INFORMED CONSENT FORM

Sponsor / Study Title:	**Attune Neurosciences Inc. / "Evaluation of Low-Intensity Focused Ultrasound for Targeted Modulation of Pain Circuits in Chronic Pain"**
Protocol Number:	**GPA**
Principal Investigator:	**Keith Murphy, Ph.D.**
Telephone:	**(516) 302-6932 (24 Hour)**
Address:	**Attune Neurosciences** **2325 3rd St** **Suite 424** **San Francisco, CA 94107**

This is a clinical research study. Study staff will explain the study to you.

You are being invited to take part because you are between 22-80 years of age (inclusive). This Informed Consent Form contains information to help you decide if you want to participate in the study. Twenty people will take part in this study at Attune, San Francisco Clinical Research Center.

Take your time, read this form carefully, and ask the study staff any questions you may have, and/or to explain any words, terms, or sections that are unclear to you. You should not sign and date this form until you understand all the information presented in the following pages and until all of your questions about the research study have been answered to your satisfaction.

Your participation in this study is entirely voluntary and you may withdraw at any time. If you decide to participate in this study, you may then choose to stop taking part in the study at any time for any reason. You are encouraged to discuss the study with your family, friends, and primary care physician, should you have one, prior to signing and dating the consent.

The Sponsor, Attune Neurosciences, Inc., is paying for conducting this study.

An investigator on this study has an ownership interest and holds an executive position in Attune Neurosciences Inc., the company sponsoring this research study. As a result, the investigator may benefit financially from a successful study. Additional steps have been taken to manage the potential conflict of interest that this financial arrangement may create. Please speak with your investigator if you have questions about this.

About this study

ATTN201 (the study device), is currently being developed by Attune Neurosciences, Inc. as a medical device for modulating brain activity through ultrasound stimulation to disrupt pain circuits in people with chronic pain.

ATTN201 is a non-invasive headband worn during the time of the study treatment that uses ultrasound focusing guided by magnetic resonance imaging (MRI).

The study is conducted in three visits with some additional optional visits. During the first visit, we will explain the study to you, collect further information on personal and medical history, complete any baseline assessments, and perform a cranial MRI with an MRI-compatible version of the ATTN201 device.

Focused ultrasound (FUS) is a form of non-invasive brain stimulation that utilizes sound waves (the same form of energy used in fetal ultrasound imaging during pregnancy) to target and alter activity in areas of the deep brain. As FUS is highly precise, it can accomplish this task without impacting the surrounding brain tissue. ATTN201 uses ultrasound stimulation parameters that are within safety limits determined by the American Institute for Ultrasound in Medicine (AIUM) and International Transcranial Ultrasonic Stimulation Safety and Standards consortium (ITRUSST).

The ATTN201 headband features two ultrasound transducers, one on each side of the head (on top of the temporal bone, between the ear and the eye), to deliver stimulation to small regions of the deep brain such as the cingulate cortex and ventrolateral thalamus. Both the cingulate cortex and ventrolateral thalamus are proven targets for disrupting pain circuits and improving chronic pain.

In order to position the study device to focus properly on your specific brain targets, you will need to undergo brain magnetic resonance imaging (MRI) before starting the first stimulation. This only has to be completed once, and you will need to wear a mock study device during the MRI study. No contrast dye will be administered to you. The brain MRI takes about 30 minutes after which an Attune Neurosciences scientist will perform imaging analysis to compute optimal focusing paradigms tailored to your brain anatomy. The headband will be adjusted to fit your head precisely to guarantee each time you wear the study device, it is placed in the same location.

ATTN201 is a wearable study device ultimately intended for at-home use to improve chronic pain.

This study will be the fourth time ATTN201 will be used on humans. The study device has not been approved by the Food & Drug Administration (FDA) for doctors to prescribe. Its use in this study is experimental.

The purpose of this study is to ascertain whether ATTN201 stimulation can help improve your chronic pain. We are doing this study to find out:

- Does the study device reduce your chronic pain?
- Does the study device have any side-effects?

This is a “single arm, non-randomized (like the flip of coin) study,” meaning there is an unfocused (sham/dummy) stimulation that will be included in the study. This means that you will receive at least one FUS sham stimulation which will sound like the focused stimulation without any substantive brain effects.

The data collected in this study will help evaluate the efficacy of the ATTN201. Approximately 20 participants will be enrolled in this study.

The study device may produce warmth on your skin and will likely be audible. A very small portion of participants have reported feeling a tingling sensation on the skin during stimulation. The headband must be adjusted to the head to guarantee the positioning of the stimulating transducer in the temporal region of the skull. Wearing the headband has been tested as tolerable, but it may be noticeable for you.

