# FINAL REPORT PROSPECTIVE, SINGLE-CENTER AND CLOSED CLINICAL STUDY TO EVALUATE THE CLINICAL EFFICACY AND SAFETY OF MEDICAL DEVICE INSTALIFE BY INDUSTEX IN PATIENTS DIAGNOSED WITH BACK PAIN, SCIATICA OR SIMPLE PIRIFORMIS SYNDROME.

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## CONFIDENTIAL

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SYNOPSIS OF THE STUDY
CLINICAL RESEARCH OF INSTALIFE BY INDUSTEX

Device name: INSTALIFE

Device description: Instalife is a brace that fits under the knee made of neoprene with metal anchors (sliding belt). It has a rigid plate for applying pressure on the sciatic nerve.

Objectives: The purpose of this study is to evaluate the elimination or improvement of low back pain, sciatica and piriformis syndrome that relate only to the sciatic nerve.

Population of subjects: Patients diagnosed with low back pain, sciatica or piriformis syndrome mechanical or simple related to the sciatic nerve between 25 and 65 years old.

Estructure: Prospective, closed, controlled, single-center clinical study designed in accordance with the guidelines of ICH Good Clinical Practice and FDA; ISO 14155 (2011): standard clinical research of medical devices; and national requirements (Local Health Department).

Sample size: Up to fifty volunteers are recruited for the study.

Concurrent control: In the experiment includes 50 volunteers to serve as study group. The study will be conducted for about four weeks - an initial consultation in which the patient's condition will be evaluated without undergoing the treatment, a second consultation at 2 weeks of treatment where changes are checked in pain study group (treatment Instalife), and finally a final consultation in which the changes are checked in pathology

Variable performance: Device placement is evaluated, and its ergonomics.

Assessment methods: Percussion test sciatic nerve and Lasegue test will be performed on volunteers to determine the initial state of the disease and improvement in pain after treatment with Instalife.

Safety Variables: Safety will be assessed taking into account the previous experience of the product on the market, especially the possible skin reactions caused by the use of the product.

Promoter of the Study: Industex SL
1 INTRODUCTION

Low back pain is localized in the lower back. Sciatica pain is caused by compression of the sciatic nerve or its roots. Piriformis syndrome is a condition in which the piriformis muscle is a contraction or spasm, and irritates the sciatic nerve that passes under.

Considering the length of the pain, low back pain (lasting no more than six weeks and chronic when it exceeds 6 weeks) is classified into acute.

According to the characteristics of pain is classified as mechanical or simple it is one that has no warning signs, worse by movement and subsides with rest and specific mechanical or not is secondary to infectious processes, tumor, inflammatory disease, etc., usually day and night, does not yield even worse with rest and you can wake up at night.

Low back pain in Spain cause more than 2 million visits in primary care and major cause of temporary disability. The prevalence is 60-80% in a lifetime and annual incidence is 5-25% with a peak age of 25-45 years. (Patología dolorosa de columna vertebral. Dolor lumbar y ciático. Ruta asistencial de integración AP-E. Servicio de Salud de Castilla la Mancha, 2007)

Overall, it is estimated that 5 to 10% of patients with low back pain have sciatica, while the prevalence of low back pain throughout life is 49 to 70%. It is estimated that the annual prevalence of sciatica related to disc disease in the general population is 2.2%. There have been few personal risk factors and occupational, including age, height, mental stress, smoking, and exposure to vibration of vehicles. The evidence on the association between sciatica and sex or physical condition is conflicting. (Autor: Dres. B W Koes, M W van Tulder, W C Peul Fuente: Traducción y resumen objetivo: Dra. Marta Papponetti. Especialista en Medicina Interna. Diagnosis and treatment of sciatica. BMJ 2007;334;1313-1317)

Instalife: Gate theory applied to the sciatica pain.

Performance of the product is based on la “Gate theory” (Ronald Melzack y Patrick D. Wall, 1965):

In 1965 Melzack and Wall proposed the theory of Gate or Gateway to explain the phenomena related to pain. Gate theory of pain is an explanation of how the mind plays an essential role in the perception of pain.
They suggested that there is a "system that locks" in the central nervous system that makes open or pain pathways are closed. As you can see in the scheme of control system gate fiber "L" long receives impulses from the central part of the nervous system.

L: thick myelinated fibers A alpha and beta low threshold, easy adaptation, with proprioceptive functions, touch, pressure and reflex activity. Afference the increases with L and decreases with S.

S: A low delta thin myelin gives sharp stabbing pain and responds to touch fibers, surface and visceral pain (6 to 30 m / s); unmyelinated C fiber with Schwann cells gives dull pain, high threshold mechanoreceptors and terminociceptores.

(0.5 a 2 m/s) Such stimuli, as a gate can be opened, letting the pain flow through the afferent and efferent fibers and from the brain, or vice versa, the doors can be closed to block these pain pathways. Efferent impulses from the central region, are motivated by a wide variety of psychological factors. This theory of pain integrates physiological, psychological, cognitive, and emotional components that regulate the perception of pain.

The Gate theory explains why the pain is decreased when the brain is experiencing a sense of distraction or simultaneously produces a tactile stimulus, which in turn faster nerve (30 meters / sec) arrives first at the gate and closes the door partially the pain that comes from the fiber "s" small- small one (m / sec). In these circumstances, the perception of pain is diminished because the interpretation of pain is modulated by the experience of distraction.
By this theory:

1. The activity of the cells of the gelatinous substance (SG is at the apex of the rear along the entire spinal cord horn, is related thermoalgic and tactile, Plate II or III of the dorsal horn) modulate and regulate the entry of nerve impulses from afferent cells or T cell transition (Plate V) fibers. This is known as spinal gate.

