A pilot study of the Signal Relief patch for the treatment of musculoskeletal pain

Protocol Number:	Signal-01-21
Sponsor	Signal Relief
Investigational Product	Signal Relief Patch
Study Phase:	Pilot
Version	Version 1.2; 9Mar2022

CONFINDENTAL

The information provided in this document is confidential and is intended for the use of clinical investigators. The information in this document may not be disclosed unless federal or state law or regulations require such disclosure. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know it, with the obligation not to further disseminate this information.

DOCUMENT HISTORY

Document	Date	Overall Rationale
Original Protocol	30 Aug 2021	Not applicable
Version 1.1	26 Oct 2021	Update SAE reporting email address.
Version 1.2	9 Mar 2022	Amend protocol and ICF to allow NSAID use

TABLE OF CONTENTS

DOCUMENT HISTORY 2
TABLE OF CONTENTS 3
List of Figures 5
List of Tables 6
INVESTIGATOR STATEMENT OF COMPLIANCE 7
ABBREVIATIONS 8
1 PROTOCOL SUMMARY 9
1.1 Synopsis 9
1.2 Schedule of Activities 11
2 BACKGROUND AND RATIONALE 13
2.1 Chronic Musculoskeletal Pain 13
2.2 Signal Relief Patch 13
3 OBJECTIVES AND ENDPOINTS 15
3.1 Primary Objective 15
3.2 Secondary Objectives 15
3.3 Exploratory Objectives 15
4 STUDY DESIGN 15
4.1 Study Duration 16
4.2 End of study 16
5 STUDY POPULATION 16
5.1 Inclusion Criteria 16
5.2 Exclusion Criteria 16
5.3 Lifestyle Considerations 16
5.3.1 Exercise 16
5.4 Screen Failures 17
5.5 Strategies for Recruitment 17
6 STUDY INTERVENTION 17
6.1 Study Intervention Overview 17
6.2 Investigational Product 17
6.2.1 Investigational Product Supplies 17

6.2.2 Accountability and Compliance 17
6.3 Adverse Event Management 18
6.3.1 Insufficient Pain Management 18
6.4 Concomitant Medications and Therapies 18
6.4.1 Prohibited Medications and Therapy 18
6.5 Duration of Therapy 18
6.5.1 Criteria for Study Discontinuation 18
7 STUDY ASSESSMENTS 19
7.1 General Assessments 19
7.1.1 Participant Consent 19
7.1.2 Medical History 19
7.1.3 Concomitant Medications 20
7.2 Safety Assessments 20
7.2.1 Physical Examinations 20
7.2.2 Vital Signs 20
7.2.3 Adverse Events 20
7.3 Efficacy Assessments 20
7.3.1 Visual Analog Scale (VAS) 20
7.3.2 Pain Medication Diary 20
7.4 Correlative Studies 21
8 ADVERSE EVENTS 21
8.1 Adverse Event Definitions 21
8.1.1 Adverse events 21
8.1.2 Adverse Device Effect 21
8.1.3 Unanticipated Adverse Device Effect 21
8.1.4 Serious Adverse Events 21
8.1.5 Serious Adverse Device Effect 22
8.1.6 Anticipated Serious Adverse Device Effect 22
8.1.7 Unanticipated Serious Adverse Device Effect 22
8.1.8 Device Deficiency 22
8.2 Adverse Event Characterization 23
8.2.1 Severity Assessment 23

8.2.2 Causality Assessment....23
8.2.3 Expectedness....24
8.2.4 Action Taken and Event Outcome....24
8.3 Adverse Event Reporting....25
8.3.1 SAE Reporting....25
8.3.2 Device Deficiency Reporting....25
9 Statistical Considerations....26
9.1 Sample size determination....26
9.2 Populations for Analysis....26
9.2.1 Safety Population....26
9.2.2 Modified Intent-to-Treat Population....26
9.2.3 Per-Protocol Population....26
9.3 Endpoint Analyses....26
10 ETHICAL AND REGULATORY CONSIDERATIONS....26
10.1 Human Subjects Protections....26
10.2 Personal Data Protection....26
10.3 Independent Ethics Committee Review....27
10.4 Protocol Amendments....27
10.5 Investigator Responsibilities....27
10.6 Protocol Deviations....27
11 DATA HANDLING....28
11.1 Recording and Collection of Data....28
11.2 Data Management....28
12 PUBLICATION PLAN....28
13 REFERENCES....29

List of Figures

Figure 1. The Signal Relief Patch....14

List of Tables

Table 1: Severity Assessment 23
Table 2: Causality Assessment 24
Table 3: Event Outcome 24

INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title:	A pilot study of the Signal Relief patch for the treatment of musculoskeletal pain
Protocol Number:	Signal-01-21
Protocol Date:	16 Sep 2021
Version:	1.0

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this Protocol, the associated site agreement, the International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable United States (US) Code of Federal Regulations (CFR). I will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

I agree to maintain all study documentation for a minimum of two years after the study has been completed or for longer periods as required by law and regulations. Publication of the results of this study will be governed by the conditions stipulated in the Study Site Agreement. I agree to supervise the use of the Investigational Products at my institution and ensure that the informed consent document is obtained before subject enrollment.

