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PROTOCOL & SAP

Medical Pain Consultants

Study Protocol

HF-01

NCT04391842

Sustained Acoustic Medicine (SAM) Combined with a Diclofenac Ultrasound Coupling Patch for Knee Osteoarthritis

July 1st 2019

1.0 Background and Scientific Rationale

1.1 Background Information

Approximately 50 million people in the United States suffer from some form of arthritis pain, and Osteoarthritis is the most common form of the disease. The prevalence of osteoarthritis is greater among women than men, increases with age, and affects all race/ethnicity groups.

Osteoarthritis affects articular cartilage, the smooth fibrous connective tissue essential for smooth movement and cushioning of the joint. As the disease progresses, the cartilage becomes thinner and may completely wear away. Inflammation of the synovial membrane, the lining that surrounds the knee joint and contains the synovial fluid, is often a result of these changes. Osteoarthritis can form in any joint but is more common in weight bearing joints such as the knee and hip, and results in joint space narrowing, severe pain and loss of mobility.

Ultrasound therapy for the treatment of Osteoarthritis may be used as conservative care (see reference: cochrane review).

1.2 Investigational Product Description

Low intensity therapeutic ultrasound (LITUS) will be delivered in this study using ZetrOZ's Ultrasonic Diathermy Device called sam®. The device package consists of a Power Controller, 2 Applicators (ultrasound generators), Ultrasound Coupling Bandages 1% Diclofenac, Ultrasound Gel, Y-Adapter, Charger and User Manual.

1.3 Hypotheses

It is hypothesized that users of the LITUS device (sam®) device will be able to successfully apply and remove the device daily to the knee. It is hypothesized that treatment with the LITUS device (sam®) will yield improvements in pain and stiffness in subjects with knee Osteoarthritis.

1.4 Potential Risks to Subjects

The risks of using ultrasound devices to administer physical therapy are well established and include: burn, itching and/or pain. These risks decrease when using lower intensity ultrasound, as in this study. The Ultrasound Diathermy Device uses existing technology to deliver ultrasound therapy in a portable and convenient fashion. The subjects will be given the chance to ask any questions regarding the trial procedures, requirements, and purposes. Once the subjects are fully informed of the possible risks and benefits of participation in the study and all of their questions have been satisfactorily answered, they will be required to sign the informed consent form in order to participate in the study. All subjects must give consent themselves and no legally authorized representatives will be accepted on their behalf.

2.0 Study Objectives and Design

2.1 Objectives

Evaluate the usability of the device for proper design.

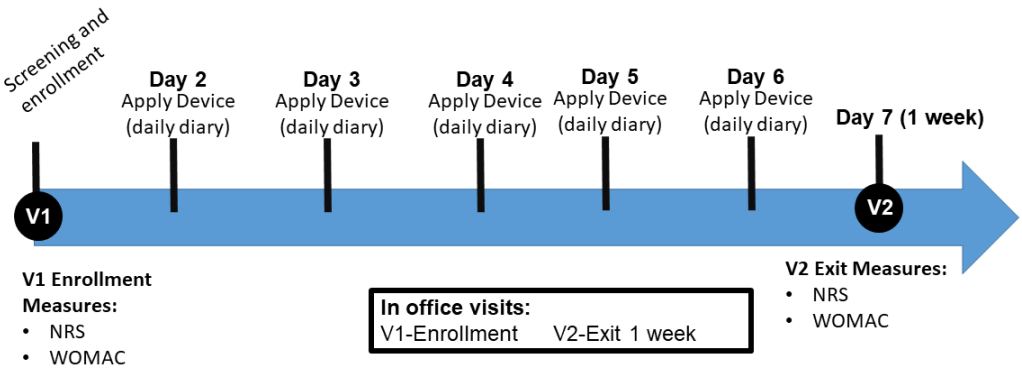
Evaluate the ability of LITUS to reduce pain, stiffness as measured by NRS scale and the Western Ontario and McMaster Universities Arthritis Index (WOMAC)

2.2 Study Design

2.2.1 General Study Design

This study is designed as a single cohort case series. After screening and enrollment, subjects will self-administer LITUS daily for 7 consecutive days.