2. Cells gelatinous substance influencing two ways afferent impulse transmission to T cells
   
a) Presynaptically level: Blocking pulses or reducing the amount of neurotransmitter released by axons of A delta and C fibers.
   
b) Postsynaptic level: changing the responsiveness of the pulses arriving.

3. The fibers A delta and C facilitate transmission (gate open) inhibiting cells gelatinous substance.

4. The fibers A alpha and beta excite cells gelatinous substance inhibiting the transmission and closing gate.

5. Plate cells V (T cells) are excited or inhibited by cells gelatinous substance.
6. Stimulation of A alfa fibers immediately activated the central mechanisms. The activity of these fibers ascends the dorsal columns of the spinal cord and the back side airways through the medial lemniscus to the ventrobasal complex posterior thalamus; providing information long before the arrival of the pain pathways. This system becomes alert and active central receptors selective mechanisms such as:

- Previous experience.
- Emotions.
- Cognition.
- Answers.

It then descends information cortical efferent fibers to turn on the spinal gate; before central activation of T cells.

7. The combination of peripheral afferent impulses modulated by S.G. and downstream stations produce the net activity of the transmission cells of the spinal cord.

In this case the lumbar nerve causing pain in the lower back area extending to the ankle being in the back of the knee accessible to pressure.

Therefore, when applying INSTALIFE by rigid pad device, the nerve is pressed without producing pain with an acute excitation (distraction) that is transmitted by rapid conduction pathways closing the gate and inhibiting transmission is achieved acute pain in the lower back area transmitted by the same nerve.

In this case, INSTALIFE performs its action on the sciatic nerve is formed from the union of the L3-L4 and L5 nerves, once these nerves anastomose the sciatic nerve is created, the nerve crosses from the buttocks and down the back of the thigh and reach the height of the knee branches into two. On the one hand it descends external and lateral peroneal and also makes it back touring the twin. This two-way function is affected dermatome and may be root of L4-L5 or L5-S1

With the pressure INSTALIFE correctly positioned (see IFU’s) thereon nerve (sciatic) that causes chronic back pain is achieved stimulate behind the knee (branch nerves) and send a stimulus that blocks sent by the original pain and thus get relief and modulate nerve pain as demonstrated by the attached literature and the experience of similar products on the market that base their mechanism of action in the theory gate by producing stimuli not painful transmitted by expressways and block the entrance of chronic pain that is transmitted by slow lanes:

Electrostimulation: TENS
Pressure: Back Angel
Thermotherapy: application of cold / heat.
Current treatments for sciatic pain

Currently the treatment of sciatic pain is based on pharmacological treatments based on anti-inflammatory and rest.

In general, the clinical course of acute sciatica is favorable and the pain and functional disability are resolved in a few weeks. For example, in a randomized study comparing non-steroidal anti-inflammatory drugs (NSAIDs) with placebo for the treatment of acute sciatica in primary care, 60% of patients recovered within three months and 70% within 12 months. Approximately 50% of patients with acute sciatica from placebo group in randomized studies on non-surgical interventions improved within 10 days and about 75% after 4 weeks. Therefore, the prognosis is good in most patients, but at the same time there is a significant proportion (30%) with pain continues for 1 year or more.

Conservative treatment main objective is pain relief, either by analgesics or by reducing the pressure on the nerve root. A recent systematic review found that conservative treatments do not improve the whole natural course of sciatica in most patients not fully reduce their symptoms. Adequate information is provided to patients about the causes and prognosis can be an important part of the therapeutic strategy. However, educating patients about sciatica has not been investigated in randomised controlled trials.

Still missing evidence of the effectiveness of most interventions available. It has been found little difference between the effect of bed rest and the continuation of the activity on pain and functional status. As a result of this finding, increasingly is less recommended bed rest which was, for a long time, treatment of sciatica. Analgesics, NSAIDs and muscle relaxants don’t seem to be more effective than placebo in reducing symptoms. Evidence of opioids and various compounds missing. A systematic review reported that there is no evidence that traction, NSAIDs, steroids intramuscular or tizanidine are better than placebo. This review showed that epidural steroid injections may be effective in patients with acute sciatica. However, a recent systematic review of a large number of randomized studies reported no evidence of positive short-term effects of corticosteroid injections was found, and that the effects are not known long term. The same systematic review reported that the activity (exercise) did not seem to be better than the inactive treatment (bed rest) and other conservative treatments such as traction, handling, hot soaks or corsets.
The surgery is aimed at removing the disc herniation and eventually partial removal of the disc or stenosis of the foramen, in order to eliminate the cause of sciatica. The goal of treatment is to relieve leg pain and associated symptoms and not reduce back pain. By consensus, the cauda equina syndrome has the absolute indication surgery. Elective surgery is the choice for unilateral sciatica. Up to now only a relatively old randomized study in which surgery with conservative treatment was compared was known. This study showed that surgery had better results after 1 year, while 4 to 10 years gone by, the differences were not significant.

A Cochrane review, summary randomized clinical studies that evaluated disc surgery and quemonucleólisis. This is done by enzyme chymopapain, which is injected into the disc to destroy the nucleus pulposus. In patients with severe sciatica long-standing (between 4 weeks and 4 months) review showed better results with surgery disc than with quemonucleólisis. This was also more effective than placebo. Therefore, indirectly, the review showed that disc surgery is more effective than placebo. Based on the data from three studies, the authors concluded that there is sufficient evidence to accept that surgical removal of the disc provides an effective clinical relief for carefully selected patients who did not respond to conservative treatment. A recent review came to the same conclusion. Moreover, the Cochrane review concluded that the long-term effects of surgery are unclear and lack evidence on what is optimal time for surgery.