I have read and understood the information in this Protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed of the obligations incurred by their participation. I will attest to the delegation of any obligation under this Protocol to my associates, colleagues, and employees by signing such delegation in the Study Delegation Log.

Signature of Site Principal Investigator | Date

Name of Site Principal Investigator

ABBREVIATIONS

Abbreviation	Definition/Explanation
ADE	Adverse device effect
AE	Adverse event
ASADE	Anticipated serious adverse device effect
BP	Blood pressure
CFR	Code of Federal Regulations
CDC	Center for Disease Control
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COX-2	Cyclooxygenase-2
eCRF	Electronic case report form
e.g.,	Exempli Gratia (for example)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HEAL	Helping to End Addiction Long-term
i.e.,	Id Est (that is)
IEC	Independent ethics committee
IDE	Investigational Device Exemption
IRB	Institutional review board
NCC	Nano-capacitive arrays
NIH	National Institute of Health
NSAID	Non-steroid anti-inflamatory
SADE	Serious adverse device effect
SAE	Serious adverse event
SOA	Schedule of activities
TENS	Transcutaneous electrical nerve stimulation
UADE	Unanticipated adverse device effect
USADE	Unanticipated serious adverse device effect
VAS	Visual Analog Scale

1 PROTOCOL SUMMARY

1.1 Synopsis

Title:	A pilot study of the Signal Relief patch for the treatment of musculoskeletal pain
Protocol number:	Signal- 01-21
Study Description:	This is an open-label pilot study.
Phase:	Pilot
Investigational Device:	Signal Relief Patch
Objectives:	Primary Objective: To assess the efficacy of the Signal Relief patch for the management of general musculoskeletal pain. Secondary Objectives: • To assess additional measures of efficacy of the Signal Relief patch for the management of musculoskeletal pain. • To assess the safety of the Signal Relief patch for the management of musculoskeletal pain.
Endpoints:	Primary Endpoint: The proportion of subjects achieving at least a 30% reduction in reported pain on the visual analog scale score from baseline to the end of treatment. Secondary Endpoints: • The proportional change in subject-reported visual analog scale score from baseline to the end of treatment. • The change in subject-reported daily use of other medications intended for pain management. • The proportional change in subject-reported scores on the Brief Pain Inventory Form from baseline to the end of treatment. • The frequency of adverse events characterized by type, severity, seriousness, duration, and relationship to study therapy.
Study Population:	Key Inclusion Criteria: • Male or female subject aged ≥ 18 years.

	• Currently seeking treatment for chronic musculoskeletal pain management. • Visual analog scale score > 4 at baseline. • Willing to refrain from the use of prescription pain medications during study participation. • Able and willing to provide informed consent. Key Exclusion Criteria: • Receiving other investigational agents or on another clinical trial. • In emergent need for pain management. • Acute injury requiring rapid intervention or treatment. • The subject is using prescription medications (e.g., celecoxib, codeine, oxycodone, prednisone, etc.) for pain management regularly or PRN. • The subject is currently undergoing or planning to begin physical therapy. • The subject is planning to begin a new exercise routine. • Subject has implantable pain device, pacemaker, defibrillator, or other neuromodulation implantable device • Known to be pregnant.
Study Duration:	4 months
Participant Duration:	8 days
Study Centers:	Single site

1.2 Schedule of Activities

Protocol Activities	Screening	Day 1	Day 7
Window	-14 days		
Informed Consent	X		
Demographics	X		
Medical History	X		
Eligibility Criteria	X		
Registration	X		
Clinical Assessments			
Vital Signs[1]	X	X	X
Physical Exam	X	X	X
Adverse Event Collection[2]		X	X
Concomitant Medications	X	X	X
Efficacy Assessments			
Visual Analog Scale	X	X	X
Brief Pain Inventory		X	X
Pain Medication Diary[3]		X	X
Study Intervention			
Device use education[4]		X	
Signal Relief Patch use[5]		X	X
Signal Relief Patch log[6]		X	X
Laboratory Studies			
Correlative Blood		X[7]	X

[1] Vital signs will include blood pressure, heart rate, respiration rate, pulse oximetry, and body temperature, weight, and height (height will be measured at screening only).
[2] Adverse events will be collected from day 1 to day 7. Any device-related adverse events will be followed until stabilization or resolution.
[3] Pain medication diary to be dispensed to subjects to record the use of medications for pain management. Subjects will return the completed diary on day 7.
[4] The study team will provide education on proper device use and placement on day 1 of study participation.
[5] Subjects must wear the patch continuously from day 1 to day 7 and should only remove the patch when showering or swimming.
[6] Subjects will be asked to maintain a log of where and how a patch is placed, for how long it is worn, and if removed for any reason. The log will be dispensed to subjects on day 1 and subjects will return the completed log on day 7.
[7] Blood will be drawn prior to patch placement.

