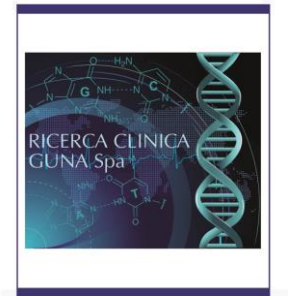

GUNA
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CLINICAL INVESTIGATION PLAN CONCERNING THE MEDICAL DEVICE

"*AKI*TENMED"

TITLE: Evaluation of collagen-based medical device treatment combined with physiotherapy in subjects with achilles tendinopathy. Multicenter randomized clinical investigation; AKITENMED STUDY.

IDENTIFICATION CODE: MDG20180000

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CLINICAL INVESTIGATION PLAN VERSION AND DATE: n° 4.4 modif. of 01 December 2021

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1. LISTA DELLE ABBREVIAZIONI

AE	Adverse Event
ECM	Extracellular matrix
NSAIDs	Non-steroidal anti-inflammatory drugs
GCP	Good clinical practice
Gly	Glycine
Hyl	Hydroxylysine
Hyp	Hydroxyproline
MD	Medical Device
NaCl	Sodium chloride
Pro	Proline
PRP	Platelet Rich Plasma
MR	Magnetic resonance
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction

2. INTRODUCTION

2.1 Insertional-non-insertional-mixed yarrow tendinopathy

Achilles tendinopathy is a condition characterized by inflammation of the Achilles tendon. The latter is the largest tendon in the human body, is about 15 cm long, and originates from the triceps muscle of the sura, formed by the twin muscles, whose tendon fibers insert postero-laterally to the calcaneal bone, and the soleus, whose tendon fibers insert antero-medially to the calcaneal bone, giving rise precisely to the Achilles tendon.

Two types of forces act on the Achilles tendon: one exerted by the tendons of the gastrocnemius and soleus muscles, and one resulting from the compressive action of the calcaneal bone on the tendon. In case of excessive mechanical stress by these two forces, the tendon undergoes degeneration triggering tendinopathy [1].

Approximately 6% of the general population suffers from achilles tendinopathy during their lifetime [2]. Achilles tendinopathies are classified into insertional tendinitis and noninsertional tendinitis. Insertional tendinitis involves the lower part of the tendon, where the tendon inserts at the level of the calcaneus, and can affect even patients who are not particularly athletically active [3].

Noninsertional tendinitis occurs when the fibers in the middle portion of the tendon are affected, affects young and athletic people the most and has a high incidence (30-50%) in middle-aged individuals. Such pathology in the young and athletic patient often requires a complete cessation of physical activities for long periods of time and may go so far as to interfere with work activities, thus in fact constituting a significant social cost, as well as a highly disabling and impacting factor on the patient's quality of life.

Clinically, patients present with reduced dorsiflexion and plantarflexion deficits with acupressure tenderness in the insertional and noninsertional sites of the affected achilles region. On inspection of the posterior calcaneal portion, patients may present with an erythematous and mildly edematous area associated with an initial picture of swelling at the achilles site. Patients also report pain aggravated by exercise (running, jumping, walking).

Regarding diagnosis, in the first instance, it is advisable to perform a standard loaded radiograph of the foot to visualize any enthesopathy and peri- and intra-tendinous calcifications. It is also advisable to perform a musculoskeletal ultrasonography and as a second-level investigation an MRI, in order to visualize optimally the soft tissues and thus a tendon degeneration, although signs of tendon degeneration are not always accompanied by a positive clinical picture, either in the acute or subacute phase.

We can distinguish conservative and nonconservative treatments.

Conservative treatments include: exercise in an eccentric regimen as recommended by the 2010 "American Physical Therapy Association" guidelines (Grade A) [4]; focused shock wave physical therapy as suggested by the recent study by "Chimenti et al. " of 2017 (Grade B) [1]; the use of nocturnal splints,

on the other hand, does not present sufficient evidence to justify their use; corticosteroid and platelet-rich plasma (PRP) infiltrations, although frequently used in clinical practice, are not supported by solid scientific evidence.