Randomized controlled trials have not yet been included in systematic reviews. There have been two randomized controlled trials comparing disc surgery with conservative treatment works. One study (n = 56) compared microdiskectomy with conservative treatment in patients whose sciatica had 5 to 12 weeks. Overall, there were no significant differences in leg pain, lumbago and subjective functional impotence in the 2 years of follow-up. In the United States a large randomized study on the evolution of patients and an observational study cohort was made. They were invited to participate in one of the studies patients with sciatica of at least 6 weeks and confirmed disc herniation. Patients were randomized to disc surgery or conservative treatment. Patients of cohort entered one of the two study groups (surgery or conservative treatment) by therapeutic preference. In the randomized study (n = 501) both treatment groups improved substantially received treatment for two years, according to primary and secondary measurements. small differences in favor of the surgery group were found, but were not statistically significant for the primary outcome measures. Only 50% of those randomized to the surgical group patients underwent surgery within 3 months of
incorporation, compared with 30% of those assigned to conservative treatment group. After 2 years of follow-up they were operated 45% of patients in the conservative group and 60% in the surgical group. The observation cohort included 743 patients. Both groups improved significantly over time, but the surgery group had better results on pain and function than the group with conservative treatment. The authors were cautious in interpreting the findings due to error factors derived from the display and measurements of evolution were self-referential reports.

The results indicate that both conservative and surgical treatment are important for patients with sciatica of at least 6 weeks duration options. The surgery can provide faster relief of symptoms compared with conservative treatment, but there are no big differences in the evolution year or 2-year follow-up. Patients and physicians can therefore analyze the benefits and disadvantages of both options to make individual decisions. This is very important because the patient preference can positively influence the magnitude of the effect obtained.


**Instalife for the treatment of sciatica pain**

Instalife is a non-invasive medical device for the treatment of pain associated with sciatica that is placed behind the knee of the leg branch of the sciatic nerve associated for two hours a day. The device, using a semi-rigid plate, causes a moderate pressure on the nerve preventing or moderating nerve transmission of pain.

The product already has CE marking and market experience to be a safe treatment which only caused some mild skin reactions in patients allergic to neoprene.

Misuse only causes discomfort without causing complications in pathology treatment.

### 2 DESCRIPTION OF THE DEVICE IN RESEARCH

Bracing neoprene for individual adjustment by Velcro anchors with semi-rigid plate.
Instalife is made of biocompatible quality neoprene. It has the following technical specifications:

The manufacturing process of the probe is similar to the external orthosis marketable. Manufacturing is done by tailoring and sewing of orthotic and anchoring systems.
3 INDICATIONS FOR USE

Instalife is indicated for the treatment of mechanical or simple pain associated with the sciatic nerve in case of lumbago, sciatica and piriformis syndrome.

4 OBJECTIVES OF THE STUDY

The purpose of this clinical study is to evaluate the efficacy and safety of the device in patients diagnosed Instalife mechanical or simple pain associated with the sciatic nerve in case of lumbago, sciatica and piriformis syndrome.

4.1 Primary objectives:

The study evaluates the effectiveness of Instalife on improvement, elimination and / or mitigation of pain associated with sciatic nerve during the 4 weeks of treatment.
4.2 Secondary objectives:
The study will evaluate the safety of Instalife in patients in the study assessing the possible adverse reactions occurring during use.

4.3 Safety assessment:
The safety assessment will be based on the medical examination of patients during the study to detect potential adverse reactions associated with the use of Instalife. In addition, unexpected adverse events were recorded. See section “Adverse Events” for definition and classification. Based on the excellent safety profile of use in the market and the usability test report in healthy volunteers, the expected response to the use of Instalife is not expected to give rise to different adverse reactions to those already registered.

4.4 Effectiveness evaluation:
4.4.1 The following aspects will undergo extensive testing to evaluate the effectiveness of the new device:
- Level of pain reduction based on the initial recognition and subsequent test results of mobility.
- Ergonomics device.
- Level of discomfort after use of the product.
- Level of mobility with the device

5 POPULATIONS AND SELECTION OF PARTICIPANTS

5.1 POPULATION OF THE STUDY
Patients diagnosed with low back pain, sciatica or piriformis syndrome mechanical or simply related to the sciatic nerve between 25 and 45 years.

5.2 SELECTION

5.2.1 Inclusion criteria
The study was performed with a group of 50 volunteers who meet all the following inclusion criteria detailed below:

1. Subjects of both sexes (men and women).
2. Aged between 25 and 65 years
3. Existence of low back pain, sciatica or piriformis simple syndrome.
4. Appropriate cultural level and adequate level of understanding of the clinical study
5. Agree to participate voluntarily in the study and have given their written informed consent

5.2.2 Exclusion criteria

Eligible subjects must not meet any of the following exclusion criteria:

☐ Subjects that are in any known state and confirmed or suffering from any known condition and confirmed from the following list:

1. Present acute pain at the time of baseline or during the 3 weeks preceding the presence of disease or treatment related.
3. Subjects with allergy to any component of the product under study.
5. Low back pain, sciatica or piriformis syndrome secondary or specific.

At the beginning of the study we recommend:

- not apply (other than the tested) products in the experimental area
- not begin drug treatment.
- not engage in practices that could adversely affect the pain, continue normal life.

