SPONSOR: FUNDACIÓN SEMERGEN
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NAME OF THE DRUG EVALUATED: Solanum malacoxylon 9CH

TITLE OF THE STUDY: Pilot phase II clinical trial, randomized, double-blind, controlled, single-center study to evaluate the efficacy and safety of Solanum malacoxylon 9CH in patients with calcific tendinitis of shoulder.

INVESTIGATION CENTER: Centro de Salud Montesa (Madrid-Spain)

This trial was approved by the AEMPS on 04-06-2016, after receiving a favorable opinion from the CEIC on 01-14-2016.

The protocol version 2.0 of 02-26-2016 establishes the main objective of determining the efficacy of Solanum malacoxylon 9CH, in terms of differences in the evolution of injuries in calcific tendinitis of the shoulder, by means of ultrasound compared to those subjects taking placebo.
As secondary objectives, the clinical improvement, measured in terms of pain, functionality and mobility, patient satisfaction and safety.

Design: Phase II pilot, single-center, randomized, double-blind, placebo-controlled clinical trial. During the study, four visits were carried out: a screening or baseline visit (V0), visit 1 (10 ± 5 days after V0), final visit (3 months after starting treatment) and a follow-up visit (4 weeks after the final visit).

Number of expected patients to be included: N= 104 (52 in each arm)

Inclusion criteria:
-Patients > 18 years old
-Diagnosis of calcific tendinitis of the shoulder confirmed by imaging (standard radiography [Rx] and / or ultrasound in the 3 months prior to the start of study treatment.

Exclusion criteria:
- Main calcifying lesion smaller than 2 millimeters
- Pregnant women or nursing.
- Patients who are receiving homeopathic treatment.
- Patients who are candidates for scheduled surgery in the following 2 months.
- Patients who have received treatment with corticosteroids (oral or infiltrate) or invasive procedure (shock waves, ultrasounds, etc.) in the last 3 months.

Treatment:
Study patients were randomly assigned to study treatment (Solanum malacoxylon 9CH, granules) or control treatment (placebo).
All patients who have been assigned to the study treatment group will receive orally 5 granules of Solanum malacoxylon twice a day, for the next 3 months.
Those assigned to control group receive placebo with the same posology.

Development of the study:
The study had a planned period of 12 months (until 22/09/2017) but due to a low rate recruitment was extended 3 months, until 30th of November 2017.
The study will be concluded on March 30, 2018, until the end of the last patient recruited follow-up.
The AEMPS is notified on 04-23-2018 of the end of the clinical trial.

Outcomes criterias:

Main objective

The primary endpoint will be the change in the lesion area, as measured by ultrasound. This assessment has been carried out by an external and independent sonographer from the SEMERGEN Ultrasound group, using the ultrasound machine from the Montesa Health Center.

Secondary objectives

• Clinical improvement is defined as changes in the score of the pain, functionality and mobility domains of the Constant test.

• Satisfaction with treatment will be measured using a numerical rating scale (NRS).

• The consumption of NSAIDs will be evaluated by recording the consumption of these drugs with respect to the initial consumption.

Safety parameters

For this secondary objective, variables to be measured were frequency of adverse events, the frequency of serious adverse events, and frequency of adverse events that may require discontinuation of treatment.

Results of the study:

First patient was included on 09/22/2016 and ended on 04/02/2018.

- A total of 61 patients have been included in this study, of which 50 completed the treatment.

During the follow-up period, there have been 11 early dropouts from the study:

- 2 patients by their own decision before the start of treatment and after being randomized.
- 3 patients due to loss of patient follow-up.
- 5 patients were withdrawn due to major deviation.
- 1 patient by choice.

It is found after end 22.9.2017 the recruitment period initially expected that 56 patients were included instead of the required 104.

After closure of the database, no statistical treatment thereof is performed in view of the low number of patients who completed the study (50), which represents only 48% of the total expected.

It is not declared as early termination as the planned inclusion period has been exceeded.

As specified in the protocol for the safety assessment objective, all adverse events (AAs) were recorded throughout the follow-up visits, classified according to their intensity, severity, and relationship to treatment.

Total:

22% (11; n = 50) of AA were recorded during the follow-up period, none of them being classified as severe.

6% (3; n = 50) were of moderate intensity and 16% (8; n = 50) of mild intensity. 4% (2; n = 50) were related to the treatment and 18% (9; n = 50) were evaluated as unrelated.

Diarrhea was the most frequent and represented 27% (3; n = 11) of the total AA registered. With a proportion for each of 9% (1; n = 11) the AAs reflected in the following table were recorded:

GRUPO TRATAMIENTO	DESCRIPCIÓN	DESENLACE	INTENSIDAD	GRAVE	RELACIÓN CON EL TRATAMIENTO
Solanum malacoxylon 9 CH	Diarrea	Resuelto (sin secuelas)	Leve	No	Relacionado
Solanum malacoxylon 9 CH	Diarrea	Resuelto (sin secuelas)	Leve	No	No relacionado
Placebo	Diarrea	Resuelto (sin secuelas)	Moderado	No	No relacionado
Solanum malacoxylon 9 CH	Infección odontógena	Resuelto (sin secuelas)	Leve	No	No relacionado
Solanum malacoxylon 9 CH	Gonalgia	Sin resolver	Leve	No	No relacionado
Solanum malacoxylon 9 CH	Exacerbación dolor	Resuelto (sin secuelas)	Leve	No	No relacionado
Solanum malacoxylon 9 CH	Estreñimiento	Resuelto (sin secuelas)	Leve	No	Relacionado
Solanum malacoxylon 9 CH	Sensación vertiginosa	Resuelto (sin secuelas)	Leve	No	No relacionado
Solanum malacoxylon 9 CH	Estudio alergológico	Resuelto (sin secuelas)	Leve	No	No relacionado
Placebo	Infiltración corticoides hombro derecho	Resuelto (sin secuelas)	Moderado	No	No relacionado
Placebo	Dorsalgia	Desconocido	Moderado	No	No relacionado

By treatment group:
6% (3; n = 50) belonged to the placebo group and 16% (8; n = 50) to the group that received Solanum malacoxylon 9CH.
Both AEs related to the treatment belonged to the group that received Solanum malacoxylon 9CH; one patient had diarrhea classified as mild intensity and the other constipation, also classified as mild intensity.
The annual monitoring reports and two DSURs (May 2017 period 06.04.2016 to 05.04.2017 and April 2018 covering period 06.04.2017 to 05.04.2018) corresponding to the experimental phase of the study have been sent to the authorities.
The safety data analysed in this period did not show a risk for the study population.

CONCLUSION

The pilot phase II clinical trial to determine the efficacy and safety of Solanum malacoxylon 9CH in calcific tendinitis of the shoulder did not allow to obtain efficacy data, with a recruitment rate of 48% above the established objective to have sufficient statistical power. The safety results obtained during the follow-up period revealed a favorable security profile for the study population.