In the literature, by contrast, we recall the 2012 study by Monto RR. who reports the satisfaction of 28 out of 30 patients with achilles tendinopathy treated with PRP [5] and several other Authors who have gained experience in this regard [6;7;8;9;10;11]. The use of SVF adipose stromal fraction in the treatment of tendinopathies is still being studied [12;13].

Non-conservative treatments include various surgical approaches, which may involve more complex tendon transfer surgeries, such as transposition of the long flexor hallux, or simpler scarification approaches; minimally invasive endoscopic approaches; or percutaneous echo-guided procedures, all of which currently lack sufficient scientific support.

Conservative treatment alone is often found to be unsatisfactory in 40% of cases, while proposed traditional and minimally invasive surgical treatments (such as scarifications) have mixed results and are not always reproducible in the literature.

In light of this, there appears to be a clear need to find minimally invasive therapeutic alternatives that can guarantee to achieve better results than the current ones in the early treatment of acute and subacute insertional and noninsertional achilles tendinopathies.

2.2 Role of collagen in the pathogenesis of Achilles tendinopathy

Recently, a line of medical devices based on collagen and ancillary substances has been produced by Guna S.p.a., including MD-Tissue Collagen Medical Device. Collagen is the most abundant protein in mammals, accounting for about 5 to 6 % of an adult human's body weight. A third to a quarter of all protein mass in higher animals is collagen: from bones to tendons, joint capsules to muscles, ligaments to fasciae, teeth to serosae, and skin to extracellular matrix (ECM). It is found in most tissues, and particularly in those tissues that require both flexibility and strength such as skin, tendons, and muscle fascias. There are 14 types of collagen, the most represented type being type I. In humans, the peak of collagen biosynthesis occurs from age 45 to 60. Thereafter, its production drops very rapidly, along with that of elastin and proteoglycans. The unit-base of collagen is tropocollagen, a glycoprotein formed by the intertwining of three left-handed polypeptide chains carrying glucose and galactose molecules, attached only to the amino acid molecule Hydroxylysine (Hyl), one of only four amino acids constituting tropo-collagen with Glycine (Gly), Proline (Pro) and 4-Hydroxyproline (Hyp). This tight triple helix provides the structural strength and rigidity, but also the strength and flexibility necessary for perfect collagen function. The arrangement of fibrils in the formation of collagen fibers, provides the structure with great robustness in terms of strength, inextensibility, incompressibility, but also plasticity, flexibility, resistance to loading, and resistance to twisting. Due to its abundance in nature (more than 90 % of fibrous proteins are made up of type I collagen) and its unique physical and

biological properties, type I collagen has been used extensively to produce medical devices, and among these are the injectable medical devices produced by Guna S.p.a. called Collagen Medical Devices based on porcine collagen. In orthopedics and traumatology and in rehabilitation medicine, this evidence on the structural role of collagen holds particular importance since all extra- and intra-articular structures are basically made up of this molecule [14;15;16].

2.3. Collagen in the therapy of achilles tendinopathy

In view of the morpho-structural changes that characterize Achilles tendinopathy, the use of injectable medical devices such as Collagen Medical Devices might find therapeutic indication. For some years now, in fact, the use of injectable medical devices based on porcine collagen and ancillary substances of natural origin (*Collagen Medical Devices* GUNA) has been introduced in the treatment of painful and degenerative pathologies of the locomotor system, which allow a more effective and specific placement of collagen in situ with the function of vehiculation and stabilization. The collagen used in Collagen Medical Devices GUNA undergoes a special process of tangential filtration, sterilization, and molecular weight control, resulting in a pure product. Infiltrative therapy based on *Collagen Medical Devices* would make it possible to replace, reinforce, structure and protect (adhesion barrier) cartilage, tendons, ligaments, joint capsules, etc., improving the arrangement of collagen fibers and all the anatomical structures in which it is present and, at the same time, provide mechanical type support to the affected district.

