CLINICAL INVESTIGATION PLAN (CIP)
FOR A MEDICAL DEVICE
"SMAGENART"

TITLE: EVALUATION OF THE PERFORMANCE AND SAFETY OF A TYPE I COLLAGEN-BASED MEDICAL DEVICE (MD-SMALL JOINTS COLLAGEN MEDICAL DEVICE) IN THE TREATMENT OF RHIZOARTHROSIS. "SMAGENART PILOT STUDY"**.**

IDENTIFICATION CODE:	MDG20232202
EUDRACT:	NA
CLINICAL INVESTIGATION PLAN VERSION AND DATE:	n° 3.0 in 21 September 2023
ACTORS:	Dr. Federico Giarda, Dr. Vincenzo Miranda.
SIGNATURE OF SCIENTIFIC COORDINATOR:	Dr. Federico Giarda _____
DATE:	21-09-2023
NUMBER OF PAGE	n° 33

GENERAL INFORMATIONS

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Sponsor	**Guna S.p.a.** Via Palmanova, 71 20132 Milano, Italia Tel: +39 02280181 e-mail: *clinical@guna.it*

Study ID Name	*"SMAGENART PILOT STUDY"*

Study Type	One sample bicentric pilot Clinical Investigation

Condition	**Intervention**	**Phase**
Rizarthrosis	MD-Small Joints *Guna Collagen Medical Device*	IV Post Market

Operative Units	**ASST Grande Ospedale Metropolitano Niguarda** S.C. di Medicina Riabilitativa e Neuroriabilitazione e Dipartimento Neuroscienze Testa Collo Piazza dell'Ospedale Maggiore, 3 20162 Milano, Italia **Istituto Neurologico Mediterraneo I.R.C.C.S Neuromed** U.O.S.D. Medicina del Dolore Via Atinense, 18 86077 Pozzilli (IS), Italia

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DECLARATION OF CONFORMITY

I agree to conduct this Clinical Investigation in accordance with all the requirements of the Investigation Plan, according to the Good Clinical Practice (ICH/GCP) guidelines, the principles set forth in the Declaration of Helsinki (Fortaleza 64th, 2013), and the applicable regulations [Regulation (EU) 2017/745].

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1. SYNOPSIS

TITLE	"Evaluation of the performance and safety of a Type I collagen-based medical device (MD-Small Joints Collagen Medical Device) in the treatment of rhizoarthrosis. "SMAGENART Pilot Study"
STUDY DESCRIPTION	Multicenter pilot study based on a One sample design. The variables will be assessed at 4 different time points: at baseline (time T0), after 3 weeks (T3s), after 6 weeks (T6s), and after 16 weeks (T16s/FU), i.e., after 10 weeks from the end of the infiltrative treatment.
OBJECTIVES	The purpose of this research is to evaluate, using the Visual Analogue Scale (VAS), the performance of an intra-articular and peri-articular treatment with a collagen-based medical device in terms of pain reduction and joint function recovery in subjects affected by symptomatic rhizoarthrosis. The safety of the treatment will also be assessed.
PRIMARY ENDPOINT	The primary endpoint will consist of the evaluation, through the Visual Analogue Scale (VAS), of the performance of MD-Small Joints Collagen Medical Device in reducing pain associated with trapeziometacarpal osteoarthritis, at time T6 weeks (T6s) compared to T0. A reduction in VAS score of at least 30% is considered clinically significant.
POPULATION	A total of 42 subjects responding to the selection criteria will be progressively enrolled at the Clinical Investigation Centers involved.
SELECTION CRITERIA	Inclusion Criteria: • Male and female subjects aged between 18 and 75 years. • Subjects with clinically diagnosed symptomatic rhizoarthrosis confirmed radiographically (Stage I and II according to the classification of Eaton and Littler). • Subjects with a VAS score ≥ 5. • Subjects with joint pain for at least 1 month. • Subjects not using trapeziometacarpal orthotic devices. • Subjects who agree not to take analgesics within 24 hours before the scheduled visits. • Subjects capable of understanding and signing the Informed Consent.

	Exclusion Criteria: • Subjects with rheumatological pathology involving the hands. • Subjects who have undergone surgery on the hand affected by pathology. • Subjects who have received HA infiltrations in the trapeziometacarpal joint in the last 3 months. • Subjects who have taken anti-inflammatory drugs in the last 7 days and/or corticosteroids in the last 30 days. • Subjects undergoing physical therapy such as X-ray therapy, Tecar therapy, shock waves, laser therapy, ultrasound therapy in the last 3 months. • Subjects with neoplastic pathology. • Subjects with systemic infections. • Subjects with uncontrolled diabetes. • Subjects with neurological pathologies that may affect active participation in the study. • Subjects with coagulopathies or taking anticoagulants (vitamin K antagonists, heparin). • Subjects undergoing immunosuppressive therapy. • Subjects using drugs or abusing alcohol. • Subjects with allergy to porcine collagen. • Subjects who are pregnant or breastfeeding. • Subjects participating in other clinical studies during the same period. • Subjects unable to cooperate or for whom poor compliance is expected. • Any condition that, in the opinion of the investigator, recommends the subject's exclusion.
STUDY PHASE	Phase IV post market
NUMBER OF SITE	2 Clinical Investigation Centers
DESCRIPTION OF THE INVESTIGATIONAL DEVICE	The MD-Small Joints Collagen Medical Device is an injectable medical device composed of Type I porcine collagen. Each unit of the device contains 100µg of collagen per 2ml volume.
DUR4ATION OF THE STUDY	The entire clinical investigation will span over 8 months. It comprises a 4-month period for subject selection and recruitment, followed by a

	4-month period for treatment and observation.
DURATION OF THE STUDY FOR EACH SUBJECT	The duration of the study for each subject will be 4 months.

