

**Prospective Multi-Center Evaluation of Percutaneous Ultrasound
Guided Elbow Tenotomy (PUGET) Using the HydroCision TenJet™
HydroSurgery System**

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Sponsor

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Protocol Synopsis

Title:	Prospective Multi-Center Evaluation of Percutaneous Ultrasound Guided Elbow Tenotomy (PUGET) Using the HydroCision TenJet™ HydroSurgery System
Intervention	Percutaneous ultrasound guided medial and lateral tenotomy using the TenJet HydroSurgery System to treat elbow tendinosis
Regulatory Status	Post-market evaluation. The indication for the TenJet System utilized in this study is cleared for marketing by the FDA.
Study Objective:	To evaluate the acute and long-term clinical outcomes of Hydrotomy with the TenJet System in patients with elbow tendinosis.
Study Design:	Prospective, multi-center, nonrandomized, single arm observational study
Patient Population:	Patients presenting with chronic, refractory lateral or medial elbow pain secondary to elbow tendinosis
Enrollment Size and Number of Sites:	Up to 50 patients recruited from up to 5 sites
Primary Endpoint:	Reduction in elbow pain using the Visual analog scale (VAS) for pain
Additional Assessments:	<ul style="list-style-type: none"> • Mayo Elbow Performance Score (MEPS) • Patient-Rated Elbow Evaluation (PREE) • Pain medication usage • Neurological assessment • Additional intervention(s) • Procedure time • Pre, post-procedure and 3 month ultrasound assessments • Return to work, if applicable • Safety defined as adverse events related to the procedure or device

Inclusion Criteria	<p>All patients must meet all of the following criteria to be eligible to be enrolled into the study:</p> <ul style="list-style-type: none"> • Patient is ≥ 18 years of age • Chronic lateral or medial elbow pain ≥ 3 month duration • History and clinical examination consistent with lateral or medial epicondylitis • Sonographic evidence of medial or lateral elbow tendinosis as evidenced by <ul style="list-style-type: none"> ○ tendon thickening and hypoechogenicity, ○ with or without hypervascularity on Doppler examination and, ○ with or without cortical irregularities, <p>Or MRI findings consistent with lateral or medial tendonosis, with or without intrasubstance tear.</p> <ul style="list-style-type: none"> • ≥ 3 months of non-operative treatment that included <ul style="list-style-type: none"> ○ nonsteroidal anti-inflammatory drugs ○ activity modification ○ physical therapy ○ elbow straps ○ With or without previous steroid injections, PRP injections, or stem cell injections • Patient is willing and able to provide informed consent and comply with the study protocol
Exclusion Criteria	<p>All patients who meet any of the following criteria should not be enrolled into the study:</p> <ul style="list-style-type: none"> • Documented ipsilateral upper extremity musculoskeletal condition (other than elbow tendinosis in the same arm on the opposite side) • Bleeding disorders and/or current use of anti-coagulants with the inability to withhold anticoagulants for required time prior to procedure • Use of acetylsalicylic acid (ASA) and/or non-steroidal anti-inflammatory drug (NSAID) within 7 days of treatment • Steroid injection within 4 weeks of the study procedure • Active local or systemic infection • Patient found to have further degenerative changes of the elbow contributing to pain, such as cartilage thinning, loose body, or evidence of tendinosis other than medial or lateral, including triceps or ulnar collateral ligament.

	<ul style="list-style-type: none"> • Patient is known or suspected to be pregnant
Study Duration / Follow-up Period	<p>Patients will be followed for a maximum of 12 months post-procedure, with follow-up visits at 2 weeks, 6 weeks, and 3, 6, and 12, months post-procedure. The 12-month follow-up may be done via a phone call and/or mailing of patient questionnaires.</p>
Baseline Visit	<ul style="list-style-type: none"> • Demographics: gender, age, height, weight • Diagnosis and indication for procedure • History <ul style="list-style-type: none"> ○ Previous elbow surgery ○ Conservative care ○ Duration of symptoms • Visual analog scale (VAS) pain score • Patient-Rated Elbow Evaluation (PREE) • Mayo Elbow Performance Score (MEPS) • Pregnancy test for women of childbearing potential
Post-Operative Follow-ups	<ul style="list-style-type: none"> • Visual analog scale (VAS) pain score • Patient-Rated Elbow Evaluation (PREE) • Mayo Elbow Performance Score (MEPS) • Additional intervention(s) • Return to work, if applicable • Complications / Adverse events
Principle Investigator	<p>Reginald W. Kapteyn, D.O. Orthopaedic Associates of Muskegon 1400 Mercy Drive Suite 100 Muskegon, MI 49444 Phone: (231) 733-1326</p>