5.2.3 Informed consent

Informed consent must be obtained in writing of each study subject before inclusion in the study. A copy of informed consent will be given to the subject. The of informed consent form signed will be maintained with the study records at the participating center. It is the responsibility of the researcher to ensure that the informed consent of each subject is obtained in accordance with the guidelines of Good Clinical Practice.

The subject may at any time withdraw their consent to participate in the study without prejudice. The researcher may withdraw a subject if, following their clinical judgment, believes that it is in the interest of the subject or the subject can not comply with the protocol. It should try to complete scans and shall be notified to the sponsor all withdrawals.
6 DESIGN OF THE STUDY
The purpose of the trial is to evaluate the efficacy in treating pain associated with the sciatic nerve and safety of Instalife device when used in the manner indicated in patients. For this purpose, up to 50 subjects will be enrolled.
6.1 GENERAL DESCRIPTION

The proposed clinical study is a prospective, single-center, closed, crossover, randomized clinical study. Subjects will be evaluated by the principal researcher in accordance with the criteria for inclusion / exclusion of the study. Subjects who meet the criteria for inclusion in the study will be assigned randomly to test the test according to their recruitment and provided with a sample of the device along with appropriate instructions for proper use. Studio groups and duration of each phase are detailed in Section 7.2. During the study, the safety-related events, including the successful integration, operation and removal of the device, adverse events and complications were recorded.

Medical and demographic information on the patient acquired her guardian / legally authorized representative or the patient's medical history including age, sex, medical history, and relevant past medical information will be recorded in the corresponding collection notebooks previous data to study. The data obtained in the radiologic physical examination (if any) will also be recorded in the corresponding data collection notebooks (CRD) prior to the study. Clinical assessment and evaluation shall be conducted in accordance with the schedule described below (Section 7, procedimientos del estudio).

The intra procedure data includes identification of the physician. These data will be recorded in the CRD, along with adverse events that occur during the procedure.

All adverse events (or are not related to the device) shall be reported during the course of study clínico. Todos adverse / serious complications events will immediately notify the sponsor and the monitor of the study. All clinical data will be recorded in the Journal of relevant data collection.

7 PROCEDURES OF THE STUDY

7.1 Patient recruitment

Patients were selected according to the criteria of inclusion / exclusion study described in el protocolo study (See la sección 5.2). Before carrying out the procedures related to the study, the patient will be asked to sign the informed consent.
7.2 Experimental groups
In the experiment they included 50 patients who serve as study group. The study was conducted for 4 weeks about - first consultation initial assessment and study group assignment, second consultation review and por último, the last visit of final assessment.

7.3 Pre-procedure assessment.
See 1 “Prior evaluation of patients”.
7.4 Using Instalife and Placement Procedure:
The device is used in accordance with their instructions. Before using the device, the integrity of the device is inspected. They are inspected and recorded data subjects. When the product is provided, the researcher shall provide an adequate explanation to the patient on the device characteristics and its correct use finally realizing a demonstration for proper placement.

Intra assessment procedure described in Section 8, Evaluation study.
7.5 Operation of Instalife:
The user with the device should not notice discomfort during use.

Debenseguirsevariospasosantesyduranteelaccionamientoinicialdeldispositivo (see Manual delInvestigadorparadetalles complete):

1. Identification of the pressure point sciatic nerve behind the knee of the affected nerve branch.
2. Positioning of the device around the calf.
3. Anchors and Velcro fastening.
4. Setting the proper working pressure without causing discomfort or inconvenience.

7.6 Initial efficiency of Instalife
Patients using Instalife two hours a day during the conduct of the trial should note a moderate stimulation (painless) sciatic nerve pain moderate pathological form that allows them to lead a normal life without pain from the first day of application.

This efficacy was assessed by the researcher and his collaborators through mobility test where mobility is verified painless subject.

7.7 Removing Instalife.
After two hours of use of the device the patient should remove it by loosening the anchors and keeping it until its next application.

If a condition that needs urgent attention is manifested during or after the procedure, the doctor will try to pacientede that condition. Operation of the device is interrupted.

7.8 Instalife post-procedure management
The data recorded in the CRD are the functional data to relatives Instalife, pain and other sensations after actuation Instalife, and adverse events.
8 EVALUATION AND PHYSICAL EXAMINATION OF SUBJECTS

8.1 PRE-ASSESSMENT PROCEDURE

Patients identified as candidates for using Instalife will be screened for eligibility for the study according to the inclusion and exclusion criteria. Patients who meet the eligibility requirements will be asked to participate in the study. Once eligibility has been determined for the study, the patient will explain the background of the proposed study and its risks and benefits and will be asked to sign an informed consent form.

8.1.1 Prior assessment of the procedure

The following information is recorded in the data collection notebooks (CRD) regarding all subjects participating in the study:

8.1.1.1 Personal history

Medical and demographic information on the patient acquired subject or patient history is recorded, including age, sex and medical history, information including: a history of clinically significant abnormalities of all systems of the body; concurrent diseases, relevant medical history. The background specifically include: etiology of the disease, risk factors such as alcohol and snuff and consumption of drugs. In addition, a summary of interventional procedures and pre-surgical and non-surgical procedures were recorded. The background will also include data on gastroesophageal previous diagnoses. This information shall be recorded in the notebooks data collection regarding all subjects participating in the study.