The study is being sponsored by Attune Neurosciences, Inc. (2325 3rd Street, Suite 424, San Francisco, CA 94107).

What will I be asked to do?
If you choose to take part in this study and it is determined you are eligible and able to participate, your length of involvement will be approximately 3 weeks.

- On visit 1 we will obtain informed consent and further information on personal and medical history. You will be fitted with the study device and will be asked to take an MRI scan while wearing an MRI compatible version of the study device.
- On visits 2 and 3, you will come to our study site where a study staff member will explain the procedure and place the ATTN201 device on your head. You will be seated in a comfortable chair while stimulation is delivered. Focused or unfocused ultrasound will be delivered. We will administer various chronic pain scales before, during, and after stimulation and throughout the session. You may be asked to wear a heart rate monitor during the session. At the end of each session, we will collect additional scales related to your chronic pain. You may be asked to undergo an optional functional Magnetic Resonance Imaging (fMRI) scan to collect additional data.
- There will be optional visits if you are interested and available. This visit will be identical to visits 2 and 3.
- At intervals of 24 hours after visit completion, you will self-assess your pain using the Numerical Rating Scale for pain (NRS). We will provide printouts of the NRS scale for you to complete. This self-assessment should take less than 1 minute. The NRS should be completed each day between visits.
- After your final visit we will collect some basic information.

During your stay at the study site, refreshments will be provided for you. Please inform the study staff if you have any special dietary requirements.

What will happen during the study visits?
Please refer to the Schedule of Assessments for additional information.

Visit 1: screening visit
This visit will involve informed consent, study device fitting, and cranial MRI.
Informed consent:

- The study staff will make certain you fully understand the study, its procedures, and requirements. Please make sure you ask any questions you may have about the study before or during this visit. You will need to sign and date this consent form to confirm you are willing to

participate in this study and that you will follow all instructions provided by the study staff, as well as abide by any study restrictions (these are detailed in the 'What are my responsibilities in this study' section).

- Following your consent, you will undergo a medical examination which will include:
    - Documentation of demographics (race, gender, ethnicity).
    - Medical/surgical history and current medications.
    - Vital sign measurements (blood pressure, heart rate, and temperature).
- You will be asked about any alcohol use and history, any medications that you are taking or have taken in the past, and about any other products that you are currently using.
- If applicable, you will be asked whether you are pregnant and the date of your last menstrual cycle.
- Please make sure you tell study staff as much information as possible.
- Once you have signed and dated this informed consent, the technician will confirm that it is safe for you to undergo a study device fitting and cranial MRI.

Study device fitting and cranial MRI:

- A study staff member will fit the study device to your head. To make sure the study device does not move before the scan, a washable marker may be used to mark the position of the study device. You will lay on the machine table, and you will be positioned inside the scanner. You must lay down for approximately 30 minutes while the scan is being acquired. You will hear some sounds that may be noisy. No drugs or contrast dye will be given to you. After completing the exam, you will leave the imaging facility and come back to the study site to complete your visit.
- Any side effects will be recorded by the study site.

Visits 2, 3, and optional visits 4-8: study treatment visit

Participants who remain eligible will undergo the following:

- Prior to stimulation some pain scales will be administered to you.
- A study staff member will position ATTN201 study device on your head (the study device has millimetric adjustments for repositioning it in the same location each visit).
- You may be given a heart rate monitor to wear during the visit.
- After the study device is positioned, you will be asked to answer a series of questions. Questions will be about study device comfort and any symptoms you may be feeling.
- If you are experiencing no discomfort after this assessment, you will continue onto study device stimulation.
- The study device will be worn for up to 2 hours. You may remove the study device for any reason during any part of the study.
- Various chronic pain scales will be administered before, during and after stimulation and throughout the session. At the end of each session additional scale data will be collected related to your chronic pain.
- You may be asked to take an optional fMRI scan after the visit to collect additional study data.

Following study device stimulation, the following procedures will be performed:

- A check of how you are feeling.
- Measurement of your vital signs.
- Recording of any side effects by the study site.

After visits 2-3/4-8 (if applicable): study treatment visit

- At intervals of 24 hours after visit completion, you will self-assess your pain using the Numerical Rating Scale for pain (NRS). We will provide printouts of the NRS scale for you to complete. This self-assessment should take less than 1 minute. The NRS will be completed daily between visits.

Post final visit:

- Following the last visit, additional clinical wellness measures may be taken.