Table of Contents

1	INTRODUCTION	7
1.1	Background and Rationale	7
1.2	Report of Prior Investigations	10
2	DEVICE DESCRIPTION	10
2.1	Device Indications for Use	10
3	STUDY PURPOSE AND OBJECTIVE	11
4	STUDY ENDPOINTS	11
4.1	Primary Endpoint	11
4.2	Additional Assessments	11
5	STUDY DESIGN	11
5.1	Overview	11
5.2	Sample Size and Number of Centers	11
5.3	Study Duration	11
6	STUDY PROCEDURES	12
6.1	Patient Eligibility, Pre-Screening and Exclusions	12
6.2	Enrollment and Written Informed Consent	13
6.3	Baseline Evaluation	13
6.4	Procedure / Discharge	14
6.5	Post-Operative Procedures and Outcomes	15
6.6	Patient Early Discontinuation / Withdrawal and Replacement of Patients	17
6.7	Lost to Follow-up Patients	17
7	Risk / Benefit Analysis	17
7.1	Benefits	17
7.2	Risks	17
8	STATISTICAL SECTION	18
8.1	Statistical Considerations	18

8.2	Sample Size Justification	18
9	DATA MANAGEMENT	18
9.1	Data Collection	18
10	ADVERSE EVENTS	19
10.1	Definitions.....	19
10.2	Adverse Event Reporting.....	20
11	STUDY ADMINISTRATION	20
11.1	Statement of Compliance.....	20
11.2	Investigational Review Board Approval (IRB)	20
11.3	Informed Consent.....	20
11.4	Amending the Protocol	21
11.5	Protocol Deviations/Violations and Medical Emergencies	22
11.6	Criteria for Terminating Study.....	22

1 INTRODUCTION

1.1 Background and Rationale

Lateral Epicondylitis is the most common cause of elbow pain affecting active populations. The diagnosis of lateral humeral condyle pain was first made by Runge in 1873 when describing pain and difficulty with writing.^{1, 2} Major, in 1893 used the term “lawn tennis elbow” as it was common in tennis players.³ However, lateral epicondylitis is actually more common in non-tennis players. The prevalence of lateral epicondylitis has been estimated to range from one to three percent of the population.⁴ Men and women are equally affected and the typical age range of patients with lateral epicondylitis is 35-54 years of age.^{5, 6, 7, 8, 9, 10, 11, 12, 13}

Work-related movements and risk factors attributing to the cause of lateral epicondylitis include repetitive and forceful elbow flexion and extension, repetitive wrist extension and pronation/supination. Shiri et al. performed a study of the Finnish general population in 2006 and identified a combination of repetitive and forceful activities as well as longer exposure to these activities as risk factors for lateral epicondylitis.⁸ There has been a strong correlation of smoking history as a risk factor and possibly a role of obesity and diabetes mellitus in the population with lateral epicondylitis.^{5, 8, 13} There doesn't appear to be a strong relationship between socioeconomic class and diagnosis.

The pathology of lateral epicondylitis was initially thought to be due to an inflammatory process. However, it has now been established that it is typically associated with tendon degeneration resulting from microtrauma, cellular apoptosis, and autophagic cell death. Nirschl has demonstrated that the pathological process is indeed a degenerative process.¹⁴ Bunata described the histology as consisting of disorderly tendon fibers in combination with fibroblasts and atypical vascular granulation-like tissue, focal hyaline degeneration and calcific debris surrounded by hypercellular and degenerative tissues.¹⁵ For these reasons, the terms tendinosis and tendinopathy more accurately portray the condition than epicondylitis. A microscopic view of tendinosis reveals an increase of immature type III collagen fibers (mature type I fibers dominate in healthy tendon tissue), loss of collagen continuity so that collagen fibers are no longer aligned with each other, an increase in ground substance (the material between the body's cells), and a haphazard increase of vascularization. The appearance of the tendon shifts from a reflective, “white, glistening and firm” surface to a “dull-appearing, slightly brown and soft” surface. The pathologic differences between normal tendon tissue and areas of degeneration of the tendon's collagen evident in tendinosis are significant parameters in not only visualizing affected parts of the diseased tendon radiographically (e.g., increased signal intensity on MRI) or under ultrasound (focal