2. LISTA DELLE ABBREVIAZIONI

AE	Adverse Event
ALP	Abductor Pollicis Longus"
DASH	Disability of the Arm, Shoulder and Hand
E-CRF	"Electronic Case Report Form.''
FIHOA	Functional Index for Hand OsteoArthritis
FU	Follow Up
GCP	Good clinical practice
HA	Hyaluronic acid
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
LIM	Intermetacarpal Ligament
MD	Medical Device
SAE	Serious Adverse Event
TM	Trapeziometacarpal Joint
VAS	Visual Analogue Scale

3. INTRODUCTION

3.1 Overview of the Functional Anatomy of the Trapeziometacarpal Joint

The trapeziometacarpal joint (TM) can be considered a "saddle" or reciprocally interlocking joint, with movements primarily occurring in two planes: anterior/posterior movement on the sagittal plane and abduction/adduction on the frontal plane [1;2].
Additionally, the relatively lax joint capsule allows axial rotation of the metacarpal around its longitudinal axis [2]. This third degree of articulation enables thumb opposition movement in bi-digital grips. The most significant movement is the pinch grip between the thumb and index finger, which can be distinguished as terminal, more refined and precise for securely grasping small objects, and sub-terminal, more recurrent and instinctive, where the thumb and index finger oppose with the palmar aspect of the fingertip and can grip objects of various sizes. In this latter grip, significant radial tension force is created on the metacarpal base, stretching the joint capsule and the intermetacarpal ligament over time, making them increasingly lax. This laxity results in joint instability, causing radial subluxation of the metacarpal and joint degenerative processes [1;3].
The genesis of rhizoarthritis lies precisely in TM instability, which can be primary or secondary (traumatic). In ligamentous laxity, instability is due to excessive range of motion, where the palmar ligament, limiting metacarpal hyperextension, and the intermetacarpal ligament (LIM), stretched between the base of the first and second metacarpal bones, which normally limits abduction movement of the first metacarpal bone, play a key role. Its relaxation is the basis for external subluxation of the base of the first metacarpal bone, leading to incongruity of the joint surfaces and initiating joint instability [2;3].
Another recognized and considered frequent cause is instability due to the absence of insertion of the abductor pollicis longus (APL) on the trapezium. In cases where the APL has a double distal insertion on the trapezium and the base of the first metacarpal bone, with each contraction of the APL, the entire thumb-metacarpal-trapezium column moves into abduction, maintaining normal trapeziometacarpal joint relationships. Conversely, if the insertion on the trapezium is absent, all abduction force is exerted on the base of the first metacarpal bone, causing significant subluxation tension with a deleterious effect on the TM cartilage [4].

3.2 Osteoarthritis of the Trapeziometacarpal Joint

The term rhizoarthritis refers to the arthritic process involving the TM joint. It is a condition that affects approximately 20% of the population over 50 years of age and is more common in females (ratio 4:1), typically manifesting around menopause. In 50% of cases, symptoms are bilateral [5; 6; 7].
The repeated grasping of small objects results in radial stress on the base of the first metacarpal bone,

with a significant increase in the destabilizing force transmitted at this level and progressive laxity of the capsulo-ligamentous apparatus [8; 9]. Consequently, joint laxity, altered load distribution, cartilage deterioration, and the onset of pain occur [1]. Disease progression is accompanied by a reduction in the strength of the thenar muscles and progressive subluxation of the TM joint, which in advanced stages can lead to complete dislocation of the base of the first metacarpal bone. As a compensatory phenomenon, the first ray metacarpophalangeal joint tends towards hyperextension in an attempt to preserve grip function: the thumb assumes a characteristic deformation called "Z-thumb" [12].
From a clinical standpoint, patients present with localized pain at the base of the thumb, exacerbated by active radial abduction and/or passive rotation-opposition movements [13], resulting in functional limitation and a decline in quality of life [10; 11].
The diagnosis of rhizoarthritis is clinical, confirmed by the presence of bone deformities and the above-described signs and symptoms. Radiographic examination allows instrumental staging of the disease. Eaton and Glickel first described a classification of the pathology based on the appearance of the joint in standard radiographic projections and under stress [14; 5]. The classification most commonly used today is the Eaton-Littler classification modified by Brunelli, which, in addition to the radiographic picture, also considers the clinical-functional aspect [5].
In the first stage of rhizoarthritis, treatment is usually conservative; in the second stage and early third stage, surgical treatment may be indicated using techniques for biological stabilization of the joint [3; 15; 16]. In Eaton's third stage, prosthetic joint replacement may also be indicated, while in the fourth stage, the current trend is to perform a suspension arthroplasty surgical intervention [17].

Multiple alternatives have been proposed in the conservative management of symptomatic rhizoarthritis, with varying degrees of evidence and efficacy. These include:

Orthoses: In a recent meta-analysis, orthosis use has been shown to be beneficial in reducing moderate/severe pain in the medium term (3-12 months) and improving function, and can avoid surgery in some patients [18; 19]. Additionally, they act as an insulating layer, which can help reduce worsening symptoms related to cold. For some patients, taping may be a good alternative [20].
Motor rehabilitation: Treatments performed by therapists experienced in hand pathology lead to significant improvement in pain and function [21]. Specific manual exercises help increase grip strength, reduce pain, and improve thumb joint mobility [22].
Pharmacological therapy: The American College of Rheumatology in 2012 and the European League against Rheumatism recommended the use of one or more of the following drugs for patients with hand osteoarthritis: topical capsaicin, oral NSAIDs, including selective COX2 inhibitors, and oral chondroitin sulfate. There is no literature evidence of the superiority of one specific anti-inflammatory treatment over another [23; 24].