Table 1: Schedule of Assessments

Visit Number	0	**1**	**2**	**3**	**4 - 8 (Optional)**	**3/4(b)**
Visit Title	**Screening**	**Consent + Cranial MRI**	**Stim or Sham-Visit 2**	**Stim or Sham-Visit 3**	**Stim or Sham-Visits 4-8**	**Post - Final Stim/Early Discontinuation**
Administrative Procedures						
Informed Consent – Participant		X				
Inclusion/Exclusion Criteria	X					
Alcohol, Use/History		X				
Medical History		X				
Prior Medication Review		X				
Self-reported Pregnancy Assessment		X				X
Clinical Procedures/Assessments						
NRS Pain Scale[1]	X		X	X	X	
Body Height/Weight Measurement		X				
Study Device Fitting		X				
Cranial MRI		X				
Visual Analog Scale (VAS) Pain Scale[2]			X	X	X	
Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Intensity, PROMIS Depression, and PROMIS Anxiety Scale[3]			X	X	X	

Focused Ultrasound Stimulation (FUS) or Unfocused (Sham) Stimulations			X	X	X	
Behavioral Notes			X	X	X	
Vital Signs		X	X	X	X	
Adverse Event (Side Effect) Review		X	X	X	X	
Optional fMRI		X	X	X	X	

[1] For visits 2, 3, and optional visits 4-8, the NRS scale will be administered pre- stimulation and at intervals of 24 hours after visit completion. The NRS will be completed on days 1, 3, 5, and 7 days post-study treatment at minimum.
[2] For visits 2, 3, and optional visits 4-8, the VAS pain scale will be administered pre- stimulation, after each stimulation/sham target, and at the end of the session.
[3] For visits 2, 3, and optional visits 4-8, the PROMIS pain intensity, PROMIS depression, and PROMIS anxiety scale will be administered pre-stimulation.

What are my responsibilities in this study?
The following things are important during your participation in this study:

- Please inform study staff of any herbal supplements, dietary supplements, over the counter or prescription medication you have taken in the month prior to your visit, as these will need to be recorded.
- You must be willing to refrain from consuming alcohol 12 hours prior to each study and refrain from heavy use of alcohol for the duration of the study, particularly as a form of self-medication for pain symptoms.
- You must not have received an investigational study drug in another clinical study within 30 days prior to stimulation.
- You must report any changes in the way you are feeling to study staff at any point throughout the study.

What effects could the tests have on me?
Brain MRI/fMRI: MRI is a common diagnostic test that has been demonstrated to be very safe. The two most common complaints are being in an enclosed tube during imaging and the noise the machine produces. The only risks relate to the presence of metal in the body such as surgical artery clips or pacemakers. Please tell study staff if you are claustrophobic (afraid of being in small, enclosed spaces) during your screening visit. If the noise is disturbing to you, you may wear ear plugs during imaging (the MRI technician will offer these to you).

Electroencephalogram (EEG): There is a possibility of minor irritation or rash of the skin as a result of the gel or patches that may be placed on your skin as part of an inactive EEG system not used in this study.

If you are having suicidal thoughts, call or text the National Suicide & Crisis Lifeline at 9-8-8 or 1-800-273-TALK (8255). The Lifeline numbers are answered 24 hours a day every day of the year by a skilled, trained counselor. You can also present to a healthcare provider, your local emergency room, or call 9-1-1 to be connected to local emergency services.

What are the possible risks of the study device?

The ATTN201 study device is a headband that houses electronics and delivers ultrasound. The possible risks of these three components are explained below.

Headband: The headband is made of comfortable parts, but it must be fitted securely on your head. We have calculated that the pressure is comfortable, but you may feel some pressure that may bother you. If this is the case, let the study staff know and they will explore the best way to make it comfortable for you.
Electronics: The headband is connected to an external unit from which it receives electrical power and instructions for delivering ultrasound. The electronic components are isolated and will not create any damage.

Ultrasound transducer*:* The two discs placed on the sides of the headband deliver ultrasound stimulation to the brain. Ultrasound has been used as a diagnostic tool for decades, including its application to the brain through the skull. The transducer should not produce any excess heat or noise. The ultrasound is going to be delivered to very specific regions of the deep brain involved in chronic pain. Because these same regions are involved in other sensory activities, you may experience some transient (short-lasting) sensations on your face, arms, or legs, such as numbness or tingling. If this occurs, please make study staff aware immediately. They will record symptoms, check the placement of the headband, and stop the stimulation if required. Such sensations are transient and will disappear as soon as the stimulation finishes.