2.2.2 Study Design Schematic



3.0 Study Population

3.1 General Characteristics of the Proposed Subject Population(s)

This study will enroll subjects with physician confirmed knee Osteoarthritis pain. The long duration wearable therapeutic ultrasound treatment has multiple benefits likely to aid the patients enrolled in this study with knee Osteoarthritis pain. Acoustic waves mechanically stimulate tissue, triggering biological effects including the down regulation of inflammatory cytokines, increased transport kinetics, protein synthesis, and extracellular matrix deposition. It is therefore hypothesized that the wearable device has the potential to provide sustained OA symptom management.

3.2 Anticipated Number of Research Subjects

Enrollment will be monitored at the assumed rates of Screen Failures and Discontinuation may be found to differ in this study from historical controls. The objective is to screen and enroll towards a target of 30 completed subjects.

Subjects to be Screened	50
Assumed Screen Fail Rate	30%
Subjects to be Enrolled (sign ICF)	35
Assumed Discontinuation Rate	10%
Total Number Completers (complete 24-wk treatment phase)	30

3.3 Inclusion Criteria

Subjects to be enrolled in the trial will:

- Have physician-diagnosed mild to moderate knee OA (OARSI atlas grades 1-2)
- Fulfill the American College of Rheumatology clinical and radiological diagnostic criteria for knee OA
- Are between 35-80 years of age
- Report a frequent pain score between 3-7 (range: 0-10) during the week preceding enrollment
- Report that knee pain negatively affects quality of life
- Are willing not to use any cream, gel, or topical solution during the administration of treatment other than the approved ultrasound gel provided to the subject at the initiation of the study
- Are deemed appropriate by their physician or by the study site physician to participate.
- Be willing and able to self-administer treatment daily within their place of residence or during normal daily activity, excluding bathing, showering, or other water activities which may result in submersion of the study device.
- Not use or initiate opioid and/or non-opioid analgesic medications.
- Be willing to discontinue any other interventional treatment modalities on the knee during the study period (e.g., transcutaneous electrical nerve stimulation, electronic muscle stimulation, traditional ultrasound).

3.4 Exclusion Criteria

A potential subject will be excluded from participation in this study if he or she:

- Cannot successfully demonstrate the ability to put on and take off the device.
- Displays any condition which, in the judgment of the investigator, would make participation in the study unacceptable including, but not limited to, the subject's ability to understand and follow instructions.
- Participated in a clinical trial for an investigational drug and/or agent within 30 days prior to screening.
- Is pregnant.
- Is a prisoner.
- Is non-ambulatory (unable to walk).
- Has a pacemaker.
- Has a malignancy in the treatment area.
- Has an active infection, open sores, or wounds in the treatment area.
- Has impaired sensation in the treatment area, such as caused by chemotherapy or anesthesia.
- Has a known neuropathy (disease of the brain or spinal nerves).

- Has a hereditary disposition (tendency) for excessive bleeding (hemorrhage).
- Have knee replacement, other surgical intervention, or hyaluronidase injection in the affected knee in the past 6 months
- Are currently taking steroids
- Have any contraindication to radiograph
- Have a secondary cause of arthritis (metabolic or inflammatory)

4.0 Study Procedures

4.1 Subject Recruitment

It is planned at one site to enroll subjects into this trial. Therefore, based on the assumptions presented in Section 3.2, we will need to screen approximately 50 subjects to meet the target enrollment number of 30 subjects, and support a target completion number of 30. The target enrollment period for this study is 2 months.

4.1.1 Subject Compensation

Subjects will be compensated up to $50 for participation in the study. Subjects will not be compensated for the initial screening/enrollment visit, but will $50 for completed Visit 2.