Infiltrative therapy: Corticosteroid injections into the trapeziometacarpal joint can result in pain reduction and functional improvement, but mainly in the short term and with significant side effects [25; 26; 27]. Hyaluronic acid injections represent an alternative to anti-inflammatory infiltrative therapy [28] and result in reduced resting pain with lasting benefit from 4 to 12 weeks [29].

3.3 Clinica Clinical Investigation Rationale

Collagen is a structural protein biopolymer composed of three polypeptide chains wound together to form a right-handed triple helix. Its structure, characterized by the presence of glycine every third residue, a high content of proline and hydroxyproline, is stabilized by interchain hydrogen bonds and electrostatic interactions, which confer high mechanical strength, incompressibility, and, simultaneously, extensibility, plasticity, and flexibility to the molecules, making tissues abundant in collagen particularly resistant to stress and load [30].

In humans, collagen is particularly present in the skin, subcutaneous tissue, cartilage, bone, joint capsule, tendons, muscles, and ligaments [31; 32; 33]. Growing evidence supports the infiltrative use of type I collagen in the treatment of musculoskeletal pathologies [34]. In particular, the intra-articular and peri-articular use of collagen has been proposed in the treatment of osteoarthritis of various body districts with the aim of limiting joint hypermobility, stabilizing the structure of joint and peri-articular components, reducing pain, and consequently improving function. Several clinical studies have demonstrated how its infiltrative intra-articular use, characterized by a series of 5 injections spaced one week apart, was able to determine pain reduction and improvement of functionality in different cases of knee and hip osteoarthritis [35; 36; 37; 38; 39]. Regarding the conservative management of symptomatic rhizoarthritis, some studies, although on limited case series, have shown how the use of type I collagen at the joint and peri-articular level in this condition is able to control painful symptoms, improve functionality, and reduce joint instability [40].

Recently, Randelli F. et al. studied the in vitro effects on tenocytes induced by type I porcine collagen (MD-Tissue Collagen Medical Device). In vitro results seem to demonstrate that this medical device can induce proliferation and migration of tenocytes and synthesis, maturation, and secretion of type I collagen, favoring tendon repair [41].

Randelli F. et al. also demonstrated the predominantly mechanical activity of MD-Tissue Collagen Medical Device, which is able to induce modifications of the morpho-functional properties of tenocytes [42].

In this Clinical Investigation, the performance and safety of use of an injectable medical device based on type I porcine collagen called MD-Small Joints Collagen Medical Device in the treatment of symptomatic rhizoarthritis will be investigated.

4. SCIENTIFIC REQUEST

4.1 Research Title

"Evaluation of the Performance and Safety of a Type I Collagen-Based Medical Device (MD-Small Joints Collagen Medical Device) in the Treatment of Rhizoarthritis: The SMAGENART Pilot Study."

4.2 Research Objective

The aim of this research is to evaluate, using the Visual Analogue Scale (VAS), the Disability of the Arm, Shoulder and Hand (DASH) questionnaire, the Functional Index for Hand Osteoarthritis (FIHOA) questionnaire, and the Pinch Strength Test, the performance of an intra-articular and peri-articular treatment with a collagen-based medical device in terms of pain reduction and recovery of joint function in subjects with symptomatic rhizoarthritis. The safety of the treatment will also be assessed.

4.3 Study Design

This multicenter pilot clinical investigation will be based on a One Sample design. The variables will be assessed at 4 different time points: baseline (time T0), after 3 weeks (T3s), after 6 weeks (T6s), and after 16 weeks (T16s/FU), which is 12 weeks after the end of the infiltrative treatment.

4.4 Duration of Investigation

The total duration of the investigation will be 8 months. It is expected that the selection and recruitment of subjects will take 4 months, followed by a treatment and observation period of 16 weeks (Figure 1).

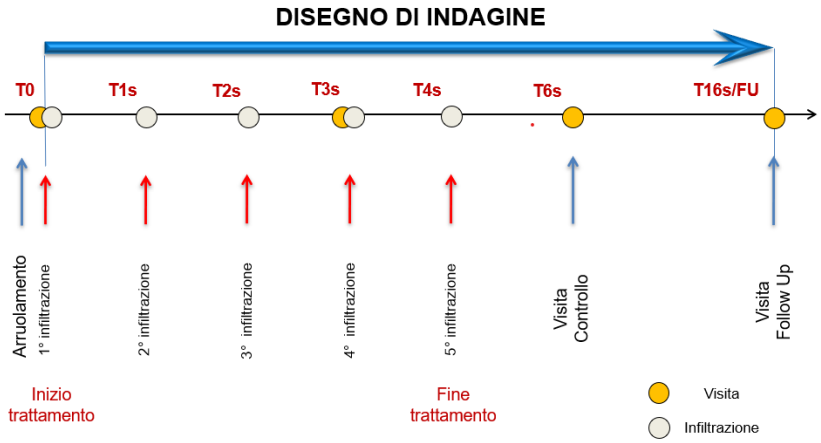


Fig.1 Study Clinical Design

4.5 Participant Population

A total of 42 subjects with thumb carpometacarpal osteoarthritis will be enrolled. The recruitment phase will not be closed until the number of subjects specified in the Clinical Investigation Plan is reached.