areas of low echogenicity of the associated with thickening of the tendon) but also enables the device proposed for use in this study to differentiate between healthy, normal tendon and areas of pathologic tissue.

Typically, patients present with pain over the lateral elbow sometimes accompanied by swelling. Patients may also complain of difficulty holding objects and diminished grip strength. Although pain is focused more in the elbow, it is important to examine the cervical spine and the entire upper extremity in order to make a conclusive diagnosis. Diagnostic studies often play a role in diagnosis or are at least helpful in ruling out other sources of pathology, which may be causing elbow pain. Radiographs provide limited information but may demonstrate calcification near extensor origin or demonstrate loose bodies within the elbow joint and MRI can demonstrate tendon thickening with increased T1 and T2 signal.^{16, 17, 18, 19}

Medial epicondylitis ("golfer's elbow" or more appropriately, tendinopathy of the medial elbow) is similar to the more common lateral epicondylitis in many respects. Medial epicondylitis represents approximately 10%-20% of all cases of epicondylitis (0.4-1.3% overall prevalence).¹⁴ Medial epicondylitis shares many of the same risk factors as its lateral brethren and is also a degenerative condition with similar histology representing a tendinosis with angiofibroblastic hyperplastic changes.

Most patients with tendinosis to either the lateral or medial elbow respond to one or a combination of therapies including activity modification, NSAIDS, bracing, physical therapy, lidocaine and steroid injections as well as use of autologous blood, platelet-rich plasma (PRP), extracorporeal shock wave therapy, and alternative medicine techniques such as acupuncture.^{20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32}

Although many patients respond to these therapies, 10%-15% will be refractory and are therefore considered surgical candidates. Multiple open, arthroscopic, and percutaneous surgical procedures have been described to treat elbow tendinopathy toward the goals of debridement and tendon release.^{33, 34, 35, 36, 37} As percutaneous surgery may improve the ability to use the arm normally, compared with open surgery,³⁸ there has been increased interest in minimally invasive and percutaneous procedures to access and remove pathologic tissue causing the tendinitis for those patients that have failed to improve with non-surgical treatment. One such procedure is sonographically guided percutaneous tenotomy using ultrasonic energy to remove diseased tissue; this procedure utilizes the TX1 device manufactured by Tenex Health, Inc. The procedure utilizes standard ultrasound guidance to place a needle into the affected region. Ultrasonic energy is used to oscillate the needle tip

of the device at a high frequency to emulsify the diseased tendon tissue. This emulsified tissue is subsequently removed by an inflow-outflow circuit of the device.^{39, 40, 41, 42}

A number of studies have been performed using this percutaneous method. Koh et al studied use of this procedure with the TX1 device in 20 patients with refractory lateral tendinosis. The study showed that one-week post procedure pain and function was significantly improved and these results were maintained at one-year follow-up.³⁹ Recently the same cohort was followed 3 years post minimally invasive percutaneous ultrasonic tenotomy with sustained pain relief and functional improvement.⁴³ Results also demonstrated tendon hypervascularity was resolved in 94% of patients, and 100% had reduction in tendon thickness. Overall reduction in the hypoechoic scar tissue was observed in all subjects, with a 90% response achieved by 6 months. Between 6 and 36 months, further reduction in the scar was observed in around 60% of patients, with 20% of patients having complete resolution of the hypoechoic scar. Another recently published study used the same device in nineteen patients and showed similar results of acute efficacy maintained through one year.⁴⁴ Both studies showed excellent safety profile partly due to its percutaneous access and well established ultrasound guidance techniques. Shortcomings of this technique include a high grade of subcutaneous edema that develops at the incision site due to high volumes of saline injected into the tissue during the procedure to assist in the debridement process. Although this technology holds great promise, it can be cumbersome to use with a complicated in-flow/outflow mechanism that is essential to providing a clear surgical field and removing emulsified tissue.

