordance with the following procedure.

PRESENTATION OF SAMPLES

Investigational product Comparator:

Folding box x 30 capsules. Each folding box contains 3 blister packs x 10 capsules

The capsules of this product are: Hard capsule No. 2 with a translucent blue cap and a translucent orange body.

Nifedipine Richmond:

Folding box x 30 capsules. Each folding box contains 3 blister packs x 10 capsules

The capsules in this product are: Hard capsule No. 2 with a translucent blue cap and translucent orange body.

Identification of samples

The reference product samples and the Nifedipine Richmond samples will be assigned a code. This code will only be known to the project leader on behalf of the Sponsor and the Pharmaceutical Chemist responsible for dispensing the medication.

The samples of the Comparator Nifedipine and Nifedipine Richmond products will be identified as follows:

Blister pack

Each blister pack containing 10 capsules will have the batch number and expiry date printed in low relief.

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The blister pack of the reference product and the product under study will have the following information printed on the aluminum foil:

Clinical Study Code

Generic name of the product and concentration

Batch number and expiration date

Pharmaceutical form and route of administration

Name of the sponsor

Folding box

The comparator Nifedipine and Richmond Nifedipine will be packaged in folding boxes printed with the same information as the blister pack:

Product Batch

Expiration date and storage conditions Generic name of the

product and concentration

Pharmaceutical form, route of administration, and number of units Clinical

Study Code

Participant Code and Visit Number Name and

Address of Sponsor

Legend: "Medication for use in clinical studies only" Legend: "Keep out of

reach of children"

NUMBER OF SAMPLES TO BE DELIVERED

The number of samples required for the study depends on the number of patients, the duration of the study, and the daily dose, which in our case is:

a) Fifty patients

b) Eighteen weeks

c) Daily dose of 60 mg, equivalent to two capsules per day

For the products Nifedipino Comparador and Nifedipino Richmond, 500 boxes of 30 capsules of each product must be delivered.

DELIVERY OF SAMPLES

Samples of Nifedipino Comparador and Nifedipino Richmond will be delivered to the Méderi Pharmaceutical Service by letter and referral from Laboratorios Richmond Colombia S.A.S., indicating the number of corrugated boxes, the contents of each box, and the total number of samples of each product (reference and study samples).

A sufficient quantity of Nifedipine Comparator and Nifedipine Richmond must be delivered, duly blinded and controlled.

These samples must be listed by Méderi in the Inventory Traceability format. Research Products (F-FAR-33). In addition, a sealed envelope containing the identification letter for each sample (comparator Nifedipine and Richmond Nifedipine code) must be delivered to the Chemist responsible for the Pharmaceutical Service, indicating the protocol number, the name of the drug, the Center number, and the Investigator.

ADDITIONAL DOCUMENTATION REQUIRED

Laboratorios Richmond Colombia S.A.S. must provide the following documentation:

Instructions for handling and storing the study drug, specifying: Proper and safe drug receipt procedure

Storage conditions. Method of delivery

to participants.

Final disposal of medication not used in the study.

CONTRAMOSTRES

Laboratorios Richmond Colombia S.A.S. must store counter samples of the products Nifedipino Comparador and Nifedipino Richmond in the sample retention area for a period of ten years (10 years).