2 BACKGROUND AND RATIONALE

2.1 Chronic Musculoskeletal Pain

In 2019, the National Center of Health Statistics reported that 20.4% of adults in the United States have chronic pain and 7.4% have high impact chronic pain (pain that limits life or work activities). [1] Data from the National Health Interview Survey showed that chronic pain is higher in women, persons over the age of 65, and non-Hispanic white adults. The prevalence of chronic pain also increases with age and as the place of residence becomes more rural.[1] While the underlying cause of chronic pain can vary (e.g., inflammation, underlying disease or condition, injury, medical treatment, etc.), it is associated with a decrease in quality of life and depressive and anxiety disorders.[2,3]

First-line therapy for chronic pain includes the use of over-the-counter analgesics such as acetaminophen and ibuprofen or COX-2 inhibitors such as celecoxib. When these treatments are ineffective in managing pain, opioids have dominated the treatment paradigm. After the publication of two small studies in the early 1980s demonstrating that opioids were not addictive, opioids became a welcome relief for the management of chronic pain. Unfortunately, this misinformation led to the long-term use of opioids that laid the foundation of our current opioid crisis.[4] In a recent survey, 22.1% of adults with chronic pain reported using opioids over the past three months.[5] Since 1991 the number of drug overdose deaths has quadrupled, and 70% of the 70,630 deaths in 2019 involved an opioid.[6] The Center for Disease Control (CDC) has initiated an extensive program to help curb the crisis through public education, state funding, and information tracking strategies.[7] The National Institute of Health started the Helping to End Addiction Long-term (HEAL) initiative to provide funding to researchers addressing questions around addiction and to support the development of alternative non-opioid therapies for pain management.[8]

There is a need for safe and effective non-opioid options for pain management. Nanotechnology and nanomaterials have the potential to offer non-pharmacologic therapy for these patients without the adverse effects of systemic use.[9]

2.2 Signal Relief Patch

The Signal Relief Patch is an innovative, non-invasive technology that exists as a thin, flexible patch. The patch contains no drugs, wires, or batteries. Nano-capacitors utilized within the Signal Relief Patch were originally developed to replace military antenna systems with no additional power supply. Since development, it was incidentally found that these nano-capacitors may help control pain by working with the body's electrical system. Although the details of how these nano-capacitors facilitate the alleviation of pain are still under investigation, the possibility of reducing pain through a non-invasive, nonpharmacological method is extremely appealing.[10]

This is not the first time that manipulation of neural electrical activity has been used to treat pain. TENS (Transcutaneous electrical nerve stimulation) is an FDA-approved treatment that works by blasting the nervous system with a static sensory white noise which is used to drown out the pain message or distract the brain from sensing pain.[11] The nano-capacitors function in a seemingly opposite direction. These nano-capacitors allow the absorption of energy which results in a decrease in pain messaging to the brain, resulting in attenuation of pain sensation.[12]

The Signal Relief Patch is currently being sold as a general wellness device as a way to alleviate pain. An image of the Signal Relief Patch is shown in Figure 1.



Figure 1. The Signal Relief Patch

The Signal Relief patch is constructed of 3 basic layers.

- The top layer, designed to be protective and electrically insulated.
- The middle layer, containing the nano-capacitive arrays (NCC).
- And lastly, an electrically insulated and protective bottom layer.

When laminated together these layers create the thin, flexible, and water-resistant Signal Relief device.

The Signal Relief Patch is supplied with FDA-cleared adhesive strips that patients have the option of utilizing given the location where the pain is being felt. The device has several options of applying the nano-capacitive material externally to the affected area including adhesive, athletic tape, or wraps. Refer to the Instructions for Use for further information about patch placement.

3 OBJECTIVES AND ENDPOINTS

3.1 Primary Objective

To assess the efficacy of the Signal Relief patch for the management of musculoskeletal pain.

Primary endpoint: The proportion of subjects achieving at least a 30% reduction in reported pain on the visual analog scale score from baseline to the end of treatment.

3.2 Secondary Objective s

- To assess additional measures of efficacy of the Signal Relief patch for the management of musculoskeletal pain.

  Secondary endpoints:

  - The proportional change in subject-reported visual analog scale score from baseline to the end of treatment.
  - The change in subject-reported daily use of other medications intended for pain management.
  - The proportional change in subject-reported scores on the Brief Pain Inventory Form from baseline to the end of treatment.

- To assess the safety of the Signal Relief patch for the management of musculoskeletal pain.

  Secondary endpoint:

  - The frequency of adverse events characterized by type, severity, seriousness, duration, and relationship to study therapy.

3.3 Exploratory Objectives

- To assess biomarkers of response to study therapy.

  Exploratory endpoint:

  - The change in serum Substance P during study therapy.
  - Correlation of serum of Substance P with patient-reported visual analog scale scores.

4 STUDY DESIGN

This is a prospective, open-label pilot trial of the Signal Relief patch for the treatment of musculoskeletal pain. The trial is designed to detect early signals of safety and efficacy of the study device. 40 eligible subjects seeking treatment for musculoskeletal pain will be enrolled in the trial and treated with the Signal Relief patch for seven days. During that time frame, subjects will be asked to rate their pain on a VAS. Subjects who achieve at least a 30% reduction in pain will be considered a treatment response.

4.1 Study Duration

From the first subject enrollment to the completion of the study analysis, it is anticipated that the study will last for up to four months.

4.2 End of study

The study will end when the last subject completed the last visit or contact, discontinues from the study, or is lost to follow-up, whichever occurs first. In addition, the sponsor may terminate the study at any time.

5 STUDY POPULATION

Potential study subjects must meet all inclusion criteria and none of the exclusion criteria to be deemed eligible for the clinical trial.