Currently, HydroCision (HydroCision, Inc. 267 Boston Road, Suite 28, North Billerica, MA 01862) commercializes a proprietary fluidjet technology that is the basis of a surgical modality, HydroSurgery. The HydroCision device - HydroCision General Surgery FluidJet System - uses a controlled hair-thin supersonic stream of water in a precise manner to provide an effective cutting, ablation, and collection system for medical applications. The technology consists of a single-use device that has the capability of selectively discriminating between different tissue densities. By adjusting the pressure and nozzle parameters appropriately, the device is capable of selectively debriding targeted tissue while leaving the healthy surrounding healthy tissue intact and unaffected. The HydroCision General Surgery FluidJet System is currently FDA cleared for orthopedic joint procedures where the cutting and removal of soft and hard tissue is required. The tendon specific configuration of the device is known as the TenJet. The components of the TenJet System include a reusable power console unit, a sterile, disposable pump cartridge, a handpiece assembly, and a tubing set. The system tip is made using an echogenic material allowing for visualization via ultrasound guidance. The design and functional attributes of the

HydroCision device make it particularly amenable for percutaneous tenotomy procedures under ultrasound guidance.

1.2 Report of Prior Investigations

The HydroSurgery technology has been used safely and effectively for over a decade in a variety of minimally invasive differential tissue removal procedures including wound tissue debridement and spinal disc nucleus debridement.^{45, 46, 47, 48} In preparation for this clinical evaluation study, HydroCision has performed cadaveric studies to demonstrate the safety of the TenJet system when used specifically for tendon debridement and to determine the performance settings when used in tendinous tissue.⁴⁹

The objective of the cadaver study was to establish that using focused water jet technology for debridement and aspiration of chronic scar tissue in and around a scarring tendon is both safe and effective for various tendinopathy applications. For the study, various tendons were utilized to assess the safety and performance of the TenJet system (patella tendon, one Achilles tendon, one extensor tendon). Various pressure setting (1 to 10) and times (30s to 3 minutes) were studied and both tissue emulsification product characterization (i.e., weight and tissue type removed) and histologic analysis of the treated tendon were performed.

Results from the studies demonstrated that pressure settings on the device between 3 and 7 provoked miniscule gross disruption to the cadaver tissue. There was no continuous residual channel visualized with ultrasound which would otherwise suggest a region of “cut” tissue. None of the settings showed a residual channel. In particular though, the settings of “3”, “5”, and “7” appeared to show increased possibilities for debridement, without damage to otherwise relatively “healthy” cadaver tendon. Multiple sections of tendons subjected to histological analysis demonstrated tendon with no evidence of damage or degeneration.

Presently, HydroCision would like to evaluate the currently approved HydroSurgery technology (i.e., TenJet) in the specific clinical elbow tenotomy indication. This study is being undertaken to evaluate the short term and long term outcomes of percutaneous tenotomy using the HydroCision TenJet System when performed under local anesthesia and ultrasound guidance.

2 DEVICE DESCRIPTION

2.1 Device Indications for Use

The HydroCision TenJet System is indicated for orthopedic surgical procedures where the cutting and removing of soft tissue and the ablation and removal of hard tissue is required. Specific functions include cutting, ablation and shaping of soft tissue in a variety of surgical procedures including small and large joint arthroscopic procedures.

The indications for use for the HydroCision TenJet System that will be utilized in this study are indications that are already cleared for marketing by the FDA.

3 STUDY PURPOSE AND OBJECTIVE

The purpose of this study is to evaluate acute and long-term clinical outcomes of Hydrotenotomy with the TenJet System in patients with elbow tendinosis.

4 STUDY ENDPOINTS

The following endpoints will be evaluated in all patients enrolled in the study.

4.1 Primary Endpoint

The primary endpoint is reduction in elbow pain using the visual analog scale (VAS) for pain.