8.1.1.2 Physical exploration

All subjects will undergo a physical examination of mobility associated with low back pain, sciatica and piriformis syndrome (percussion test sciatic nerve and test Lasegue) performed by a licensed physician. The physical examination will include the diagnosis and recording of any anomalies or significant disease.
8.2 EVALUATION INTRA PROCEDURE

Among the intra procedure include the following data:

- Physician Identification
- Date of the procedure
- Identification data of Instalife device
- Test result mobility pain diagnosis.
- Time the device is used (hours per day).
- Datos Utilization data (compression of the instructions for use)

These data are recorded in the CRD, along with adverse events that occur during the procedure.

The device must be visually examined and photographed immediately after withdrawal.
8.3 SAFETY ASSESSMENT

Complications and adverse events observed in the patient during the procedure or during follow-up period of the study are recorded in logbook data collection.

All complications were recorded, whether mild or severe, method of detection, and treatment administered; the researcher will determine if the event was detected by observation, diagnostic techniques or any other method.

9 RISKS AND BENEFITS

9.1 RISKS

Instalife is designed and tested in accordance with international standards for medical devices in general, and in accordance with art manufacturing methods for external orthoses.

Compliance with these standards and methods ensures that the device can be used safely in humans. The purpose of this study is to demonstrate the safety and efficacy of initial Instalife in humans. Starting from the fulfillment of the requirements of the standards and the results of bench testing, preclinical animal testing and testing clinical safety is not expected that the risk of adverse events occurring is significantly greater than the risk notified about other procedures or similar devices. adverse events reported by subjects or observed by study personnel are recorded.

The device is made of the same biocompatible materials, and have been widely used in the medical field for the same intended purpose. The device meets all the requirements of biocompatibility, as it is established in the relevant certificates. The test results show that the device can be used in humans for the intended purpose, without increased risk.

Refer the researcher to complete data on materials, specifications, design and validation rules Manual, and the results of clinical trials, animal bank and made.

They have special considerations when designing Instalife to ensure safe and reliable operation of the device. The risk analysis activities conducted by Industex SL meet the requirements of Standard ISO14971: 2007 - Medical Device - Application of Risk Management to Medical Devices.
Instalife is currently considered a class I device on the market with CE marking issued by the manufacturer in accordance with Directive 93/42. Therefore, the benefits outlined in this section should be considered assumptions corroborated by clinical and preclinical studies and the use of the product in the market. The object of the study is to evaluate the efficacy and the safety of the device in patients with sciatic nerve pain associated. The possible benefit obtained will be the reduction of pain associated with sciatic nerve.

Instalife is designed as an external prosthesis for placement on an accessible point of the sciatic nerve stimulation and painless non-invasive treatment for sciatic pain associated with back pain, sciatica and piriformis syndrome. These conditions have thus invalidating capacity use of the device helps control pain facilitating normal life pacientes.Como Instalife use in this study is limited to two hours a day during aproximadamente 4 weeks of the study, it is obvious that this potential benefit is limited to the study time.
9.3 RISK-BENEFIT ANALYSIS

Based on the risks and benefits previously exposed and supporting test data provided in the Researcher also use Manual already on the market without notification of risks associated with its use so far, it can be concluded that the potential benefit counteracts possible risks. Therefore, it can justify a clinical trial to assess initial efficacy and safety of Instalife device of Industex SL in human clinical use.

10 STATISTICAL PLAN

The design of the present study was conducted with 50 volunteers, whereas if the proportion of volunteers subjected to treatment with Instalife in which improvement in pain occurs is higher than the proportion bibliographically improvement with placebo treatment, which is 50%, we could determine that using Instalife is beneficial for the treatment of pain associated with sciatic nerve.

Starting, as we have noted, that with placebo treatment 50% improvement is obtained after 4 weeks of treatment, and that exists a previous Usability Test for Instalife (IN-USE TEST UNDER PHYSIOTHERAPIST CONTROL CLINICAL STUDY FOR THE APPRAISAL OF THE CUTANEOUS ACCEPTABILITY OF A MEDICAL DEVICE INVESTIGATIONAL PRODUCT, APPLIED UNDER THE NORMAL CONDITIONS OF USE, FOR 1 WEEKS, IN BOTH SEX ADULT SUBJECTS), which gives us an improvement rate of 80% in two weeks, it is expected to obtain, after the test clinical done within 4 weeks, an improvement of at least 80% of volunteers treated with Instalife.

Thereby, a null hypothesis according to which there is no differences between patients treated with placebo (as source is) and treated with Instalife can be set, and an alternative hypothesis (to demonstrate) in which patients treated with Instalife have a 30% improvement over placebo treatment.

The sample size was obtained from the following formula, for a significance level of 95% (1-α = 0.95) and a test power of 80% (1- β = 0.8):

\[ n = \frac{\left( \frac{Z_\alpha \times \sqrt{2p(1-p)}}{Z_\beta \times \sqrt{p_1(1-p_1)+p_2(1-p_2)}} \right)^2}{p_1-p_2} \]
Where:

n = subjects required in each of the samples, parameter to be determined.

\[ Z_\alpha = Z \text{ value corresponding to the desired risk} = 1.645 \]

\[ Z_{\beta} = Z \text{ value corresponding to the desired risk} = 0.842 \]

\[ p_1 = \text{Value of the proportion in the reference group, placebo, control or treatment as usual} = 0.75 \]

\[ p_2 = \text{Value of the ratio in the group of the new treatment, intervention or technical} = 0.9 \]

\[ p = \text{Average of the two ratios } p_1 \text{ and } p_2 \]

Obtaining a sample size \( n \) 34 subjects.