5.1 Inclusion Criteria

1. Male or female subject aged ≥ 18 years.
2. Currently seeking treatment for chronic musculoskeletal pain management.
3. Visual analog scale score > 4 at baseline.
4. Willing to refrain from the use of prescription pain medications during study participation.
5. Able and willing to provide informed consent.

5.2 Exclusion Criteria

1. Receiving other investigational agents or on another clinical trial.
2. In emergent need for pain management.
3. Acute injury requiring rapid intervention or treatment.
4. The subject is using prescription medications (e.g., celecoxib, codeine, oxycodone, prednisone, etc.) for pain management regularly or PRN.
5. The subject is currently undergoing or planning to begin physical therapy.
6. The subject is planning to begin a new exercise routine.
7. Subject has implantable pain device, pacemaker, defibrillator, or other neuromodulation implantable device
8. Known to be pregnant.

5.3 Lifestyle Considerations

5.3.1 Exercise

During study therapy, subjects will be asked to refrain from beginning any new exercise regimens. Subjects should avoid exercise that may result in muscle soreness. However, subjects will be encouraged to continue established exercise routines or other physical activity as deemed appropriate by the treating investigator.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but do not meet subject eligibility criteria. These subjects will not be entered into the study or begin study intervention. However, minimal information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements. Minimal information includes, but may not be limited to, demography, screen failure details, eligibility criteria, and any serious adverse event (SAE) experienced during screening, but before being deemed ineligible. Adverse events and SAEs will not be collected after a subject is deemed ineligible. Any AEs/SAEs related to a screening procedure will be followed until resolution.

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened at a later date at the Investigator's discretion.

5.5 Strategies for Recruitment

Subjects will be recruited from among the patient population within enrolling investigator's clinics.

6 STUDY INTERVENTION

6.1 Study Intervention Overview

Eligible subjects will be provided a Signal Relief patch, the instructions for use, and patch placement materials (adhesive, athletic tape, or wrap as applicable for the location of the pain). Subjects will be instructed to use the patch daily for seven days. The patch must be worn constantly except when showing or swimming. Study staff will help educate the subject on the proper use and placement of the patch. Study staff will apply the patch for the first time with the patient in the clinic.

During study therapy, subjects may use acetaminophen to help with pain management. However, the use of prescription medications for pain management is prohibited. Subjects may begin new pain management therapy only after meeting the criteria described in Section 6.3.1.

6.2 Investigational Product

6.2.1 Investigational Product Supplies

The investigational device and patch placement materials will be provided to sites by the study Sponsor. The Investigator will ensure appropriately trained and delegated personnel will receive, inventory, and store all investigational products. Records of device receipt, use, or disposition will be maintained by the site according to 21 CFR 812.140. Records should include the type and quality of the device, date of receipt, batch number or code, and name of persons receiving, using, or disposing of the device. If device units are returned to the Sponsor, repaired, or disposed of the reason why must also be documented.

6.2.2 Accountability and Compliance

Subjects will be asked to keep a daily diary indicating where the patch was placed, how it was attached, and for how long it was worn. Any reason for patch removal or non-compliance should

be documented. Any unused investigational supplies will be required to be returned to the study site.

6.3 Adverse Event Management

It is not anticipated that there will be many study device-related adverse events experienced. However, skin irritation may occur. All dermal reactions should be managed according to the standard of care procedures maintaining optimal patient care. Subjects who develop a severe, device-related dermal reaction/adverse event must discontinue study therapy. All device-related adverse events must be followed until stabilization or resolution.

6.3.1 Insufficient Pain Management

Subjects meeting the following criteria may discontinue study therapy and begin alternative pain management:

- Subject report inadequate pain control utilizing the study device and acetaminophen.
- Study staff has confirmed proper device use and placement.
- The subject has appropriately used the device for at least three days.

6.4 Concomitant Medications and Therapies

All administered concomitant medications (including herbal supplements) and non-medicinal therapies (including physical therapy) used for pain management within seven days before the start of study therapy will be recorded in the subject's research chart and corresponding eCRF. Medications used to treat adverse events should be documented in the eCRF.

6.4.1 Prohibited Medications and Therapy

Subjects are prohibited from taking the following medications and therapies during study therapy:

- Other investigational drugs or devices.
- Herbal remedies taken with the intent of pain management or inflammation.
- Prescription medications for pain management (e.g., celecoxib, codeine, oxycodone, prednisone, etc.).
    - Subjects on a stable disease-modifying drug (e.g., adalimumab, etanercept, hydroxychloroquine, methotrexate, etc.) at the time of study entry may continue this medication during study participation.
- Physical therapy.

6.5 Duration of Therapy

Subjects will receive study therapy for seven days or until an alternative study discontinuation criterion is met.

6.5.1 Criteria for Study Discontinuation

Subjects may withdraw from the study or study treatment at any time at their request without prejudice to future treatment. They may also be withdrawn at the discretion of the Investigator or

Sponsor for safety, behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures. The following will result in treatment discontinuation:

- Completed the study intervention and end of treatment visit.
- The subject requests to discontinue study treatment and/or study procedures.
- Adverse events or intercurrent illness that in the opinion of the investigator warrants the subject's withdrawal from study treatment.
    - Subjects discontinued for a device-related adverse event should be followed until stabilization or resolution of the event.
- Significant noncompliance with the protocol schedule or treatment administration in the opinion of the Sponsor or investigator.
- Inadequately controlled pain and meeting the criteria described in Section 6.3.1.
- Lost to follow-up.