4.2 Additional Assessments

- Patient-Rated Elbow Evaluation (PREE)
- Mayo Elbow Performance Score (MEPS)
- Pain medication usage
- Neurological assessment
- Additional intervention(s)
- Procedure time
- Pre and post-procedure ultrasound assessments
- Return to work, if applicable
- Safety defined as adverse events related to the procedure or device

5 STUDY DESIGN

5.1 Overview

This is a prospective, non-randomized, single arm post-marketing clinical study of patients undergoing percutaneous ultrasound guided medial and lateral tenotomy using the TenJet HydroSurgery System to treat elbow tendinosis. All patients are expected to undergo clinical assessments at selected follow-up visits.

5.2 Sample Size and Number of Centers

The study will be conducted at up to five centers with a target maximum of 50 patients.

5.3 Study Duration

Enrollment of subjects in this study is anticipated to take 6 months. Patients will be followed for a maximum of 12 months post-procedure, with follow-up visits at 6 weeks, and 3, 6, and 12, months post-procedure. The 12-month follow-up may be done via a

phone call and/or mailing of patient questionnaires. The total study duration is expected to be at least 30 months.

6 STUDY PROCEDURES

6.1 Patient Eligibility, Pre-Screening and Exclusions

All patients presenting to the Investigator experiencing pain with resisted wrist flexion and palpable tenderness over the medial epicondyle or pain over the lateral elbow or who has already confirmed lateral or medial epicondylitis will be considered for the study. A Screening/Enrollment Log will be utilized in order to maintain a cumulative tracking of all screened patients with documented lateral/medial epicondylitis.

Patients must meet all inclusion/exclusion criteria for enrollment in the clinical study. Reasons for screening failure(s) will be documented.

6.1.1 Inclusion Criteria

Patients must meet ALL of the following criteria to be eligible for participation in the study:

- Patient is ≥ 18 years of age
- Chronic lateral or medial elbow pain > 3 month duration
- History and clinical examination consistent with lateral or medial epicondylitis
- Sonographic evidence of medial or lateral elbow tendinosis as evidenced by
 - tendon thickening and hypoechogenicity,
 - with or without hypervascularity on Doppler examination and,
 - with or without cortical irregularitiesOr MRI findings consistent with lateral or medial tendonosis, with or without intrasubstance tear.
- ≥ 3 months of non-operative treatment that included
 - nonsteroidal anti-inflammatory drugs
 - activity modification
 - physical therapy
 - elbow straps
 - With or without previous steroid injections, PRP injections, or stem cell injections
- Patient is willing and able to provide informed consent and comply with the study protocol

6.1.2 Exclusion Criteria

Patients must be EXCLUDED from participation in this study if ANY of the following criteria are met:

- Documented ipsilateral upper extremity musculoskeletal condition (other than elbow tendinosis in the same arm on the opposite side)
- Bleeding disorders and/or current use of anti-coagulants with the inability to withhold anticoagulants for required time prior to procedure
- Use of acetylsalicylic acid (ASA) and/or non-steroidal anti-inflammatory drug (NSAID) within 7 days of treatment
- Steroid injection within 4 weeks of the study procedure
- Active local or systemic infection
- Patient found to have further degenerative changes of the elbow contributing to pain, such as cartilage thinning, loose body, or evidence of tendinosis other than medial or lateral, including triceps or ulnar collateral ligament.
- Patient is known or suspected to be pregnant

6.2 Enrollment and Written Informed Consent

Patients that meet all of the inclusion and exclusion criteria will be asked to sign the study-specific IRB approved Informed Consent form before any study-specific tests or procedures are performed. The investigator will inform the potential subject of the elements of the clinical study including, risks, potential benefits and required follow-up procedures prior to obtaining the potential subject's informed consent.

6.3 Baseline Evaluation

The following evaluations are required at the time of patient screening/baseline.