In particular, MD-Tissue *Collagen Medical Device* could play a positive role in the treatment of Achilles tendon pathology.

3. SCIENTIFIC REQUIREMENTS

3.1. Title of the research

Evaluation of collagen-based medical device treatment combined with physiotherapy in subjects with achilles tendinopathy. Multicenter randomized clinical investigation; AKITENMED STUDY.

3.2. Purpose of research

Considering that there are no strong evidence-based guidelines in the area of treatment of achilles tendinopathy, the purpose of this research project is to understand through a multicenter, randomized clinical investigation the impact of treatment with a porcine collagen-based medical device administered in the peri-tendon area in combination with physiotherapy on pain reduction and functional improvement of the investigated tendon.

3.3. Design of the clinical investigation

The multicenter, randomized clinical investigation is prospective, and will have a total duration of 8 weeks.

After enrollment, subjects will be randomized and assigned to two experimental groups:

- **Group A** which, alongside physiotherapy (eccentric strengthening protocol) will receive MD-Tissue Collagen Medical Device.
- **Group B** which, will implement only physiotherapy (eccentric strengthening protocol).

Variables will be assessed at baseline (T0 time), after 1 week (T1w), after 2 weeks (T2w), after 3 weeks (T3w), or at the end of injection treatment, and after 6 weeks after enrollment (T6w/FU). Further evaluation will be carried out after 2 weeks, or after 8 weeks T8w/FU) from the start of the clinical investigation.

After enrollment, subjects in both groups will begin a 6-week physiotherapy course (eccentric strengthening protocol). Each session will consist of Achilles tendon stretching exercises. See § 3.12.

3.4. Duration of the clinical study

The clinical study will last for 8 weeks (see Figure 1). A subject selection and recruitment period of 8 months is expected. The total duration of the clinical study will be 10 months.

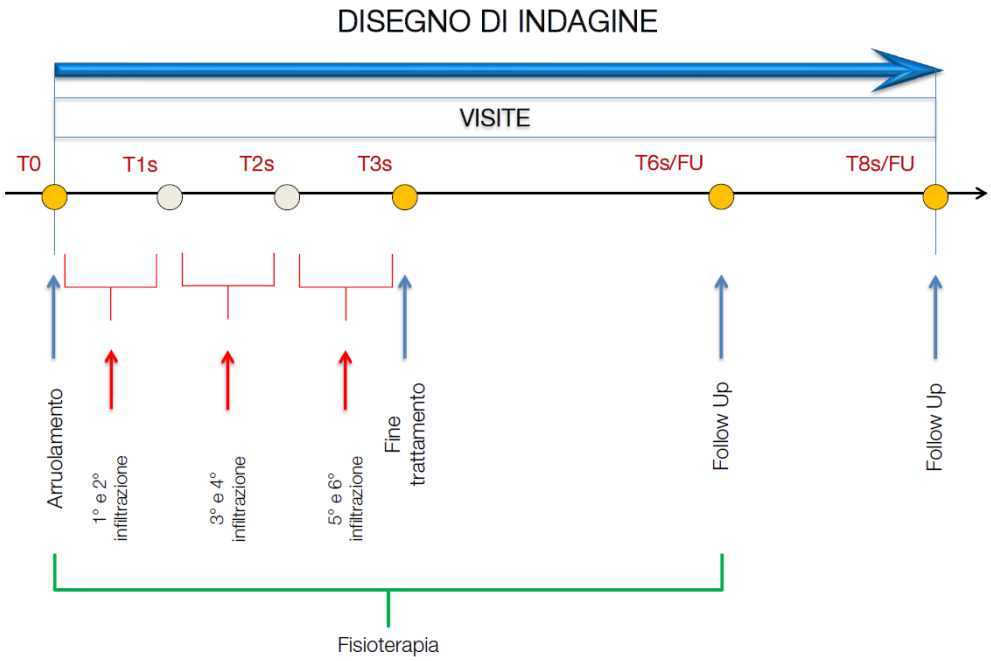


Fig.1 Study design flow chart

3.5. Participant population

A total of 72 subjects with achilles tendinopathy will be enrolled. The recruitment phase will be closed no sooner than the number of subjects in the clinical investigation plan has been reached.
Only subjects will be included in the two experimental groups:

- belonging to the departments of the experimental centers;
- who meet the inclusion criteria and have no exclusion criteria.