7 STUDY ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that there may be circumstances, outside of the control of the Investigator that may make it unfeasible to perform a required test. In these cases, the Investigator will take all steps necessary to ensure the safety and well-being of the subject. When extenuating circumstances prevent a protocol-required test from being performed, the Investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible.

7.1 General Assessment s

7.1.1 Participant Consent

Before the initiation of any study procedures, all potential subjects or their legally authorized representative must be fully informed of the risks and potential benefits of trial participation. Subjects will be informed of the voluntary nature of study participation and their right to withdraw at any time during trial conduct without prejudice to future treatment. An informed consent document must be signed and dated by the participant indicating that they understand the risks and consent to participation. The Principal Investigator or their trained and delegated study personnel conducting the informed consent discussion must also sign and date the document. The original signed document must be filed in the subject's research chart and a copy of the signed document should be provided to the subject.

7.1.2 Medical History

The Investigator or trained and delegated study personnel will collect medical history to the extent that supports the assessment of eligibility and captures the history of a subject's pain. The medical history will include any active conditions and any conditions deemed to be clinically

significant by the treating investigator. If possible, terms describing the principal condition or syndrome should be used and symptom terms should be avoided.

7.1.3 Concomitant Medications

All medications currently being used by a study participant, regularly or as needed, must be reviewed and documented by the Investigator or qualified designee. Specific attention should be given to medications taken for the management of pain 14 days before the start of study therapy.

7.2 Safety Asses sments

7.2.1 Physical Examinations

Subjects will have physical examinations at the time points indicated on the Schedule of Activities. Physical exams will include all major body systems and exams conducted after screening may be replaced with a focused assessment. Focused assessments will be guided by the subject to areas of concern. Subjective data and objective data from a focused assessment should be utilized to detect the occurrence of any adverse events during study participation.

7.2.2 Vital Signs

Vital signs will include blood pressure, heart rate, respiration rate, pulse oximetry, and body temperature, weight, and height (height will be measured at screening only). Vitals signs should be recorded at the time points described in the Schedule of Activities.

7.2.3 Adverse Events

Adverse events experienced during trial participation will be collected per the Schedule of Activities. Each study participant will be questioned about the occurrence of adverse events in a non-leading manner. If a study subject reports the occurrence or if the Investigator or study team identifies an adverse event, event characterization, assessment, and reporting will be performed as described in the Adverse Event Section.

7.3 Efficacy Assessments

7.3.1 Visual Analog Scale (VAS)

A visual analog scale will be used to assess subject pain throughout study participation. Subjects will be asked to mark on a 10 cm line the intensity of their current pain. The line will progress from left to right 0 to 10 with 0 indicating no pain and 10 indicating the worst pain possible. The study team will measure the distance from 0 to the patient’s mark in millimeters and record the value in the eCRF.

7.3.2 Pain Medication Diary

Subjects will be asked to maintain a diary of all medications taken for the management of pain. This daily log should account for all over-the-counter medications, such as acetaminophen. The study team will provide the log to subjects at the start of study therapy (day 1) and subjects will return the log to the study team at the end of treatment. The medication taken and the number of doses taken in a day will be recorded in the eCRF.

7.4 Correlative Studies

Peripheral blood samples will be taken at the time points indicated on the Schedule of Activities. The sample collected on day one must be collected prior to patch placement. The blood will be used to assess the level of Substance P for evaluation as a treatment biomarker. Refer to the lab manual for further details of specimen processing and management.

8 ADVERSE EVENTS

8.1 Adverse Event Definitions

8.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence or clinical signs (including abnormal laboratory findings), unintended disease or injury in subjects, users, or other persons, whether or not related to the investigational medical device, and whether anticipated or unanticipated. This definition extends to the worsening of any preexisting condition or symptom.

8.1.2 Adverse Device Effect

An adverse device effect (ADE) is any adverse event that is considered to be related to the investigational medical device.

8.1.3 Unanticipated Adverse Device Effect

An unanticipated adverse device effect (UADE) is an adverse event deemed to be related to the investigational device that by its nature, incidence, severity, or outcome has not been identified in the current risk assessment.

8.1.4 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward event that is:

- Death
- Serious deterioration in the health of the subject as defined by one or more of the following:
    - a life-threatening illness or injury, or
    - permanent impairment of a body structure or a body function including chronic diseases, or
    - in-patient or prolonged hospitalization, or
    - medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,
    - fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment.
- Medically significant

Investigator judgment must be used to assess an event as medically significant. The event may not be life-threatening or cause disability but may jeopardize the subject and require intervention to prevent the other SAE outcomes.

The following situations should not be reported as an SAE:

- Hospital admission not associated with a precipitating AE such as:
    - Treatment for a preexisting condition not associated with a new AE or the worsening of a preexisting condition
    - Admission for social or administrative reasons
    - Optional admission or elective surgery
    - Observation
    - Preplanned treatments or surgical procedures as noted at baseline
    - Admission for the administration of blood products.
    - Admission as required for study participation.

8.1.5 Serious Adverse Device Effect

A serious adverse device effect (SADE) is any adverse device effect that results in any consequences characteristics of a serious adverse event.