Mild to moderate side effects, including neck pain, difficulty paying attention, muscle twitches, and anxiety have been reported with similar devices.

Since the study device is investigational, there may be other risks that are unknown.

Are there pregnancy risks?
Ultrasound imaging is commonly used during pregnancy and considered very safe. However, the effects of the study device on human pregnancy and the unborn child (fetus) are unknown. Because of this, it is important that you are not pregnant or breastfeeding and do not become pregnant during the course of the study.

You must not participate in the research if you are pregnant, trying to become pregnant, or breastfeeding and should avoid becoming pregnant for a period of 30 days after you complete this study. If you are female and childbearing is a possibility, you will be required to disclose if you are pregnant and as a result may be disqualified from participation.

For female participants
You may be eligible for this study if any of the following apply:

- You are surgically sterile (have had a hysterectomy [uterus removed], bilateral oophorectomy [ovaries removed], or tubal ligation [tubes tied] at least 6 months prior).
- You are of post-menopausal age and have not had a menstrual period for 12 months.
- You have a vasectomized partner (performed at least 6 months prior) who has been documented to no longer produce sperm.
- You are using a highly effective method of contraception to avoid pregnancy throughout the study and for 30 days after you complete this study.

Examples of acceptable forms of highly effective contraception include:

- Established use of oral, injected or implanted hormonal methods of contraception plus use of a condom for your male partner.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS) plus use of a condom for your male partner.
- True abstinence when this is in line with your preferred and usual lifestyle.

NOTE: Periodic abstinence (for example, calendar, ovulation, symptothermal, post ovulation methods), condoms alone, or double barrier are not acceptable methods of contraception.

For male participants
Male participants must ensure a condom is used for all sexual intercourse and follow the acceptable methods of contraception listed above for their female partner. You must ensure that they are used for the entire duration of the study, and for at least 90 days after you complete this study.

It is highly recommended that you inform your partner of your participation in the study and the need to avoid pregnancy.
Study staff will advise on medical attention for your partner should this be necessary.

Study staff will discuss effective methods of avoiding pregnancy with you.

If you are unsure if your method of contraception is adequate, please speak to study staff.
If your partner does become pregnant while participating in the study, or within 90 days after the completion of this study, you should advise study staff immediately.

You will be told in a timely manner about significant new information that might affect your decision to stay in the study.

Additional information you need to know
It is important that you tell your study staff if you feel that you have been injured as a result of taking part in this study. You can tell study staff in person or call the telephone number listed on the first page of the consent form.

Treatment and compensation for injury
If you have a serious side effect or other problem during this study, you should immediately contact study staff at the phone number listed on the first page of this form.

The sponsor of this study will pay for medical treatment at no cost if you have an injury or illness as a direct result of being in this study. The sponsor and the investigator will decide if your injury or illness is research related. “Research-related” means an injury directly caused by devices or procedures you would not have received if you didn’t join the study. The treatment may include first aid, emergency care and follow-up care, as needed. Payments will not be offered for other expenses (such as time off work, lost wages, childcare, etc.) You do not give up any legal rights by signing this form.

For the sponsor to pay these medical expenses, they will need to know some information about you like your name, date of birth, and your Medicare Beneficiary Identifier (MBI). This is because the sponsor has to check if you receive Medicare, and, if you do, report the payment it makes to Medicare. The sponsor will not use this information for any other purpose.

What benefits could there be from taking part in the study?
This study is for research purposes only. There is no direct benefit to you from your participation in the study. Information learned from the study may help other people in the future.

Compensation for participation
You will receive $50 for Visit 1, $50 for Visit 2, $50 for Visit 3, and $50 for any additional days that visits are required. This money should be used towards parking and/or gas if needed. You will be paid upon completion of the study.

If you do not complete the study, for any reason, you will be paid for each study visit you do complete.

You will not be paid for the video or phone screening call prior to informed consent. Study payments are taxable income. Please ensure you file appropriately with the Internal Revenue Service.

If you have any questions regarding your compensation for participation, please contact the study staff. You should also be aware that your study payment may be reduced or forfeited if you fail to follow any of the restrictions specified in this informed consent form. You will receive full payment if you are withdrawn from the study because of medical reasons or a medical event related to the study.

Are there alternatives to participation?
Since this study is intended only to test the effect of the study device in participants, your alternative to being a participant in this study is to choose not to participate in the study.

Are there any costs to me for taking part in this study?
The study will cover all study-related items and services provided during this study. These services include the study device, study visits, and study related tests and procedures such as the physical exams, and laboratory tests as listed in this consent form.