4.2 Screening Procedures

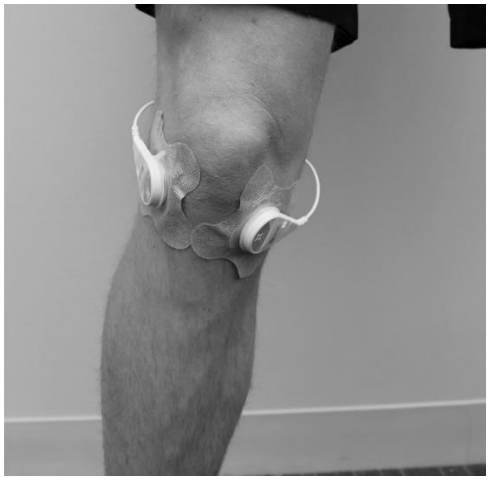
Subjects will come to the clinic to be screened for inclusion in the study. The investigator or a sub-investigator will review the Eligibility Screening Checklist with the subject. All subjects must have physician-diagnosed mild to moderate knee OA (OARSI atlas grades 1-2).

4.3 Study Treatment

4.3.1 Treatment Groups

Subjects will participate in one treatment arm. All devices are manufactured by ZetrOZ Systems (Trumbull, CT) and are all identical. The 3 MHz device was FDA cleared in November 2013, and is marketed in the United States under the brand name sam®. All study subjects will apply 2 applicators affixed to the coupling bandages to their knee on the medial and lateral sides as shown in the figure below. The applicators are connected via a Y-adapter to a single power controller. The subjects will set the power controller to a 4-hour treatment duration for each daily treatment.

Sample
Applicator Placement



This device delivers continuous ultrasound with a maximum acoustic power output of 1.3 W/cm^2 ±20% when 2 applicators are used. The frequency is 3 MHz ± 20%. The maximum treatment duration permitted is 4 hours per day.

Treatment protocol: subjects will self-administer the LITUS therapy for 4 hours per day at least 5 days (and up to 7 days) for the 1-week study.

4.3.2 Randomization
Not Applicable.

4.3.3 Breaking the Blind
Not Applicable

4.3.4 Treatment Adherence/ Study Compliance
Treatment compliance will be assessed by review of daily diaries and count of remaining bandages at the end of the study. The Research Coordinator will remind the subjects of the treatment protocol and retrain them on use of the device if necessary. Study visits should be completed within 3 days of the specified time in the Schedule of Assessments (Section 4.6).

4.4 Follow-Up Procedures

4.4.1 Procedures to Assess Usability and Efficacy
Usability and Efficacy will be assessed at the end of the study. Subjects will maintain a Daily Diary at home, which will be a printed booklet that they will complete manually daily throughout the study period.

Daily Diary
Subjects will complete a Daily Diary throughout the 1-week treatment period to collect usability and pain ratings before, during and after treatment.

Numeric Rating Scale (NRS)
Subject-reported rating of pain severity, 0 = no pain, 10 = worst pain imaginable

Western Ontario and McMaster Universities Arthritis Index (WOMAC)
Subject reported rating of pain, stiffness and function validated for knee Osteoarthritis.

Exit Assessment
At the conclusion of the trial, each subject will be asked to complete an exit assessment form which solicits the subject's feedback on their use of the device, and satisfaction with therapy.

4.4.2 Procedures to Assess Safety

Adverse events will be recorded at each study visit.

4.5 Use of Non-Study Drugs and Procedures

Not Applicable. Not Allowed.

4.6 Schedule of Assessments

Visit Number	V1	V1	V2
Visit Type	Screening	Start Treatment	End of Treatment /Early Terminati on (3)
Visit Day (1)	0	0	7
Inclusion/Exclusion Criteria	x		
Informed Consent	x		
Medical history	x		
Treatment history	x		
Device Assignment Form		x	
Physical Examination	x		
Confirm baseline pain >4 week preceding	x		
Train Subject on sam Device		x	
Confirm subject and put on and take off device		x	
WOMAC Scale		x	x
Adverse Events		x	x
Protocol Deviations			x
Distribute Daily Diary		x	
Review/Collect Daily Diary			x
Assess Compliance (2)			x
Distribute sam Device with patches		x	
Distribute Patches		x	
Issue Subject Compensation and Signed Receipt			x
Collect sam Device and Unused Patches			x
Exit Assessment Questionnaire			x

1 - Visit window: ±3 days

2 - Research coordinator should review subject diaries to ensure completeness, and evidence that subject is using the device per protocol.