If we adjust the sample size to losses, we expect to get a 15% loss:

\[ \text{Sample adjusted to losses} = n \left(1 / (1-R)\right) \]

\[ n = \text{number of subjects lossless} \]

\[ R = \text{expected loss ratio} \]

So we get a sample size of 40 subjects of study for a significance level of 95% and a test power of 80%.

Waiting, therefore, to reject the null hypothesis will be obtained at least 80% improvement in the study volunteers after using Instalife for 4 weeks.

11 ADVERSE EVENTS REPORTING

11.1 DEFINITION OF ADVERSE EVENTS

An adverse event is any symptom, sign, illness or episode that appears or worsens during the course of the study. All adverse events were recorded in Notebook Data Collection [CRD] subject.

An adverse event related to the device is any symptom, sign, illness or episode that appears or worsens during the course of the study, which is considered related to device or procedure dispositivo. Cualquier complicación que ocurra durante el procedimiento o después del procedimiento relacionado con el dispositivo de investigación o el procedimiento se considerará un evento adverso relacionado con el dispositivo y se registrarán en Notebook Data Collection [CRD] del sujeto.
11.2 CLASSIFICATION OF ADVERSE EVENTS

Mild: Signs or symptoms, usually temporary, not requiring special treatment generally not interfering with usual activities.

Moderate: Signs or symptoms that can be improved with simple therapeutic measures but can interfere with normal activities.

Intense: Signs or symptoms are severe or debilitating and interfere with normal activities. Normally therapeutic measures often contribute to recovery.

11.3 REGARDING THE DEVICE IN RESEARCH

For all adverse events, the researcher determines the relationship with the study device or procedure using the following terms:

Very likely related: Follows a reasonable temporal sequence from the use of the study device and can not be reasonably explained by the known characteristics of the clinical data of the subject or the procedure applied.

Possibly related: Follows a reasonable temporal sequence from the use of the study device but could have been produced by the clinical condition of the subject or the procedure, regardless of the device of study, or the operation itself.

No related: no relationship is perceived with the activation of the study.
11.4 DEFINITION OF SERIOUS ADVERSE EVENTS

An event is defined as serious if:

- It is fatal.
- It is potentially fatal.
- It requires an unforeseen or prolonged hospitalization or additional procedure.
- It produces a disability or permanent disability.

In this category any event that the researcher considered serious or it could indicate a hazard, contraindications, side effects or considerable caution is also included. It may also include removing a subject from the study due to abnormal laboratory values, excluding the results of screening tests.

11.5 LIST OF ADVERSE EVENTS PLANNED

As with the devices and methods of standard external orthoses, it can be anticipated that adverse events occurring during the study.
The following adverse events may occur for similar conventional procedures:

**Surgical intervention / complications related to clinical care**

It is not anticipated that the test subjects undergoing surgical interventions associated and in case of complications related to clinical care the treatment must be stopped.

**Complications with Instalife**

- Contact dermatitis in case of hypersensitivity.
- Annoyances for misplacement.

Expected risks (although it is presumed to be rare) in connection with the investigational device are skin reactions (contact dermatitis) in case of hypersensitivity to the product materials as well as inconvenience caused by misplacement of device.

The probability of producing this effect is very low (see section "Risks" of this document).

**11.6 REGISTRO DE ACONTECIMIENTOS ADVERSOS**

The researcher will carefully evaluate each subject for the detection of adverse events. Whatever it is considered to be related to the device or not, each adverse event observed by the researcher or a member of staff, to be determined by obtaining information from the subject or recorded in the medical history of the subject, should be registered in the medical history of the patient and the notification form for Adverse Events of the CRD. The researcher shall note on the CRD if, in its opinion, the event is related to the device or not.

Serious Adverse events will be recorded in the CRD, as well as the relevant forms provided for this purpose.

**11.7 SERIOUS ADVERSE EVENTS REPORTING**

Serious adverse events, arising or not the study device, shall be notified immediately (within of 24 hours) to:
Industex SL, to:

Contact person: Francisca López Alavedra

Phone:+34 932 547 123

e-mail: pro.paqui@industex.com
The researcher will be demanded to complete a separate Form for Adverse Events from the information contained in the CRD and forward fax to Industex SL within 24 hours is requested.

A detailed description of Serious Adverse Event will be in the hospital patient report.

The researcher shall immediately report to the contact person in Industex SL any sign from the use of the study device that may indicate hazards, contraindications and considerable precautions regarding the safety of the device under study.

The researcher shall notify the Institutional Review Board (IRB) / Committee Ethical Serious adverse events within 10 days.

The copy of the letter of the report will be filed in the medical history of the subject.

The researcher will comply with the legal regulations on reporting of serious adverse events.

Preliminary reports by telephone or in writing, must be accompanied by detailed descriptions, which may include copies of the reports of death, autopsy reports or other documents as appropriate.

All serious adverse events mentioned, as well as any adverse event that has no serious basis shall be notified to Industex SL.

**11.8 PRECAUTIONS TO MINIMIZE COMPLICATIONS**

To minimize complications, the following precautions should be taken:

- The investigational device should be used in accordance with the specifications in the Instructions for Use.
• It will only be allowed to participate in proceedings related to the device medical personnel trained on the operation of Instalife (which will be taught by Industex SL).

12 MANAGEMENT RESEARCH

12.1 SELECTION OF RESEARCHERS
Researchers are general medical specialists with experience in the recognition and treatment of lumbago, sciatica and piriformis syndrome associated with sciatic nerve in these areas asícomo enfermerasespecializadas.