3.6. Inclusion Criteria

- Male and female subjects aged 18 to 60 years;
- Subjects with tendon pain for not more than 6 weeks;
- Subjects with clinically diagnosed and ultrasonographically confirmed insertional/noninsertional/mystic tendinopathy;
- Subjects with a VISA A score between 50 and 75;
- VAS ≥ 5;
- Subjects able to understand and answer the SF12 questionnaire;
- Subjects able to understand and sign the informed consent.

3.7. Exclusion Criteria

- subjects who have had surgery in the investigated area or lower extremity;
- subjects who have previously undergone physiotherapy.
- subjects with autoimmune diseases;
- subjects with peripheral neuropathy;
- subjects with calcific tendinopathy
- subjects with pain of direct traumatic origin;
- subjects with local/systemic infections;
- subjects with neoplastic diseases;
- subjects with gout;
- subjects on corticosteroid treatment at the time of enrollment;
- subjects who have used corticosteroids or fluoroquinolones in the three months prior to enrollment;
- subjects who have used NSAIDs in the week prior to enrollment;
- subjects who are pregnant and lactating;
- subjects with contraindications to acetaminophen use;
- allergy to porcine collagen.

3.8. Randomization and codification of subjects

Recruited subjects will be placed in Group A or B according to a 1:1 randomization list with 10 blocks of 9 subjects generated by software (2 blocks for each experimental center); the use of blocks will result in balanced groups.

A randomization list is planned for each Experimental Center comprising 18 subjects; the inclusion of subjects within the two experimental groups will take place progressively following the order of enrollment. Competitive enrollment is established among the participating Experimental Centers, which will end when the 72 subjects under the Clinical Investigation Plan have been enrolled. Each Experimental Center will be allowed to enroll a maximum of 18 subjects.

The randomization list will be kept by each Principal Investigator and the Clinical Research Unit of Guna S.p.a.

At the time of enrollment, each subject will be assigned a complex alphanumeric identification code consisting of the progressive enrollment number followed by an alphanumeric code generated through *Random Sequence Generator* at www.random.org.

The complex code is found to be in compliance with the current Privacy Regulations regarding coding of subjects participating in clinical trials.

3.9. Procedures

3.9.1 Timing of assessment

T0 baseline: VISIT enrollment; prior to start of treatment
T1 week: first and second treatment sessions + physiotherapy
T2 weeks: third and fourth treatment sessions + physiotherapy
T3 weeks: VISIT fifth and sixth treatment session + physiotherapy
T6 weeks/FU: VISIT - end of physiotherapy
T8 weeks/FU: VISIT - end of clinical investigation.

3.9.2 Visiting Plan

T0 BASAL: Enrollment

During the daily clinical activity, the investigators participating in the study will slect subjects with achilles tendionopathy through the criteria given in section 3.16 and identify those meeting the inclusion and exclusion criteria. After fully explaining the puposes, aims and procedures in the study investigation plan, the subject will be offered participation in the study. Finally, the selected subject will be asked to view the information form and date and sign the Informed Consent

The subject according to the randomization list will be assigned to Group A or Group B.

We will then proceed with the objective examination and collection of the information required by the appropriately prepared Electronic Data Collection Form.

It will be followed by:
- assessment of VISA-A score
- assessment of pain according to the VAS scale
- administration of the SF-12 quality of life test.

Previous or ongoing drug treatments of any kind will be documented.
In order to monitor the consumption of analgesic used during the clinical investigation in case of pain onset (paracetamol 1000 mg), a clinical diary will be given to the subject in which to indicate the day and dose of medication used.
The enrolled subject will be given a complex alphanumeric identification code consisting of the progressive enrollment number followed by an alphanumeric code generated through Random Sequence Generator at www.random.org.
All enrolled subjects will be trained to practice physiotherapy for the 6 weeks in the clinical study plan. Subjects belonging to Group A will be administered MD-Tissue.