8.1.6 Anticipated Serious Adverse Device Effect

An anticipated serious adverse device effect (ASADE) is an event that meets the definition of an SAE and by its nature incidence severity or outcome has been identified in the current risk assessment.

8.1.7 Unanticipated Serious Adverse Device Effect

An unanticipated serious adverse device effect (USADE) is an adverse device effect that meets the definition of an SAE and by its nature, incidence, severity, or outcome has not been identified in the current risk assessment.

8.1.8 Device Deficiency

A device deficiency will be defined as any inadequacy of a medical device or comparator concerning its identity, quality, durability, reliability, usability, safety, or performance. This definition includes:

- Device malfunctions as defined as a failure of the investigational device to perform according to its intended purpose when used according to the instructions for use.
- Use errors as defined as user action or lack of action while using the medical device that leads to a different result than what is intended by the manufacturer or expected by the user. This definition includes the inability of the user to complete a task, known and unknown errors, and can result from a mismatch between the characteristics of the user, user interface, task, or use environment.
- Insufficient information provided by the manufacturer.

8.2 Adverse Event Characterization

All adverse events that occur during study participation will be recorded and characterized. The following information will be required for each adverse event:

- Event severity
- The causality assessment
- Expectedness
- Event duration
- Any action taken to treat or manage the event
- Event outcome

8.2.1 Severity Assessment

The Investigator will assess each AE for its seriousness using the definitions below.

Table 1: Severity Assessment

Severity	Description
Mild	Event results in mild or transient discomfort but does not require intervention or treatment. It does not limit or interfere with daily activities.
Moderate	Event is sufficiently discomforting to limit or interfere with daily activities; may require interventional treatment (e.g., fever requiring antipyretic medication)
Severe	Event results in significant symptoms that prevent normal daily activities; may require hospitalization or invasive intervention (e.g., anemia resulting in blood transfusion).

The term “serious” is not synonymous with “severe.” Severe is used to describe the intensity of an event while serious is related to the outcome or action criteria. An AE can be classified as severe and not deemed an SAE.

8.2.2 Causality Assessment

The Investigator should assess the causality or relationship of AEs and SAEs to the investigational device. The Investigator should consider if there is evidence that the device caused the event taking into consideration timing, organ system affected, type of event, and possible alternative etiologies. The relationship of the AE to study treatment will be reported as not related, unlikely related, possibly related, probably related, and definitely related. In the final study report events categorized as possibly, probably and definitely related will be reported as related to the investigational device These categories will be defined as follows:

Table 2: Causality Assessment

Causality	Description
Definitely related	There is a reasonable causal and temporal relationship between the use of the investigational device and the AE.
Probably related	It is more likely than not that there is a reasonable causal relationship between the use of the investigational device and the AE.
Possibly related	There is a reasonable relationship between the use of the investigational device and the AE, but the causal relationship is unclear or lacking
Unlikely related	There is a temporal relationship between the use of the investigational device and the AE, but there is not a reasonable causal relationship between the investigational device and the event.
Not related	There is no relationship between the use of the investigational device and the AE.

8.2.3 Expectedness

The Investigator will be responsible for determining whether an adverse event is anticipated or unanticipated per the current risk assessment. Anticipated adverse events are those adverse events that are listed or characterized in the Instructions for Use, Investigational Plan, and/or Risk Information. Unanticipated adverse events are the reported effects that have an unknown or higher severity or are more specific than what is listed in the investigational plan and/or risk information.

8.2.4 Action Taken and Event Outcome

Start and stop dates will be required for all adverse events and serious adverse events. The action taken in response to the event should also be recorded in the subject's research chart and corresponding eCRF. If a new medication is added to treat an AE, the medication should also be added to the concomitant medications log.

All adverse events should be followed until stabilization or resolution. Event outcomes may be classified as:

Table 3: Event Outcome

Event Outcome	Description
Resolved	The event has fully recovered or returned to baseline.
Resolved with sequelae	The event has resolved but retained pathological conditions resulting from the prior disease or injury.
Resolving	The event is improved and ongoing.
Not recovered	The event is not improved and ongoing

Event Outcome	Description
Fatal	This event is determined to be the cause of death.
Unknown	Unable to determine the event status (e.g., lost to follow up)

8.3 Adverse Event Reporting

The investigator and qualified designees are responsible for the detection, documentation, reporting, and follow-up of all adverse events experienced by subjects during trial participation. All AEs must be recorded on the applicable eCRF and supporting source documentation filed in the subject's research chart. The severity of the event, the causality assessment, expectedness, event duration, action taken to treat or manage the event, and event outcome must be reported for each adverse event. AEs and SAEs will be recorded from the start of study therapy until the completion of study participation. Any unresolved device-related adverse events will be followed until stabilization or resolution.

8.3.1 SAE Reporting

All serious adverse events related (definitely, probably, or possibly) to the investigational device must be reported to the Sponsor or its designee on the study-specific Safety Event report form within 24 hours of the Investigator's first knowledge of the event. At a minimum, initial Safety Event reports must include site and subject numbers, awareness date. a description of the event, seriousness criteria, assessment of event causality, event grade, and the expectedness of the event as well as the Investigator's signature and date. Although the Investigator may not know all the information at the time of the event, the available information should be reported. An SAE follow-up may be submitted at a later date once more information is known using a new blank report form. It is required that follow-up reports be submitted until the SAE is resolved. Reports should be sent to:

Beth DuPree, MD
Beth.Bupree@signalrelief.com

Should the investigator want to discuss an adverse event with the Medical Monitor their contact information is available in the study contacts attachment.