Only subjects who meet the following criteria will be included:

- Belonging to the Clinical Investigation Centers.

- Meeting the inclusion criteria and not presenting exclusion criteria.
- Having dated and signed the Informed Consent.

4.6 Enrollment

Enrollment will commence only after approval of the Clinical Investigation Plan by the relevant Territorial Ethics Committees and notification of the study to the Ministry of Health.

Enrollment will involve subjects with thumb carpometacarpal osteoarthritis who are eligible according to the selection criteria. Diagnosis will be performed by the Principal Investigator of each Clinical Investigation Center through clinical and radiological examination. Eligible subjects will be briefed by the Principal Investigator or Co-Investigators on the rationale of the Clinical Investigation and the planned procedures. Consent to participate in the study will then be requested.

4.7 Selection Criteria

4.7.1 Inclusion Criteria:

- Male and female subjects aged between 18 and 75 years;
- Subjects with clinically diagnosed symptomatic thumb carpometacarpal osteoarthritis confirmed radiographically (stages I and II according to Eaton and Littler's classification);
- [N.B. in case of bilateral symptomatic thumb carpometacarpal osteoarthritis, treatment can be unilateral only, at the level of the thumb carpometacarpal joint that is more affected at the time of enrollment].
- Subjects with a VAS score ≥ 5;

⚠ *[The request for pain intensity (VAS) from the patient should refer to moments of hand use, nota t rest!]*

- Subjects with joint pain for at least 1 month;
- Subjects not using thumb carpometacarpal orthotic devices;
- Subjects agreeing not to take analgesics within 24 hours before the scheduled visits;
- Subjects capable of understanding and signing the Informed Consent.

4.7.2 Exclusion Criteria

- Subjects with rheumatological conditions involving the hands;
- Subjects who have undergone hand surgery for the affected pathology;
- Subjects who have received HA injections in the thumb carpometacarpal joint in the last 3 months;
- Subjects who have taken NSAIDs in the last 7 days and/or corticosteroids in the last 30 days;
- Subjects undergoing physical therapy such as X-ray therapy, Tecar therapy, shock wave therapy, laser therapy, ultrasound therapy in the last 3 months;
- Subjects with neoplastic pathology;

- Subjects with systemic infections;
- Subjects with uncontrolled diabetes;
- Subjects with neurological conditions that may affect active participation in the study;
- Subjects with coagulopathies or taking anticoagulants (vitamin K antagonists, heparin);
- Subjects undergoing immunosuppressive treatment;
- Subjects using drugs or abusing alcohol;
- Subjects allergic to porcine collagen;
- Female subjects who are pregnant or breastfeeding;
- Subjects participating in other clinical studies during the same period;
- Subjects unable to cooperate or for whom poor compliance is expected;
- Any condition that, in the investigator's judgment, recommends the subject's exclusion.

4.8 Subject Coding

Each Clinical Investigation Center will have a list containing the identification codes to be assigned to enrolled subjects. Since enrollment will be competitive, each list will contain 30 identification codes.

At the time of enrollment, each subject will be sequentially assigned such an identification code.

Lists with complex alphanumeric identification codes will be generated by GUNA S.p.a. through

The complex alphanumeric code complies with the current Privacy Regulations regarding the coding of subjects participating in clinical studies.

4.9 Procedures

4.9.1 Evaluations of Time Points

Baseline (T0): Enrollment and initiation of infiltrative treatment.

Week 1 (T1): Second infiltrative treatment.

Week 2 (T2): Third infiltrative treatment.

Week 3 (T3): 1st follow-up visit + fourth infiltrative treatment.

Week 4 (T4): Fifth infiltrative treatment.

Week 6 (T6): 2nd follow-up visit.

Week 16 (T16)/FU: 3rd follow-up visit.

4.9.2 Visit Schedule

<u>Baseline (T0): Enrollment</u>

During routine clinical practice, the Investigators participating in the Clinical Investigation will select subjects diagnosed with symptomatic thumb carpometacarpal osteoarthritis. The Principal Investigator will be responsible for the correct clinical diagnosis, also utilizing the instrumental exams specified in the Investigation Plan. Subjects meeting the selection criteria will be identified. After thoroughly explaining the purposes, objectives, and procedures outlined in the Investigation Plan, the subject will be invited to participate in the Investigation. The selected subject will be invited to review the information sheet and date and sign the Informed Consent and Personal Data Processing Consent

form. Female subjects must provide evidence of a negative pregnancy test to be enrolled. The examination will then proceed, along with the collection of information required by the electronic Data Collection Form (e-CRF) appropriately prepared.
This will be followed by:

- VAS assessment;
- DASH assessment;
- FIHOA assessment;
- Pinch Strength Test assessment using a dynamometer.

The first intra/peri-articular infiltration of MD-Small Joints Collagen Medical Device (see § 4.12) will then be performed, evaluating any Adverse Events in the moments following administration. Any previous or ongoing pharmacological treatments of any kind (concomitant medications) will be documented in the annotations section of the e-CRF. During the study, systemic and topical analgesic medications may be used in case of severe pain. Investigators will explain to enrolled subjects that such medications should only be used if absolutely necessary and will provide each subject with 1 package of oral analgesic medication and 1 package of topical analgesic medication among those permitted (see table 1), explaining the possible adverse events associated with intake or application and ensuring, under their responsibility, that the subject can take or apply the provided medication. To monitor its consumption, each subject will be given a clinical diary in which to record the day and dose of medication used, reminding them that such medications should not be taken or applied within 24 hours before each visit.