T1 week:
This visit will consist of an evaluation regarding the tolerability of the administered product. During this week, the subject will have received the first two infiltrations stipulated in the clinical investigation plan. It will be verified that the clinical diary regarding analgesic consumption used has been properly completed and that the physiotherapy course is proceeding according to the clinical investigation plan.

T2 weeks:
This visit will consist of an evaluation regarding the tolerability of the administered product. During this week, the subject will have received the first two infiltrations stipulated in the clinical investigation plan. It will verify that the clinical diary regarding analgesic consumption used is correctly completed and that the physiotherapy course is proceeding according to the clinical investigation plan.

T3 weeks:
At this visit, the sixth injection treatment will be administered (the fifth was given during the week). The investigator will then proceed with the objective examination and assessment of the end points in the clinical investigation plan.
Including:
- assessment of the VISA-A score
- assessment of pain according to the VAS scale
- administration of the SF-12 quality of life test.

The consumption of analgesic medication used in case of pain onset will be assessed through clinical diary. The subject will be invited to continue the physiotherapy course for an additional 3 weeks.

T6 weeks/FU:

At this visit, the objective examination and assessment of the end points in the clinical investigation plan will be conducted.

Including:

- assessment of the VISA-A score
- assessment of pain according to the VAS scale
- administration of the SF-12 quality of life test.

The consumption of analgesic medication used in case of pain onset will be assessed through clinical diary.

T8 weeks/FU:

The investigator after 2 weeks will re-evaluate the subjects clinically. It will be evaluated, VISA-A score, pain VAS and SF-12 quality of life test will be administered.

In addition, the consumption of analgesic drug used in case of pain onset will be assessed through clinical diary.

The occurrence of Adverse Events will be assessed at each visit. All Adverse Events (AEs), Serious Adverse Events (SAEs), and Suspected Serious and Unexpected Adverse Reactions (SUSARs) that appeared between the date the Informed Consent was signed and the end of the clinical investigation will be recorded and reported.

The collected data should be entered by the Principal Investigator of each Experimental Center in the Electronic Data Collection Form provided by Guna S.p.a.

Specifically, it is planned to obtain a data collection that is schematically described in the following table (Tab. 1), which shows the records to be made at each visit:

EXPERIMENTAL PROCEDURES	VISIT			VISIT	VISIT	VISIT
	T 0	**T 1 WEEK**	**T 2 WEEKS**	**T 3 WEEKS**	**T6/FU WEEKS**	**T8/FU WEEKS**
	Enrollment	1°-2° infiltration	3°-4° infiltration	5°-6° infiltration	Physiotherapy termination	End of clinical Investigation.
Clinical and ultrasonographic diagnosis of Achilles tendon pathology	**X**					
Evaluation of Inclusion criteria	**X**					
Signing of informed consent	**X**					

Signature of Consent to the processing of personal data	**X**					
Collection of socio-demographic data	**X**					
Medical history collection	**X**					
Evaluation VISA-A score	**X**			**X**	**X**	**X**
Evaluation VAS	**X**			**X**	**X**	**X**
SF12 questionnaire administration	**X**			**X**	**X**	**X**
Infiltrative treatment		**X**	**X**	**X**		
Physiotherapy		**X**	**X**	**X**	**X**	
Clinical diary evaluation	**X**	**X**	**X**	**X**	**X**	**X**
Evaluation of concomitant pathologies		**X**	**X**	**X**	**X**	**X**
Adverse Event Evaluation (AE/SAE)		**X**	**X**	**X**	**X**	**X**

Tab.1 Data collection during the Study

3.10. Materials needed to conduct the clinical investigation

- *Collagen Medical Device (MD-Tissue)* 2-mL vials in sufficient numbers for the needs of the clinical investigation.