The study device will be supplied by the study sponsor, Attune Neurosciences, at no cost to you while you take part in this study.

Voluntary participation / withdrawal from the study
Your participation in this study is purely voluntary. You may refuse to take part or withdraw from this study at any time without penalty or loss of benefits to which you are otherwise entitled. However, please note that the FDA requires that any information collected up to the point of your withdrawal cannot be removed from the study.

You may be withdrawn from the study if study staff feels it is best for you or if you do not comply with the requirements of the study. The Sponsor can also stop this study at any time for clinical or administrative reasons without regard to the participant consent. If you wish to withdraw from the study while at the study site, please discuss this with the study staff who will assist you in this matter and ensure you are safe to leave.

Before you leave the study, the study staff will want to examine you, measure your heart rate, blood pressure, and temperature to check your general health. Any significant new findings developed during the course of the research, which may affect your willingness to continue participation in this study, will be provided to you in a timely manner.

Termination of the study
The study may be stopped for a variety of reasons. These may include the following: unacceptable side effects, the study device being shown not to be effective, the study device being shown to work and not need further investigation, and decisions made in the commercial or other business interest of the sponsor.

Will my medical information be kept confidential?
Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total privacy. Some information from your medical records will be collected and used for this study. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Authorized representatives from the following organizations may review your research data for the purpose of monitoring or managing the conduct of this study:

- Representatives of the Sponsor, Attune Neurosciences, Inc.
- Representatives of the Food and Drug Administration (FDA).
- Representatives of the Advarra Institutional Review Board (IRB).

While Attune complies with all applicable regulations of the Health Insurance Portability and Accountability Act (HIPAA) and every effort will be made to protect the confidentiality of your information, absolute confidentiality cannot be guaranteed.

You may not be able to see your records relating to the study until after the study is over and the results are known.

To cancel your permission, please contact the investigator at the information listed on the first page of this form. If you cancel your permission, you will be withdrawn from the study. The researchers will stop collecting any additional information about you unless they need information about a side effect of the study device, ATTN201. They are permitted to use and share information that was gathered before they received your cancellation.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Whom to contact about this study
During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study such as:

- Whom to contact in the case of a research-related injury or illness.
- Payment or compensation for being in the study, if any.
- Your responsibilities as a research participant.
- Eligibility to participate in the study.
- The investigator's or study site's decision to withdraw you from participation.
- Results of tests and/or procedures.

Please contact the investigator at the telephone number listed on the first page of this consent document.

If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, contact:

- By **mail**:
  Study Subject Adviser
  Advarra IRB
  6100 Merriweather Dr., Suite 600
  Columbia, MD 21044
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00081547.

STATEMENT OF CONSENT

- I have read and understood this Informed Consent Form.
- I am aged between 22-80 years of age (inclusive) and have been given enough time to consider my participation and asked for advice if necessary.
- I have had the opportunity to ask questions and have received satisfactory answers.
- I understand that all the information will be kept confidential and that the result will be used for scientific objectives.
- I authorize my research and medical records as they pertain to this study to be reviewed by the sponsor, authorized representatives and other regulatory agencies as described in this consent form.
- I understand that my participation in this study is voluntary and that I am completely free to withdraw my consent or refuse to participate at any time without changing in any way the quality of care that I receive. If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.
- I understand that if I agree to leave the study for any reason, study staff may ask me to do some end-of-study tests.
- The nature and purpose of the research study and potential risks and discomforts associated with it have been explained to me. I understand them and agree to take part.
- I consent to my primary care physician and /or treating specialist, should I have one, being notified of my participation in this study and of any clinically relevant information noted by study staff in the conduct of the study, and to be contacted to obtain information regarding my medical history.
- I confirm that I will provide, to the best of my knowledge, a full and accurate medical and surgical history and details of any current medical conditions and medicines I am taking.
- I agree to additional tests being conducted during the study, as requested by a study staff if study staff has any concerns in relation to my health while on the study.
- As a participant, I freely consent to participate in this study.

You have been given a copy of this consent form to keep.

_____
Participant's Printed Name

_____ _____
Participant's Signature Date

STATEMENT OF PERSON EXPLAINING AUTHORIZATION

I have carefully explained to the participant the nature and purpose of this form. I have been available to answer any questions the participant has about this form.

_____
Signature of Person Obtaining Consent

_____ _____
Printed Name of Person Obtaining Consent Date

Participant must sign and date the consent form first, prior to study staff. Note: All parties signing the Consent Form must date their own signature.