5.0 Data Management and Analysis

5.1 Outcome Measures and Data Analysis Plan

5.2 Change in NRS pain score from baseline will be analyzed for pre and post-treatment each treatment day throughout the study, and WOMAC (pain, stiffness, and functional change) will be evaluated on day 1 and day 7. Data will be analyzed using t-tests and repeated measure ANOVAs.

6.0 Risk Analysis

6.1 Adverse Event Recording and Reporting

6.1.1 Adverse Event Definitions

Adverse effect. Any untoward medical occurrence in a clinical study of an investigational device; regardless of the causal relationship of the problem with the device or, if applicable, other study treatment or diagnostic product(s).

Associated with the investigational device or, if applicable, other study treatment or diagnostic product(s). There is a reasonable possibility that the adverse effect may have been caused by the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse effect. Any adverse effect that places the subject, in the view of the investigator-sponsor, at immediate risk of death from the effect as it occurred (i.e., does not include an adverse effect that, had it actually occurred in a more severe form, might have caused death).

Serious adverse effect. Any adverse effect that results in any of the following outcomes: death, a life-threatening adverse effect, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Unexpected adverse effect. Any adverse effect, the frequency, specificity or severity of which is not consistent with the risk information described in the clinical study protocol(s)

Unanticipated adverse device effect. 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 was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

6.1.2 Eliciting Adverse Effect Information

Clinical study subjects will be routinely questioned about adverse effects at study visits.

6.1.3 Recording and Assessment of Adverse Effects

All observed or volunteered adverse effects (serious or non-serious) and abnormal test findings, regardless of treatment group, if applicable, or suspected causal relationship to the investigational device or, if applicable, other study treatment or diagnostic product(s) will be recorded in the subjects' case histories. For all adverse effects, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a serious adverse effect) and; 2) an assessment of the casual relationship between the adverse effect and the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Adverse effects or abnormal test findings felt to be associated with the investigational device or, if applicable, other study treatment or diagnostic product(s) will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator-sponsor.

6.1.3.1 Causality and Severity Assessment

The investigator-sponsor will promptly review documented adverse effects and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse effect; 2) if there is a reasonable possibility that the adverse effect was caused by the investigational device or, if applicable, other study treatment or diagnostic

product(s); and 3) if the adverse effect meets the criteria for a serious adverse effect.

If the investigator-sponsor's final determination of causality is "unknown and of questionable relationship to the investigational device or, if applicable, other study treatment or diagnostic product(s)", the adverse effect will be classified as associated with the use of the investigational device or study treatment or diagnostic drug product(s) for reporting purposes. If the investigator-sponsor's final determination of causality is "unknown but not related to the investigational device or, if applicable, other study treatment or diagnostic product(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

6.1.4 Reporting of Adverse Effects to the FDA

The investigator-sponsor will submit a completed **Form** FDA 3500 A to the FDA's Center for Devices and Radiological Health for any observed or volunteered adverse effect that is determined to be an *unanticipated adverse device effect. A* copy of this completed form will be provided to all participating sub-investigators.

The completed Form FDA 3500 A will be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the investigator-sponsor first receives notice of the adverse effect.

If the results of the sponsor-investigator's follow-up evaluation show that an adverse effect that was initially determined to not constitute an *unanticipated adverse device effect* does, in fact, meet the requirements for reporting; the investigator-sponsor will submit a completed **Form** FDA 3500 A as soon as possible, but in no event later than 10 working days, after the determination was made.

For each submitted **Form** FDA 3500 A, the sponsor-investigator will identify all previously submitted reports that that addressed a similar adverse effect experience and will provide an analysis of the significance of newly reported adverse effect in light of the previous, similar report(s).

Subsequent to the initial submission of a completed **Form** FDA 3500 A, the investigator-sponsor will submit additional information concerning the reported adverse effect as requested by the FDA.