12.2 ETHICAL CONSIDERATIONS
Clinical research is conducted in accordance with Good Clinical Practice (GCP) under Standard Operating Procedures (SOPs) and the following standards and guidelines:

• ICH-E6 Consolidated Guidelines for Good Clinical Practice (July 1996);
• Food and Drugs Administration (FDA), Code of Federal Regulations (CFR) 21, parts 50, 54, 56 and 812.
• ISO 14155 (2011) –Investigación clínica de productos sanitarios parahumanos.

The researcher will ensure that this study is conducted in full compliance with the Good Prácticas Clínicas requisitos de (BPC). The researcher must allow inspection of records relating to the study, by the representative of Industex SL and regulators.

12.2.1 Approval of the Institutional Review Board (IRB) / Ethics Committee
Clinical research must be approved in writing by the Institutional Review Board (CIR) or Ethics Committee (EC) competent. Written approval must sent to Industex SL before the start of the study. The CIR / EC shall comply with national and local requirements for Ethics Committees as well as the regulations of the Institutional Review Board (CIR) of the US Food and Drug Administration (FDA) described in CFR21Parte56, ICHE 6 Guidelines BPC and requirements ISO 14155 (2011). The researcher should keep a copy of the approval letter CIR / EC in the Archives Research Study. You must send a copy of the letter to Guard Lun Ltd. before sending the investigational device the researcher.
12.2.2 Informed consent

The informed consent form should comply with regulations regarding informed of the Spanish legislation on the subject and guidelines of GCP from ICH regarding the information to be provided to participants under the study, and must comply with the Standards ISO14155 (2011). The informed consent form that must be used in the study must be approved in writing by the Institutional Review Board (CIR) or Ethics Committee (EC) competent. The researcher must obtain the written consent signed the tutor / subject's legally authorized representative, consent must be signed and dated before starting any activity related to the study.

12.3 MODIFICATIONS TO PROTOCOL

The researcher may propose an amendment to the protocol. The amendment will be prepared and approved by Industex SL, in accordance with SOPs. The amendment must be submitted to the Institutional Review Board (CIR) or Ethics Committee (EC) competent. All relevant amendment must be notified to the CIR / EC, and the application of that amendment only can be made after approval by the CIR / EC.

If for unforeseen reasons it is necessary to deviate from the previously indicated procedures, protocol deviations should be considered by the representative person from Industex SL. Any deviation must be approved by the Technical Director of Industex SL. The deviation and the reasons will be described on relevant Form Deviation Protocol, to be signed and stored in the corresponding section of Archive Studio once collected the approval of the Medical Director.

12.4 CONFIDENTIALITY OF PATIENT DATA

The name and personal data of the subject will be kept confidential and not be published in any way. However, the monitor or representative of the promoter and the representatives, auditors and inspectors from regulatory agencies may have access to medical records to verify the authenticity of the data collected.

Declaration on Transfer of Personal Data under pseudonymous
The promoter hereby certifies that the transfer of personal data under a pseudonym will be just in accordance with Articles 12 and 13 of the regulations on documentation and communication of GCP guidelines. Likewise, the promoter certifies that people who do not allow the transfer of data will not be admitted in research.

**Declaration regarding data protection**

All the requirements of data protection law will be taken into account. Access to the data is strictly limited to authorized persons. The data are protected against unauthorized access.

**12.5 WITHDRAWAL OF SUBJECTS / INTERRUPTION OF THE STUDY**

Subjects should be withdrawn from the study when deemed necessary for their welfare. The breach of protocol or the manifestation of a Serious Adverse Event may require the withdrawal of a subject. If we proceed to the withdrawal of a subject, it should indicate the reason in the notebook data collection, which will be signed by the principal researcher. If the situation is questionable, should be consulted to monitor the study or staff of the promoter. As a subject is removed from the study for Serious Adverse Event, should carry out a final physical examination. Subjects which have been withdrawn from the study due to an adverse event erán monitored until it is resolved adverse event.
Other reasons for removing a subject from the study can be:

- Subjects expressed a desire to leave the study.
- Any condition that, in the researcher's opinion, justify the interruption of study participation for reasons of subject safety.

In case of withdrawal of subjects, the researchers record the reasons. Records of excluded subject of effectiveness analysis will be maintained and included in the safety analysis and the analysis of the cohort of Intent to Treat. Should more adverse events expected to occur in the practice of similar procedures for external orthoses, clinical research will be suspended; in which case, a safety committee be constituted to decide whether you can continue the study. It will be informed of these circumstances the Ethics Committee and the conclusions of the safety committee will be submitted for assessment and decision of the EC.

The promoter may stop the study at any time.

The participation of a researcher in the study will be stopped if the recruitment rate is not the intended or is deemed not to meet the protocol requirements or regulatory requirements

### 12.6 CONTROL DEVICE

- Industex SL will supply the Instalife devices.
- Investigational devices carry an identification number and corresponding Certificate of Compliance will be saved in the Archive Study Researcher. The identification number of the device used in question recorded in the CRD of each study subject.
- The researcher kept in a safe supplies of the study registered.
- All supplies will be used exclusively for this study.
- After completion of the study, all unused devices should be returned to Industex SL in its original packaging.
12.7 MONITORING THE STUDY

The study follow-up visits include an assessment center participant prior to study initiation and a visit at the participating center, during regular surveillance visits and during research, and a final visit to be held at the end of the frequency estudio. The visits of monitoring will vary depending on subject recruitment rate, and the amount and quality of data collection.