- Demographic Information: gender, age, weight, and height.
- Medical / Surgical History / Previous conservative treatment(s) / Current Status
- Visual analog scale (VAS) pain score
- Patient-Rated Elbow Evaluation (PREE)
- Mayo Elbow Performance Score (MEPS)
- Physical Exam
 - palpation & inspection
 - point tenderness at ECRB insertion into lateral epicondyle (lateral epicondylitis) or tenderness over the origin of PT and FCR at the medial epicondyle

- Neuromuscular
 - grip strength
 - neurological exam to exclude entrapment syndromes
- Provocative tests (lateral)
 - the following maneuvers exacerbate pain at lateral epicondyle
 - resisted wrist extension with elbow fully extended
 - resisted extension of the long fingers
 - maximal flexion of the wrist
- Provocative tests (medial)
 - pain with resisted forearm pronation and wrist flexion
- Pain medication usage
- Pregnancy test for women of childbearing potential

6.4 Procedure / Discharge

For the lateral elbow procedure, the patient will be placed semi-recumbent with the shoulder slightly abducted and resting on an arm board with the elbow flexed between 60° and 90°. For the medial elbow procedure, the patient will be placed supine with the shoulder externally rotated and the arm resting on an arm board with the elbow flexed at 90°. The tendinotic region will be identified by ultrasound exhibiting an area with or without mixed hyper-echoic and hypo-echoic appearance suggesting calcific tendinosis. The target area will then be marked. For medial elbow procedures, the position of the ulnar nerve should be determined to ensure that it hasn't subluxated or dislocated volarly into the working field. Site preparation and access will be performed according to the investigator's standard procedures and practices. Operation of the TenJet will be performed according to the manufacturer's instructions for use and the manufacturer's recommendations. During treatment, the working tip of the TenJet will be guided and observed using direct sonographic guidance.

Post-procedure, the patient may be discharged from the surgical center when clinically stable, at the Investigator's discretion. The investigator will review the study requirements with the patient in order to maximize compliance with the follow-up schedule and to follow the site's rehabilitative medical regimen consisting of a standard eccentric exercise program.

The following parameters will be noted on the case report forms:

- Treated tendon

- Procedure time
- TenJet pressure setting and run time
- Pre and post procedure ultrasound
- Length of clinic stay
- Complications / Adverse events

6.5 Post-Operative Procedures and Outcomes

Follow-up visits are scheduled for appointed times after the date of the procedure. Each subject will be required to return within the first two weeks to assess the wound and determine whether they are ready to initiate the rehabilitation exercise regime.

Additionally all subjects will return to the clinic at 6 weeks, and 3, 6, and 12, months post-procedure according to the study schedule described in **Table 1** for outcome assessments.

Note: the 12 follow-up may be a phone call.

The following post-operative data will be collected:

- Ultrasound to assess tendon healing at the 3 month follow-up only
- Visual analog scale (VAS) pain score
- Patient-Rated Elbow Evaluation (PREE)
- Mayo Elbow Performance Score (MEPS)
- Pain medication usage
- Additional intervention(s)
- Return to work, if applicable
- Complications / Adverse events

Table 1: Schedule of Assessments

Assessment	Time Frame						
	Pre-op	Procedure to Discharge	1 week (+/- 1 week)	6 week Follow-up (+/- 1 week)	3 month Follow-up (+/- 1 month)	6 Month Follow-up (+/- 1 month)	12 Month Follow-up (+/- 2 months)
Informed Consent	X						
Medical History	X						
Demographics	X						
Pregnancy test for women of childbearing potential	X						
Procedure Assessments		X					
Ultra sound assessments		X			X		
Physical Exam / Neurological Assessment	X			X	X	X	X
Imaging (if required for diagnosis)	X						
Rehabilitation assessment			X				
PREE and VAS	X			X	X	X	X
MEPS	X			X	X	X	X
Pain medication usage				X	X	X	X
Work Status	X			X	X	X	X
Adverse Events*	X	X	X	X	X	X	X

*Adverse events should be recorded at any time during the course of the study

6.6 Patient Early Discontinuation / Withdrawal and Replacement of Patients

All subjects are informed of their right to withdraw from the clinical study at any time. Additionally, the investigator may prematurely discontinue any patient's participation in the study if the investigator feels that the patient can no longer fully comply with the requirements of the study or if any of the study procedures are deemed potentially harmful to the patient. However, it is anticipated that such withdrawals will be infrequent to ensure the integrity of the study. The reason for early discontinuation will be documented in the source documents and case report forms.