6.1.5 Reporting of Adverse Effects to the Responsible IRB

In accordance with applicable policies of the Institutional Review Board (IRB), the investigator-sponsor will report, to the IRB, any observed or volunteered adverse effect that is determined to meet all of the following criteria: 1) associated with the investigational device or, if applicable, other study treatment or diagnostic

product(s); 2) a serious adverse effect; and 3) an unexpected adverse effect. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse effects will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the investigator-sponsor's receipt of the respective information. Adverse effects which are 1) associated with the investigational drug or, if applicable, other study treatment or diagnostic product(s); 2) fatal or life-threatening; and 3) unexpected will be reported to the IRB within 24 hours of the investigator-sponsor's receipt of the respective information.

Follow-up information to reported adverse effects will be submitted to the IRB as soon as the relevant information is available. If the results of the sponsor-investigator's follow-up investigation show that an adverse effect that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the investigator-sponsor will report the adverse effect to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

7.0 Monitoring Procedures

Monitoring of the clinical study for clinical protocol compliance will be conducted periodically (i.e., at a minimum of annually) by the clinical team. The sponsor-investigator will permit direct access to the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of these data.

8.0 Additional Records and Reports

8.1 Data Handling and Record-keeping

A Case Report Form (will be completed at each study visit for each subject enrolled into the clinical study. The investigator-sponsor will review, approve and sign/date each completed CRF; the investigator-sponsor's signature serving as attestation of the investigator-sponsor's responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

The clinical research team will work with each site to ensure accurate completion of CRFs reconciling illegible entries, missing data, and conflicting data entries.

Source Data are the clinical findings and observations, laboratory and test data, and other information contained in *Source Documents*. *Source Documents* are the original records (and certified copies of original records); including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation

checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, etc. When applicable, information recorded on the CRF shall match the *Source Data* recorded on the *Source Documents*.

8.2 Record Maintenance and Retention

The investigator-sponsor will maintain records in accordance with Good Clinical Practice guidelines; to include:

- IRB correspondence (including approval notifications) related to the clinical protocol; including copies of adverse event reports and annual or interim reports;
- Current and past versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s) and, if applicable, subject recruitment advertisements.
- Signed Investigator's Agreements and Certifications of Financial Interests of Clinical Investigators;
- Curriculum vitae (investigator-sponsor and clinical protocol sub-investigators);
- Certificates of required training (e.g., human subject protections, Good Clinical Practice, etc.) for investigator-sponsor and listed sub-investigators;
- Instructions for on-site preparation and handling of the investigational device and/or study treatment or diagnostic product(s), and other study-related materials (i.e., if not addressed in the clinical protocol);
- Decoding procedures for blinded trials;
- Master device list;
- Signed informed consent forms;
- Completed Case Report Forms; signed and dated by investigator-sponsor;
- Source Documents or certified copies of Source Documents;
- Monitoring visit reports;
- Copies of investigator-sponsor correspondence to sub-investigators, including notifications of adverse effect information;
- Subject screening and enrollment logs;
- Subject identification code list;
- Device accountability records, including documentation of device disposal and returns to sponsor;
- Final clinical study report.

Site-subject identification numbers will be assigned to all subjects to de-identify the associated clinical data. A master subject ID log will be maintained by research coordinator separately from clinical trial data. The master log will contain the assigned site-subject identification number matched to each subject's full name, gender, and date-of-birth. The site-subject ID will be generated by a two-digit site ID separated by a dash from the subject number at that site. Subjects' names or other directly identifiable information will not be used in any reports, publication or other disclosures of clinical study outcomes.

The investigator-sponsor will retain the specified records and reports for up to 2 years after the marketing application is approved for the investigational device; or, if a marketing application is not submitted or approved for the investigational drug, until 2 years after investigations under the IDE have been discontinued and the FDA so notified.

9.0 References

Therapeutic ultrasound for osteoarthritis, Cochrane Review, 20 January 2010. http://www.cochrane.org/CD003132/MUSKEL_therapeutic-ultrasound-for-osteoarthritis