This material will be sent by Guna S.p.a. to the pharmacy of each Experimental Center in suitable quantity for conducting the study.

3.11. Gruppi in studio

- ***Group A (Collagen Medical Device):***

This Experimental Group will be treated with subcutaneous (s.c.) injections of 2 ml volume of:

- MD-Tissue (GUNA, Milan-Italy)

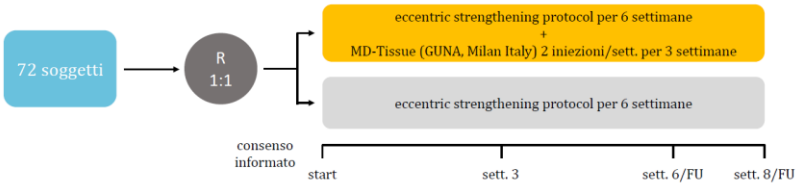
Composition for 2 ml: collagen 100 micrograms

Excipients: Ascorbic acid, Magnesium gluconate, Pyridoxine hydrochloride, Riboflavin, Thiamine hydrochloride, NaCl, Water for injection.

Subjects will be treated with No. 6 peri-tendon injections (2 infiltrations per week for three weeks).

- ***Group B:***

This Experimental Group will implement only physiotherapy (eccentric strengthening protocol) for a period of 6 weeks.



3.12. Eccentric strengthening protocol

Both Group A and Group B will undergo a 6-week eccentric training protocol of the plantar ankle flexor muscles of the affected side. The exercises will be shown to each patient by the investigating physician at the time of enrollment; a physiotherapy booklet will also be provided to each patient, which will provide all the information to repeat the exercises at home. The exercise program will be as follows:

1. Ankle plantar flexor muscles stretching in orthostatic position (gastrocnemius stretching: figure 1a; soleus stretching: figure 1b) - 3 repetitions of 30''.
2. Eccentric reinforcement 1: on a step, starting from a plantar flexion position the patient with slightly flexed knee (Figure 2a) reaches maximum ankle dorsiflexion in 5'' - return to starting position using the contralateral limb for pushing (Figure 2b) - 3 sets of 15 repetitions each.
3. Eccentric reinforcement 2: On a step, starting from a plantar flexion position the patient with extended knee (Figure 3a) reaches maximum ankle dorsiflexion in 5'' - return to starting position using the contralateral limb for pushing (Figure 3b) - 3 sets of 15 repetitions each.
4. Finish with ice application on Achilles tendon (1' application followed by 1' break) - repeat 3 times.

The entire protocol will be repeated 2 times a day, every day.

Patients will be asked to gradually increase the intensity of the exercises, including applying an overload of up to 5 kg, based on their ability to endure the exercise without pain and discomfort at the Achilles tendon region.

In Group A, the exercises will begin on the day of the first infiltration session.

To increase adherence to the intervention protocol, a physiotherapy booklet will be distributed with tables containing dates indicating the days the patient performed the protocol exercises, also with blanks to add any notes on medication use or complications that occurred.

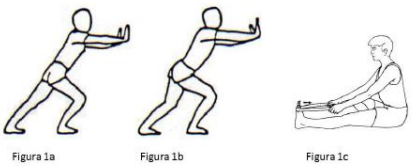


Figura 1a Figura 1b Figura 1c


Figura 2a Figura 2b


Figura 3a Figura 3b

3.13. Diagnosis of achilles tendinopathy

Subjects with symptomatology referable to Achilles tendinopathy will be included in the clinical investigation: tenderness on palpation, relief on palpation of increased size of the Achilles tendon compared with the contralateral. The clinical diagnosis will have to be confirmed ultrasonographically.

3.14. Criteria of effectiveness

3.14.1 Primary Endpoint

The primary end point will be assessed at T8s/FU and will involve:

- Assessment of the VISA-A questionnaire score at time T8w/FU compared to time T0. A difference between the two groups of 12 out of 100 points on the questionnaire can be considered clinically significant [17].