PERMISSIBBLE ORAL MEDICATIONS	PERMISSIBLE TOPICAL MEDICATIONS
Paracetamol 1000 mg. cpr.	Diclofenac 2% gel
Etoricoxib 60 mg. cpr.	

Tab. 1 Permissible topical analgesic medications

The enrolled subject will be assigned a complex alphanumeric identification code. The collected data must be entered into the e-CRF within the following 48 hours.

T1 settimana (±1gg):

At one week from T0, the second intra/peri-articular infiltration of MD-Small Joints Collagen Medical Device will be performed (see § 4.12), and the use of the analgesic medication will be evaluated through the analysis of the clinical diary. Any adverse events occurring after the first administration will also be assessed.

T2 weeks (±1 day):

At two weeks from T0, the third intra/peri-articular infiltration of MD-Small Joints Collagen Medical Device will be performed (see § 4.12), and the use of the analgesic medication will be evaluated through the analysis of the clinical diary. Any adverse events occurring after the second administration will also be assessed.

T3 weeks (±1 day):

At three weeks from T0, the fourth peri-articular infiltration of MD-Small Joints Collagen Medical Device will be performed (see § 4.12), and the use of the analgesic medication will be evaluated through the analysis of the clinical diary. The evaluation of VAS will be conducted. Any adverse events occurring after the third administration will also be assessed. The collected data must be entered into the e-CRF within the subsequent 48 hours.

T4 weeks (±1 day):

At four weeks from T0, the fifth and final peri-articular infiltration of MD-Small Joints Collagen Medical Device will be performed (see § 4.12), and the use of the analgesic medication will be evaluated through the analysis of the clinical diary. Any adverse events occurring after the fourth administration will also be assessed.

6 weeks (±2 days):

At six weeks from T0, and two weeks after the end of infiltrations, the following evaluations will be performed:

- VAS assessment;
- DASH assessment;
- FIHOA assessment;
- Pinch Strength Test evaluation using dynamometer;
- evaluation of the use of analgesic medication through the analysis of the clinical diary;

assessment of any adverse events occurring after the fifth administration. The collected data must be entered into the e-CRF within the subsequent 48 hours.

T16 weeks/FU (±7 days):

At four months from enrollment, and twelve weeks after the end of infiltrations, the following evaluations will be performed again:

- VAS assessment;
- DASH assessment;
- FIHOA assessment;

- Pinch Strength Test evaluation using dynamometer;
- evaluation of the use of analgesic medication through the analysis of the clinical diary;

assessment of any adverse events occurring between T6s and T16s/FU. The collected data must be entered into the e-CRF within the subsequent 48 hours.

The scales, questionnaires, and tests used to determine the performance of the medical device under investigation (VAS, DASH, FIHOA, and Pinch Strength Test) will be administered to the subject by the Principal Investigators or Co-Investigators. The recording of data from the clinical diary regarding the intake of analgesic medication will be carried out by them.

In the e-CRF, the medications taken for the treatment of any co-morbidities that emerge during the Clinical Investigation must also be recorded.

At each visit, the occurrence of Adverse Events will be carefully evaluated. All Adverse Events (AE) and Serious Adverse Events (SAE) appearing between the date of Informed Consent signature and the end of the Clinical Investigation will be recorded and reported.

All data collected must be entered into the electronic Data Collection Form (e-CRF) provided by Guna S.p.a. Principal Investigators, Co-Investigators, or designated Data Managers will be responsible for the correct entry of the collected data into the e-CRF.

In particular, it is expected to obtain a data collection that is schematically described in the following table (tab. 2), which lists the registrations to be made at each visit.

EXPERIMENTAL PROCEDURES *"SMAGENART PILOT STUDY"*	VISIT T0 Enrollment	VISIT T1s. ± 1day	VISIT T2s. ± 1day	VISIT T3s. ± 1day	VISIT T4s. ± 1day	VISIT T6s. ± 2day	VISIT T16s/ FU ± 7day
Clinical diagnosis of rhizarthrosis confirmed radiographically	**X**						
Evaluation of selection criteria	**X**						
Sign Informed Consent	**X**						
Sign Privacy Consent	**X**						
Collection of socio-demographic data	**X**						
Medical history collection	**X**						
VAS assessment	**X**			**X**		**X**	**X**
DASH assessment	**X**					**X**	**X**
FIHOA assessment	**X**					**X**	**X**
Pinch Strength Test Evaluation	**X**					**X**	**X**
Infiltrative treatment	**X**	**X**	**X**	**X**	**X**		
Clinical diary evaluation of analgesic consumption.		**X**	**X**	**X**	**X**	**X**	**X**
Concomitant treatment for ongoing	**X**	**X**	**X**	**X**	**X**	**X**	**X**

comorbidities							
Adverse Event Assessment (AE/SAE)	**X**	**X**	**X**	**X**	**X**	**X**	**X**

Tab.2 Procedures and data collection during the Clinical Investigation

4.10 Material necessary for conducting the Clinical Investigation

The medical device necessary to conduct the investigation is MD-Small Joints Collagen Medical Device (GUNA, Milan-Italy) marketed in 2ml vials.

This device and the auxiliary drugs provided will be sent by Guna S.p.a. to the pharmacy of the Clinical Investigation Centers with shipment at a controlled temperature (range 4°-25°C) and monitored through dataloggers, in quantities suitable for conducting the Investigation.