6.7 Lost to Follow-up Patients

Every attempt will be made to have all subjects complete the follow-up visit schedule. A subject will not be considered lost to follow-up unless efforts to obtain compliance are unsuccessful. At a minimum, the effort to obtain follow-up information will include three attempts to make contact via telephone and if unsuccessful, then a certified letter from the investigator will be sent to the subject's last known address. In general, the study site should attempt to contact the subject after each missed visit to re-schedule the visit or collect patient-reported outcomes via phone interview.

7 Risk / Benefit Analysis

7.1 Benefits

Possible benefits of percutaneous ultrasound guided tenotomy using the TenJet System may include the reduction of pain resulting from the tendinosis. Also, by participating in this study, you will contribute valuable information to medical science that may lead to treatments for future patients with the same condition.

7.2 Risks

Possible risks associated with percutaneous treatment of lateral and medial epicondylitis include:

- Failure to relieve pain
- Swelling at the surgical site
- Infection
- Potential damage to surrounding tissue (e.g., nerve)
- Nerve and/or blood vessel damage
- Puncture of the tendon
- Excessive bleeding at surgical site
- Hematoma

- Loss of strength
- Loss of flexibility
- Additional risks associated with the use of the TenJet include electrical and thermal injury

Open surgical approach is associated with an increased complication rate over conventional percutaneous needle tenotomy.^{48 49}

8 STATISTICAL SECTION

8.1 Statistical Considerations

Data collected in the study will be presented using various descriptive statistics. Descriptive summaries will be the basis of study reports to generate an overall summary of the safety and clinical performance for the device. Continuous outcome variables will be presented as means and standard deviations with 95% confidence intervals, as well as medians and ranges. For categorical outcome variables, relative frequencies and 95% confidence intervals will be provided. For variables collected at multiple follow-up time periods, tables that include change from baseline will be presented for each follow-up interval.

Descriptive tables will be produced for baseline characteristics including demographics, medical history, pre-operative values for VAS, PREE and MEPS, summary of past conservative treatment, physical exam, and ultrasound and/or radiographic assessments.

8.2 Sample Size Justification

This is a single arm study that is exploratory in nature (i.e., Phase I). As such, no formal sample size estimation has been performed.

9 DATA MANAGEMENT

9.1 Data Collection

Data will be collected on paper case report forms (CRF).

A unique study number will be assigned to each patient. All information recorded on the CRF about the patient will be recorded with the study number on it. The main database will contain only the study number to identify the patient. The code with patient name and study number will be maintained in a locked file cabinet in the secured designated location at the site. Any computerized data is password protected.

10 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Events

Adverse events (AE) are any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in which subjects, users or other persons, whether or not related to the investigational medical device.

All adverse events, regardless of relationship to the device, must be recorded, as applicable, on the case report forms provided. Adverse events that occur during this study should be treated by established standards of care, which will protect the life and safety of the patients.

Adverse events shall be assessed and documented at the time of the procedure and at all study follow-up visits. Each investigator shall provide source documentation as requested by the Sponsor to facilitate reporting and adjudication of these events.

10.1.2 Serious Adverse Events

An adverse event is considered a Serious Adverse Event (SAE) that

- a) led to death
- b) led to a serious deterioration in the health of the subject, that either resulted in
 - 1) a life-threatening illness or injury, or
 - 2) a permanent impairment of a body structure or a body function, or
 - 3) in-patient hospitalization or prolongation of existing hospitalization, or
 - 4) a medical or surgical intervention to prevent permanent life-threatening illness or injury or permanent impairment to body structure or a body function.
- c) led to fetal distress, fetal death or a congenital abnormality

10.1.3 Unanticipated Serious Adverse Device Effect

An Unanticipated Serious Adverse Device Effect (USADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death were not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other

unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

10.2 Adverse Event Reporting

Any adverse event that occurs during the course of the study must be reported using the appropriate case report form. The Investigator must determine whether the adverse event is serious or unanticipated, its intensity, and the relationship of each adverse event to the study device and/or procedure.