3.14.1. Secondaries End Points

- Evaluation of VISA-A score at time T3w andT6w/FU compared to time T0
- Assessment of the VAS score at time T3w, T6w/FU and T8w/FU compared to time T0
- Evaluation of the SF12 questionnaire at time T3w, T6w/FU, and T8w/FU compared to time T0.
- Evaluation of the fraction of subjects in each group achieving Minimal Clinical Disease (MCD) considering that the MCD of the VISA-A questionnaire is 18.5 (90% MCD).
- Assessment of analgesic drug unit consumption based on clinical diary at time T3w, T6w/FU and time T8w/FU (paracetamol 1000 mg. will be used as "rescue dose" in case of onset/recurrence of pain).
- Evaluation of the fraction of subjects in each group who drop out early in relation to Adverse Events (AE/SAE/SUSAR).

3.15. Early abandonment of the clinical study

Subjects may leave the clinical study for the following reasons:

a. at their own request (even without a reason);
b. at the discretion of the investigator;
c. if they incur an Adverse Event.

Subjects who drop out of the clinical study before its completion will undergo a final evaluation similar to the subjects who completed it, unless the subject expressly declines.

The reason for abandonment will be reported on the Data Collection Form.

4. STATISTICS

4.14. Sample size

A one-covariance analysis for two arms of 28 subjects each, in which the covariate of interest differs by 12 units in its mean value between the two arms (compared with a null hypothesis of no difference), with a common standard deviation assumed to be 15 units, and an R^2 value assumed to be 0.2 has a

power of 90.75% in discriminating the established difference between mean values, using an F-test at a significance level of 0.05.
Assuming dropout patients to be 20% of the total, the inflated sample size of the protocol becomes 36 patients per arm.

4.15. Plan of statistical analysis

The primary endpoint will be evaluated by Ancova, as described in the numerosity calculation.
Secondary endpoints will be assessed as follows: 1) the VISA-A score at time T3s andT6s/FU compared with time T0 with Anova at repeated measures between group and within group; 2) the VAS at time T3s, T6s/FU and T8s/FU compared with time T0 with Anova at repeated measures between group and within group; 3) the SF12 questionnaire at time T3s, T6s/FU and T8s/FU compared with time T0 with Anova at repeated measures or Friedman's test; 4) the fraction of subjects in each group reaching Minimal Clinical Disease (MCD) considering that the MCD of the VISA-A questionnaire is 18. 5 (90% MCD) with Fisher's exact test; 5) the units of analgesic drug consumed according to the clinical diary at time T3s, T6s/FUs and time T8s/FUs (paracetamol 1000 mg will be used as "rescue dose" in case of pain onset/recrudescence) with Friedman's exact test; 6) the fraction of subjects in each group who drop out of the investigation early in relation to Adverse Events (AE/SAE/SUSAR) with Fisher's exact test.

Statistical significance will be assumed for $p < 0.05$, unless corrected for multiple testing.

5. ETHICAL REQUIREMENTS

5.1. Information to the subject

The purposes and modalities of the investigation will be explained to each subject through an information document (Informed Consent), containing what is verbally stated by the clinician. The subject will be required to date in his or her own hand and sign the consent document.
A copy of the document will be issued to the subject while the original will be kept by the investigator.

5.2. Usefulness of the results

There are currently no studies in the literature that have evaluated the efficacy of *Collagen Medical Devices* GUNA treatment in subjects with Achilles tendinopathy. The results of the present clinical investigation may provide useful elements for integrating therapeutic options in this patient population.

5.3. Adverse Events

An Adverse Event is defined as any harmful clinical event that will occur during the course of the clinical investigation in one of the subjects comprising the study population who has undergone one of the treatments in the investigation plan.
Adverse events will be classified into serious (SAE) non-serious (AE) and Suspected Serious and Unexpected Adverse Reactions (SUSAR).