12.7.1 Assessment of the participant center prior to the study

Before the study began, the representative of Industex SL will meet with the principal researcher and analyze the content of the protocol, the study requirements and the need and availability of related personnel. In addition the suitability of the institution participating in the study will be evaluated in terms of record keeping, regulatory requirements, logistics procedures, etc.

12.7.2 Initiation meeting at the participating center

A meeting of initiation at the participating center will be held in which will be explained all documents and procedures related to the study to all staff involved in the study to ensure that the study requirements are understood before the start of the study procedures and to assess the suitability of potential subjects before inclusion.

12.7.3 Regular surveillance visits

A representative or delegate appointed by Industex SL will monitor the study by the researcher agreed with scheduled visits. The trial will be monitored to ensure that researchers conduct the trial in accordance with the protocol, and the applicable regulations of the FDA, GCP Guidelines Deiche-6 and the requirements of the ISO14155 standard (2011). The study will evaluate monitor compliance with the study protocol by the researcher, the quality of clinical data as to its accuracy, completeness and readability, and maintenance of records, reports, and research devices. In addition, the monitor will detect potential problem areas; attitudes will recommend to prevent problems from developing and solve existing problems. Notebooks Data Collection (CRD) is checked against the hospital reports to ensure accurate recording of data. completing and updating the files of the Regulatory Study evaluated.

The monitor should have direct access to all relevant source documents. It is expected that researchers and clinicians to cooperate with the monitor estudioy supply all
Monitoring of clinical research will be done in accordance with Good Clinical Practice (GCP) under Standard Operating Procedures (SOPs) for this purpose. The monitoring reports of all follow-up visits will be made by the monitor. It must include a list of all the issues that have been monitored, problems and problem solving, corrective action, follow up of corrective actions are needed, and if necessary.

12.8 DOCUMENTATION OF STUDY

12.8.1 Regulatory documentation for the initiation of the study

The following documents must be prepared before study initiation:

- Clinical Trial Protocol Approved.
- Model Informed Consent form that is to be used.
- Signed copy of the notification of approval of the Ethics Committee (or CIR).
- Contract signed with the principal researcher or medical institution.
12.8.2 Data Collection notebooks (CRD)

Data Collection Notebooks are prepared to collect demographic and clinical information required, as described in this protocol, and the variables analyzed. Notebooks Data Collection will be completed by the researcher or the person designated for this purpose, to be properly trained in the procedures of registration requirements estudion y data. In the Study Manual guidelines and specific instructions for proper completion of the CRD will be provided. The CRD will be signed by the researcher.

Industex SL provides a CRD for each subject and each CRD will be numbered with a code of the subject. To identify the subject in the CRD only the code of the subject and the initials and date of birth of the subject is used. The researcher kept a notebook of independent recruitment with the name of the subject in question, your initials and code. an original will be sent and a copy of each completed CRD to Industex SL. The data recorded immediately available as soon as possible. The CRD will be reviewed upon receipt in the data entry center before their entry into a computer database. Cases of lost or garbled data is recorded in a data query form. Consultation forms Data will be forwarded to the research center along with copies of pages of CRD that require clarification or correction where appropriate. The researcher or study coordinator will be responsible for resolving data queries and correct CRD, where appropriate. After the visit of completion at the participating center, the originals of the CRD will be returned to Industex SL, and the researcher shall keep a copy of the CRD.

12.8.3 Maintenance and conservation or records

All documentation of the study will be kept in a safe place throughout the study. Once the study is completed, the records will be kept during the period stipulated by local regulations, but that period may not be in any case less than two years from the date of marketing the product. However, the researcher shall retain the identification form of the subject, along with the informed consent form signed for a period of 15 years from the completion of the study and in accordance with local regulations.

It must be maintained a file of study in which all regulatory documentation required is collected in order to facilitate the search if carried out an audit.

The researcher will be responsible for keeping all documents under lock and key.
12.8.4 Reports

Must submit periodic progress reports Promoter Study of the completion of the second consulta. El final study report should be prepared and submitted to the CIR / EC and the promoter of the study within one month from the end of the study. The principal researcher will sign the final report of the study and approve its content, analysis, results and conclusiones. Los resultados can be compared with historical data.

12.9 AUDITS OF REGULATORS OR HEALTH AUTHORITIES

The US Food and Drug Administration (FDA), the European authorities or state and local health authorities may request access to all records of the study, including source documents for inspection. the collaboration of researchers and hospital staff in these audits requested. The researcher shall inform Industex SL of any audit by the FDA and other health authorities as soon as it has been notified the audit. In addition, a representative or designee Industex SL can perform similar audits and be present during the audit of the FDA or other health authorities.

12.10 DISCLAIMER

See the contract concluded by the promoter and the medical center.
13 BIBLIOGRAPHIC REFERENCES

• A. H. Dickenson. Gate control Theory of pain stands the test of time. BJA. Volume 88 (6), June 2006.
ADOPTION OF THE PROTOCOL

I confirm that I have read and understood this protocol and will work in accordance with its content and applicable laws and regulations of the country in which participating center radicael I am responsible. I accept the supervision of the study by the representative of the promoter. I will fulfill the plan of publication laid down in my contract with Industex SL.

CENTRO MÉDICO: Hospital Infanta Luisa
Responsable: Dr. Manuel Barrientos Morán (Dir. Médico)
Fecha: 09/09/2015
Firma/Sello:

PROMOTOR: Industex S.L.
Responsable MARI CRUZ LORENTE DIEZ
Fecha: 09/09/2015
Firma:

INVESTIGADOR PRINCIPAL
Responsable Dr. Manuel Barrientos Morán
Fecha: 09/09/2015
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