The Sponsor will notify all investigators of the occurrence of a USADE. All SAEs and USADEs should be reported by the Investigator to their local IRB or local ethics committee according to local requirements. New safety information on the device may warrant an update to the informed consent to inform study participants.

8.3.2 Device Deficiency Reporting

Device deficiencies must be reported to the Sponsor or its designee as soon as possible but no later than 10 business days of the Investigator's first knowledge of the event. All investigational device deficiencies will be documented on the appropriate Device Deficiency eCRF. The Sponsor should be contacted to determine if it is necessary to return the device to the Sponsor for analysis.

Device deficiencies are not to be reported as AEs. However, if there is an AE that results from a device deficiency, that specific event should be recorded on the appropriate eCRF.

9 Statistical Considerations

9.1 Sample size determination

As this is a pilot study, the sample size is not statistically justified. The small sample size is sufficient to assess for early signals of safety and treatment efficacy for continued product development and future trial development.

9.2 Populations for Analysis

9.2.1 Safety Population

All subjects who begin treatment will be included in all safety descriptions and tabulations.

9.2.2 Modified Intent-to-Treat Population

Analysis of all efficacy and safety endpoints will be conducted in a modified intent to treat population. The modified intent to treat population will include all subjects who begin study therapy.

9.2.3 Per-Protocol Population

The per-protocol population will include all subjects who have used the device daily during the treatment period and have not experienced any other significant protocol deviations that could confound the study results.

9.3 Endpoint Analyses

Descriptive statistics will be the primary method of all analyses. Tabulations of adverse events and device deficiencies will be used to assess safety. The proportion of subjects with a 30% reduction in reported pain will be calculated along with the associated 95% confidence interval. Other categorical endpoints will also be described with percentages. Continuous variables will be presented as mean with the standard deviation or median.

10 ETHICAL AND REGULATORY CONSIDERATIONS

10.1 Human Subjects Protections

The study will be conducted in accordance with the protocol, 21 CFR, HIPAA regulations, the Belmont Principles, ICH Guidelines for Good Clinical Practice (GCP), and the Declaration of Helsinki. Informed consent will be obtained from all research participants or their legally authorized representative before performing any study procedures. If an investigator uses a device without subject consent, the IRB and Sponsor will be notified within 5 working days of the occurrence.

10.2 Personal Data Protection

All parties will take all necessary actions required for the protection of subject personal data. Subjects enrolled in the study will be assigned a subject number and will be reference by this number. Directly identifiable data will be omitted from reports, publications, and other disclosures. All personal data will be store at the study site in encrypted electronic and/or paper form stored in a locked and secured facility. The site will be responsible for maintaining a list of

subjects linking each subject with their subject number. Data will only be accessed by appropriate personnel and will be password protected or securely stored in a locked room. In the case of a potential breach of personally identifiable data, the site will take responsibility to ensure appropriate action is taken according to institutional practice and applicable laws and regulations.

10.3 Independent Ethics Committee Review

Before the initiation of the study, the Investigator will have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, (e.g., recruitment advertisements, questionnaires, if applicable), from the responsible Independent Ethics Committee (IEC) or Institutional Review Board (IRB). The approval letter must be obtained before beginning this study and a copy must be provided to the Sponsor. All correspondence with the IEC/IRB should be retained in the Investigator's regulatory file. Changes to the conduct of the study, the protocol, or approved documents may not be made until IEC/IRB approval has been received. However, if a change is necessary to eliminate immediate hazards to the subjects, prospective approval is not necessary.

The investigator or designee should provide the IEC/IRB with reports, updates, and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

10.4 Protocol Amendments

Any amendments or administrative changes to an IRB-approved protocol will not be initiated without submission of an amendment for IRB review and approval. However, prospective IRB approval will not be sought when an amendment is required to eliminate immediate risk to subjects on the study. In these cases, amendments will be retrospectively submitted to the IRB for review and approval.

Any amendments to the protocol that significantly affect the safety of subjects, the scope of the investigation, or the scientific quality of the study will be submitted to the FDA for review.

10.5 Investigat or Responsibilities

The Investigator is responsible for ensuring the trial is conducted in compliance with the current IRB-approved version of the protocol, GCP, the Declaration of Helsinki, and any applicable national and local laws and regulations. The Investigator will ensure that IRB and FDA approval has been granted before enrolling a subject into the study. The Investigator will confirm that all subjects enrolled in the study have provided written informed consent and that all subjects provided with the device meet the study eligibility requirements. The Investigator is also responsible for safeguarding the integrity of all data reported from subjects under the Investigator's care by ensuring that data is collected and recorded accurately and consistently.

10.6 Protocol Deviations

A deviation will be defined as any noncompliance with ICH GCP or the clinical protocol requirements. The noncompliance may be either on the part of the participant, the Investigator, or the study staff. As a result of the deviation, corrective action must be implemented to ensure future deviation does not occur. It is the Investigator's responsibility to identify and report deviations from ICH GCP or protocol requirements. These deviations and corrective action

should be documented in the subject's research chart, the associated eCRF, and reported to the responsible IRB per their policy.