The Investigator will report all serious adverse events, including unanticipated adverse device effects, to the IRB according to the IRB requirements.

As the TenJet System is a cleared medical device for this indication in the U.S., the Sponsor is responsible for making reports on adverse events to the appropriate regulatory authorities per country's applicable reporting requirements (e.g., in the United States, reporting per the Medical Device Reporting regulations 21 CFR part 803 – Medical Device Reporting).

11 STUDY ADMINISTRATION

11.1 Statement of Compliance

The clinical investigations will be in accordance with the ethical principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil October 2013), ISO 14155:2011 and ICH-GCP Guidelines.

The clinical investigation shall not commence until approval by the IRB.

Any additional requirements imposed by the IRB or regulatory authority shall be followed.

11.2 Investigational Review Board Approval (IRB)

The study protocol shall be reviewed and approved by the investigator's IRB prior to patient enrollment. Significant changes to the investigational plan must be approved in writing by the IRB prior to implementation. A significant change is one which may increase the risk or present a new risk to a patient, or which may adversely affect the scientific validity of the study.

11.3 Informed Consent

Informed consent is mandatory and must be obtained from all subjects as per local regulations, prior to their participation in the study.

It is the responsibility of the Investigator to ensure written informed consent from each subject, or the legally authorized representative of the subject, is obtained prior to the initiation of any study-related procedures.

Patients who agree to participate in this study will do so voluntarily. They will be treated on an equal basis with all other patients. Choosing not to participate will not affect their care in any way.

Study personnel fully knowledgeable in the purposes and procedures of the study will approach all prospective study participants. The facilities and settings in which prospective participants will be presented with the opportunity to learn about and consent to participation in the study will provide them sufficient quiet and unhurried time to be informed of the study, to ask questions, and between consent being given and the initiation of study procedures. Study personnel will, after presenting the study to prospective participants, assess the subject's understanding and autonomy by asking the subject to explain the study in his/her own words.

Once that step is completed, consent will be able to be given by the subject's signing the consent form. A copy of the consent form will be given to all consented participants.

Signed subject consent forms must be retained in the study files by the Investigator, and available for review by the IRB and/or regulatory agencies, as applicable.

The informed consent form and any other written information provided to subjects will be revised whenever important new information becomes available, or if there is an amendment to the protocol which necessitates a change to the content of subject information and/or to the consent form. The Investigator will inform the subject of changes in a timely manner, and will ask the subject/patient to confirm his/her continuation in the study by signing a revised consent form.

Any revised informed consent form and other written information provided to subjects must receive IRB approval, as applicable

11.4 Amending the Protocol

This protocol is to be followed exactly, and will only be altered by written amendments. Amendments must be approved by all parties responsible for approving the Protocol including the IRB prior to implementation. However, in situations where the amendment is regarding safety issues and there is an immediate hazard to patients, the amendment will be submitted as an urgent amendment and can be implemented in the study prior to approval. The Informed Consent and CRFs will be reviewed to ensure these are amended if necessary.

Administrative changes that do not affect the patient benefit/risk ratio (e.g., editorial changes for clarity) may be made without any further approvals.

11.5 Protocol Deviations/Violations and Medical Emergencies

A protocol deviation or violation is a failure to comply with the requirements of the clinical study as specified in the protocol. Examples of protocol deviations include late visits, missed visits, required follow-up testing not completed. An example of a protocol violation includes enrollment of a study subject who fails to meet inclusion/exclusion criteria as specified in the protocol. Each investigator shall conduct this clinical study in accordance with the study protocol and any conditions required by the reviewing IRB.

11.6 Criteria for Terminating Study

The investigator reserves the right to terminate the study but intends only to exercise this right for valid scientific or administrative reasons and reasons related to protection of patients. The IRB will be notified in writing in the event of termination.

Possible reasons for study termination include:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study.

In the event that the study is discontinued, study patients will be contacted by phone and registered mail. Study patients contacted will be asked to come into to clinic, to have their questions and concerns addressed, as well as discuss a continued plan of care.

¹ Runge F Zur genese und behandlungdes schreibekramfes. Berl Klin Wochenschr 10:245

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