An Adverse Event is defined as serious if (ICH-GCP DM 15/07/1997):

- it causes the death of the subject involved in the investigation
- places the subject's life in danger
- is such as to require hospitalization
- is such as to require prolonged hospitalization
- is such as to cause permanent or temporary disability
- leads to a congenital anomaly or birth defect

In all other cases, the Adverse Event will be non-serious and will be classified as:
- *mild* does not interfere with normal activities of daily living and resolves spontaneously;
- *moderate*, interferes with activities of daily living but resolves spontaneously;
- *severe*, prevents daily life activities and does not resolve spontaneously.

All personnel who come in contact with study subjects must report Adverse Events reported by subjects to the Investigator, who has a duty to collect all possible data about them.

- Adverse events (AEs) will be reported within 48 h by the Principal Investigator to the Clinical Research Unit of Guna S.p.a, through telephone, email, appropriate form and simultaneously through e-CRF.
- Serious Adverse Events (SAEs) and Suspected Serious and Unexpected Adverse Reactions (SUSARs) will have to be reported to the Sponsor immediately (within 24 h maximum) through telephone, email, appropriate form and simultaneously through e-CRF by the Principal Investigator and communicated to the Ethics Committee and the Ministry of Health.

The investigator should ensure that procedures are in place to ensure that the event is resolved.
In the case of nonserious Adverse Events (AEs), it is necessary to keep in mind that they can still give rise to serious events, which is why each Adverse Event must be monitored.
Adverse Events that have not yet resolved at the end of the study will be followed up by the Investigator; each subject who has experienced an Adverse Event will be contacted at least once a month after the conclusion of the study for as many months as deemed appropriate.

5.4. Privacy Protection

The identities of data subjects will be known only to the Investigators and the Clinical Monitor in charge of monitoring the investigation. Reference will be made to Regulation (EU) 2017/745.

5.5. Data properties

All data collected will belong to Guna S.p.a. Milan, Italy, sponsor of the clinical study.
Additional information regarding data ownership can be found in the Economic Agreement document.

5.6. Data processing and publication

Full respect for the anonymity ofe the subjects participating in the sclinical study will be ensured. Data collection, data processing, any scientific publications or presentations at conferences of the results of the clnical study will be conduced in accordance with the Current Privacy Legislation. Regulation (EU) 2017/745

5.7. Funding

This research is funded by GUNA S.p.a.
Please refer to the Economic Agreement for further information.

5.8. Reference Code of Ethics.

Reference is made to the Declaration of Helsinki (Fortaleza 64th 2013) and the principles of Good Clinical Practice (GCP) will be followed (D.leg. June 24, 2003 - n.211 at G.U. n.184 of 09/08/2003).

5.9. Subjects Insurance

Insurance coverage for all enrolled subjects will be provided by GUNA S.p.a for the entire duration of the clinical study project.

6. PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

The Investigators reserve the right to discontinue the investigation at any time for reasonable medical and/or administrative reasons. Reasons for discontinuation will be documented; the Ethics Committee and the Ministry of Health will be informed of the decision.

7. GLOSSARY

Medical device: Any instrument, apparatus, implant, substance or other product, whether used alone or in combination, including computer software used for proper functioning, and intended by the manufacturer for use in man for the purpose of diagnosis prevention, control, therapy or mitigation of a disease; diagnosis, control, therapy, mitigation or compensation for an injury or handicap of study, replacement or modification of anatomy or a physiological process; of intervention in conception, which product does not exert its principal action, in or on the human body, for which it is intended, by pharmacological or immunological means, nor by metabolic process but whose function may be assisted by such means.

8. ATTACHMENTS TO THE INVESTIGATIONAL STUDY PLAN

- **A.** Synopsis of the Investigation
- **B.** Informed Consent (disclosure and consent)
- **C.** Consent to the processing of personal data (information and consent)
- **D.** VISA-A questionnaire
- **E.** Pain Visual Analog Scale (VAS)
- **F.** SF12 questionnaire
- **G.** Clinical diary
- **H.** Physiotherapy booklet
- **I.** Flow chart of the investigation

9. BIBLIOGRAFY

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