11 DATA HANDLING

11.1 Recording and Collection of Data

Primary source documentation will come directly from the subject's medical record. All source documentation should be attributable, legible, contemporaneous, original, accurate, complete, and available. All documentation should be signed and dated by applicable personnel. Relevant source data will be transcribed into the electronic case report forms (eCRFs) and should be completed as soon as possible after data availability. The eCRFs will be part of a computerized database designed to comply with 21 CFR Part 11.

The Investigator has ultimate responsibility for ensuring that all data collected and recorded is accurate and consistent. He/she will need to sign off on all eCRFs to attest that all data recorded on them is true. A separate screening log of all the subjects screened for participation in the study must also be maintained and should include gender, age, eligibility status, the reason for ineligibility (if applicable), and study allocated subject number (if applicable).

11.2 Data Management

To accommodate evaluations, inspections, monitoring, and/or audits from the Sponsor or regulatory authorities, the Investigator must maintain all study records including subject identity, source documentation, original signed consent form, safety reporting forms, monitoring logs, IP accountability records, relevant correspondence (e.g., letters, emails, meeting minutes, etc.), and any other documents pertaining to the conduct of the study. The Investigator must also agree to maintain source documents for a minimum of two years per 21 CFR 812.140: after the date of study termination or completion, or the date that the records are no longer required for purposes of supporting a premarket approval application, a notice of completion of a product development protocol, a premarket notification submission, or a request for De Novo classification, whichever date is later. For the duration of record maintenance, records must be stored in a secure location and protected from the elements. If for any reason the Investigator is no longer able to retain study records, the Sponsor should be notified before the destruction of any records to arrange for the transfer of custody to an acceptable designee. Once all retention requirements have been met, the Investigator should contact the Sponsor for approval of the destruction of records.

12 PUBLICATION PLAN

In accordance with U.S. regulations and to support the highest standards of research ethics and transparency, this study will be registered on ClinicalTrials.gov before subject enrollment. US Basic Results will be reported and available on ClinicalTrials.gov within one year of the primary completion date, regardless of formal journal publication. Regardless of the study outcome, all results will be reported objectively, accurately, balanced, and completely.

13 REFERENCES

1. Zelaya C, Dahlhamer J, Lucas J, Connor E. Chronic Pain and High-impact Chronic Pain Among U.S. Adults, 2019. NCHS Data Brief, no 390. Natl Cent Heal Stat. Published online November 2020. Accessed August 27, 2021. https://www.cdc.gov/nchs/products/databriefs/db390.htm

2. SS N, ST S, AE L, J S, JR C. Associations of health-related quality of life with sociodemographic characteristics, health, pain, and lifestyle factors, and motivation for changing lifestyle in adults living with chronic pain: a cross-sectional exploratory study. Scand J pain. 2021;0(0). doi:10.1515/SJPAIN-2021-0062

3. Tsang A, Korff M Von, Lee S, et al. Common Chronic Pain Conditions in Developed and Developing Countries: Gender and Age Differences and Comorbidity With Depression-Anxiety Disorders. J Pain. 2008;9(10):883-891. doi:10.1016/J.JPAIN.2008.05.005

4. Meldrum ML. The Ongoing Opioid Prescription Epidemic: Historical Context. Am J Public Health. 2016;106(8):1365. doi:10.2105/AJPH.2016.303297

5. Dahlhamer JM, Connor EM, Bose J, Lucas JW, Zelaya CE. Prescription Opioid Use Among Adults With Chronic Pain: United States, 2019. Natl Heal Stat Reports Number. 2019;162. Accessed August 27, 2021. https://www.cdc.gov/nchs/products/index.htm.

6. Mattson CL, Tanz LJ, Quinn K, Kariisa M, Patel P, Davis NL. Trends and Geographic Patterns in Drug and Synthetic Opioid Overdose Deaths — United States, 2013–2019. MMWR Morb Mortal Wkly Rep. 2021;70(6):202-207. doi:10.15585/MMWR.MM7006A4

7. CDC's Role in the Opioid Overdose Epidemic | CDC's Response to the Opioid Overdose Epidemic | CDC. Accessed August 27, 2021. https://www.cdc.gov/opioids/overdoseprevention/cdc-role.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fdrugoverdose%2Fprevention%2Fcdc-role.html

8. About | NIH HEAL Initiative. Accessed August 27, 2021. https://heal.nih.gov/about

9. Chen J, Jin T, Zhang H. Nanotechnology in Chronic Pain Relief. Front Bioeng Biotechnol. 2020;0:682. doi:10.3389/FBIOE.2020.00682

10. How it Works. Accessed August 27, 2021. https://signalrelief.com/pages/technology

11. Mokhtari T, Ren Q, Li N, Wang F, Bi Y, Hu L. Transcutaneous Electrical Nerve Stimulation in Relieving Neuropathic Pain: Basic Mechanisms and Clinical Applications. Curr Pain Headache Reports 2020 244. 2020;24(4):1-14. doi:10.1007/S11916-020-0846-1

12. ZY C, FY S, L J, et al. Attenuation of Neuropathic Pain by Inhibiting Electrical Synapses in the Anterior Cingulate Cortex. Anesthesiology. 2016;124(1):169-183. doi:10.1097/ALN.0000000000000942