Medical devices and auxiliary drugs must be stored by the pharmacy of the Clinical Investigation Centers within the same temperature range. Each Clinical Investigation Center will be equipped with a datalogger provided by the Sponsor for temperature monitoring.

The pregnancy tests will be sent, in suitable quantities, to the pharmacy of the Clinical Investigation Centers together with the medical devices and auxiliary drugs.

4.11 Group in the study

The Investigation Plan envisages a single experimental group which will be treated with infiltrations of: MD-Small Joints Collagen Medical Device (GUNA, Milan-Italy).

Composition per 2ml: collagen of porcine origin 100 µg

Excipients: Violet, NaCl, Water for injection.

The subjects will be treated with 1 infiltration with a volume of 2ml at the time of enrollment (T0) and on a weekly basis for a total of 5 infiltrations.

4.12 Infiltration Technique

The infiltrations will be performed using 2.5ml syringes and 26 gauge/13mm needles under complete aseptic conditions. The first 3 infiltrations will be carried out at both intra- and peri-articular levels by injecting MD-Small Joints Collagen Medical Device into the trapeziometacarpal joint until a counter-pressure is felt, preventing further penetration of the liquid; the remaining quantity (usually about 1ml) will be injected at the peri-articular level by retracting the needle tip.

The fourth and fifth infiltrations will be performed only at the peri-articular level.

4.13 Efficacy Criteria

4.13.1 Primary Endpoint

The primary endpoint will consist of evaluating, through the Visual Analogue Scale (VAS), the performance of MD-Small Joints Collagen Medical Device in reducing pain associated with trapeziometacarpal osteoarthritis at T6 weeks (T6s) compared to T0. A reduction in VAS score of at least 30% is considered clinically significant.

4.13.2 Secondary Endpoints

The secondary endpoints will include evaluating the performance of MD-Small Joints *Collagen Medical Device* through*:*

- VAS at T3s and T16s/FU compared to T0;
- DASH at T6s and T16s/FU compared to T0;
- FIHOA at T6s and T16s/FU compared to T0;
- Pinch Strength Test at T6s and T16s/FU compared to T0;
- Consumption of analgesics during various stages of the study;
- Incidence of Adverse Events.

4.13 Data Collection

All data resulting from the Clinical Investigation must be entered, within two days of their collection, into the electronic Data Collection Form (e-CRF) "Pheedit Dedagroup" provided by the Sponsor. Radiographic data will be collected and stored digitally on the hospital portal. Data entry procedures will be performed by the Principal Investigators, Co-Investigators, or the designated Data Manager.

4.14 Early Termination of the Investigation

Subjects may terminate the Investigation prematurely for the following reasons:

a. at their request (even without providing a reason);

b. at the discretion of the investigator;

c. if they experience an Adverse Event.

The reason for termination will be recorded in the e-CRF.

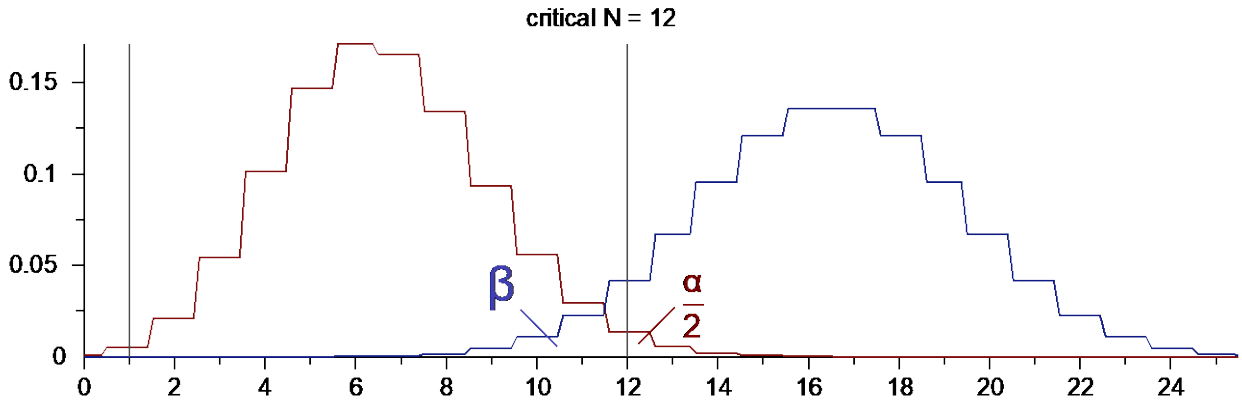
4 STATISTICS

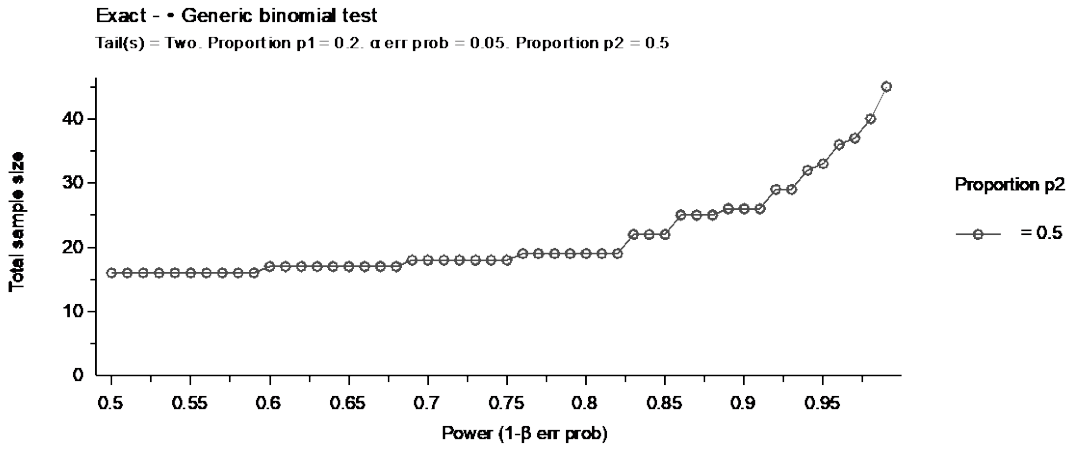
5.1 Sample Size

It is assumed that the fraction of subjects who will spontaneously reduce the VAS scale value by 30%, given their clinical characteristics, cannot exceed 20% of those enrolled (null hypothesis: $p_0 \leq 0.2$). Additionally, it is assumed that to consider the treatment with MD-Small Joints Collagen Medical Device clinically effective, the fraction of subjects who will reduce the VAS scale value by at least 30% should be at least 50% (alternative hypothesis: $p_a \geq 0.5$).

With these assumptions, using a two-tailed binomial test, the sample size will be 33 subjects, with a power of 95.99% and an alpha error of 2.75%. Assuming that dropouts are approximately 20%, the number of subjects to be recruited will be approximately 42 ($\frac{33}{(1-0.2)} = \frac{33}{0.8} \approx 42$.

Incidentally, the null hypothesis can be rejected after obtaining 12 or more clinical successes, and the alternative hypothesis can be rejected with 1 or fewer clinical successes.





5.1.1 Statistical Analysis Plan

5.1.2 Descriptive Statistics

All data will be validated according to appropriate rules based on their characteristics and then subjected to normal descriptive analyses (mean, median, mode, standard deviation, standard error of the mean, minimum and maximum values, interquartile range). Continuous variables with Gaussian distribution will be represented by mean ± standard deviation, while non-Gaussian variables will be represented by median and interquartile range. Categorical variables will be described using tables of relative and absolute frequencies.

5.1.3 Primary Endpoint

Tutti i dati saranno validati con delle opportune regole in base alle loro caratteristiche, e quindi sottoposti alle normali analisi descrittive (media, mediana, moda, deviazione standard, errore standard della media, valore minimo e massimo, range interquartile). Le variabili continue distribuite in modo Gaussiano saranno rappresentate da media ± deviazione standard, mentre quelle non

Gaussiane saranno rappresentate da mediana e range interquartile. Le variabili categoriche saranno descritte con tabelle di frequenza relativa ed assoluta.

The primary endpoint will be determined by the fraction of enrolled subjects who reduce the VAS scale value by at least 30% after 6 weeks (T6s) from the start of treatment. The percentage fraction will be calculated with its 95% confidence interval according to Clopper-Pearson.

5.1.4 Secondary Endpoints

The secondary endpoints will consist of evaluating the performance of MD-Small Joints Collagen Medical Device through:

- VAS at T3s and T16s/FU compared to T0;
- DASH at T6s and T16s/FU compared to T0;
- FIHOA at T6s and T16s/FU compared to T0;
- Pinch Strength Test at T6s and T16s/FU compared to T0: using repeated measures ANOVA within subjects, or with the Friedman test, depending on the distribution of the data.
- Consumption of analgesics in various stages of the study: through quantitative and qualitative counting of the drugs used.
- Incidence of Adverse Events: as incidence and incidence rate for each individual type of Adverse Event and cumulatively for all.

6 ETHICAL REQUIREMENTS

6.1 Ethical Authorizations

Il Piano di Indagine Clinica sarà sottomesso ai Comitati Etici Territoriali di riferimento dei Centri di Indagine Clinica per l'espressione di parere.

6.2 Amendments to the Clinical Investigation Plan

Qualsiasi modifica al presente Piano di Indagine sarà sottomessa dallo Sponsor, in forma di emendamento, ai Comitati Etici Territoriali di riferimento dei Centri Sperimentali per opportuna approvazione.

6.3 Subject Informationo

The purposes and methods of the Investigation will be explained to each subject through an informative document (Informed Consent), containing what has been verbally explained by the clinician. The subject must personally date and sign the consent document.

A copy of the document will be provided to the subject while the original will be kept by the investigator.

No activity related to the Clinical Investigation can commence before the subject signs the Informed Consent.

6.4 Adverse Events

An Adverse Event is defined as any harmful clinical event that occurs during the Clinical Investigation in one of the subjects participating in the study population who has undergone the treatment specified by the Investigation Plan.

Adverse events will be classified as serious (SAE) or non-serious (AE).

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

• it results in the death of the subject involved in the Investigation;

• it places the subject's life in jeopardy;

• it requires hospitalization;

• it requires prolonged hospitalization;

• it results in permanent or temporary disability;

• it results in 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 daily activities and resolves spontaneously;

• moderate: interferes with daily activities but resolves spontaneously;

• serious: prevents daily activities and does not resolve spontaneously.

All personnel participating in the study who come into contact with enrolled subjects must report Adverse Events communicated by the subjects to the Principal Investigator, who is responsible for collecting all possible data regarding them.

Per Evento Avverso si intende qualsiasi evento clinico dannoso che si manifesterà nel corso dell'Indagine Clinica in uno dei soggetti che compongono la popolazione in studio che è stato sottoposto al trattamento previsto dal Piano di Indagine.

Gli eventi avversi saranno classificati in serio (SAE) non-serio (AE).

Un Evento Avverso viene definito serio se (ICH-GCP DM 15/07/1997):

- provoca il decesso del soggetto coinvolto nell'Indagine;
- pone il soggetto in pericolo di vita;
- é tale da richiedere il ricovero in ospedale;
- é tale da richiedere il prolungamento del ricovero ospedaliero;
- é tale da provocare un'invalidità permanente o momentanea;
- porti ad un'anomalia congenita o ad un difetto alla nascita.

In tutti gli altri casi l'Evento Avverso sarà non-serio e verrà classificato in:

- *lieve* non interferisce con le normali attività di vita quotidiane e si risolve spontaneamente;
- *moderato*, interferisce con le attività di vita quotidiane ma si risolve spontaneamente;

- *grave,* impedisce le attività di vita quotidiane e non si risolve spontaneamente.

Tutto il personale, partecipante allo studio, che viene a contatto con i soggetti arruolati deve riferire gli Eventi Avversi comunicati dagli stessi al Principal Investigator, il quale ha il dovere di raccogliere tutti i dati possibili in merito.

All Adverse Events (AE) must be reported by the Principal Investigator to the Guna S.p.a Clinical Research Unit within 24 hours through telephone, email, specific form, and simultaneously through the e-CRF. AE must also be reported to the Pharmacovigilance Office of Guna S.p.a.

Serious Adverse Events (SAE) must be reported to the Guna S.p.a Clinical Research Unit immediately (within 24 hours at most) by the Principal Investigator through telephone, email, specific form, and simultaneously through e-CRF. SAE must also be reported to the Pharmacovigilance Office of Guna S.p.a. These events will be promptly communicated to the Ethics Committee and the Ministry of Health.

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The Principal Investigator must implement all procedures to ensure the resolution of the event. In the case of Adverse Events (AE), it is necessary to consider that these may still give rise to Serious Adverse Events (SAE), which is why every Adverse Event must be monitored. Adverse Events not resolved at the end of the study will be followed up by the Investigators; every subject who has experienced an Adverse Event will be contacted at least once a month after the conclusion of the study for a number of months deemed appropriate.

6.5 Privacy Protection

The identities of the individuals involved will be known only to the Investigators and the Clinical Monitor responsible for monitoring the Investigation. Reference will be made to Regulation (EU) 2017/745.

Full respect for the anonymity of the subjects participating in the Investigation will be ensured. Data collection, processing, any scientific publications, or presentations at congresses of the results of the Clinical Investigation will be conducted in accordance with the current privacy regulations – Regulation (EU) 2016/679.

6.6 Data Access

In compliance with the current regulations regarding Clinical Investigations on medical devices [Regulation (EU) 2017/745] and the Good Clinical Practice Guidelines (ICH/GCP), the Clinical Investigation Centers and Investigators will allow monitoring of the study according to the monitoring plan developed by the Sponsor. Furthermore, they will allow the Competent Authorities direct access to the documentation related to the study during audits.

6.7 Data Ownership

All collected data will belong to Guna S.p.a. Milano, Italy, the Sponsor of the Clinical Investigation. Further information regarding data ownership is provided in the Contract.

6.8 Data Processing and Publication

The results of this study will be summarized and presented in a final report aimed at drawing reliable conclusions regarding the performance of the injectable medical device MD-Small Joints Collagen Medical Device in the treatment of trapeziometacarpal osteoarthritis. The scientific article will then be drafted and submitted to a peer-reviewed journal in the field for publication to disseminate the obtained results to the scientific community.

6.9 Financing

This research is funded by Guna S.p.a.

For further information, please refer to the Contract.

6.10 Reference Ethical Code

Reference is made to the Helsinki Declaration (Fortaleza 64th 2013), and the principles of Good Clinical Practice (GCP) (Legislative Decree 24 June 2003 – no.211 in G.U. no.184 of 09/08/2003) will be followed.

6.11 Subject Insurance

For the entire duration of the Investigation project, insurance coverage will be provided by Guna S.p.a. for all enrolled subjects.

7 PREMATURE INTERRUPTION OF THE INVESTIGATION

The Principal Investigators, reserve the right to prematurely terminate the Clinical Investigation at any time for reasonable medical and/or administrative reasons. The reasons for the interruption will be documented, and the Ethics Committees and the Ministry of Health will be informed of the decision.

8 TRIAL REGISTRATION

Guna S.p.a., Sponsor of the Clinical Investigation, will register the study on the Clinicaltrials.gov portal.

9 GLOSSARY

Medical device: any instrument, apparatus, implant, substance, or other article, whether used alone or in combination, including software, intended by the manufacturer to be used on humans for the purpose of diagnosis, prevention, monitoring, treatment, or alleviation of disease; diagnosis, monitoring, treatment, alleviation, or compensation for injury or disability; investigation, replacement, or modification of the anatomy or of a physiological process; intervention in conception, which does not achieve its principal intended action by pharmacological, immunological, or metabolic means, but which may be assisted in its function by such means.

10 ANNEXES TO THE INVESTIGATION PLAN

A. Informed Consent (information and consent)
B. Consent for the processing of personal data (information and consent)
C. Clinical Diary
D. Visual Analogue Scale (VAS)
E. Disability of the Arm, Shoulder and Hand (DASH)
F. Functional Index for Hand OsteoArthritis (FIHOA)

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