

Sponsor-Investigator:	J. Lawrence Marsh, M.D.
NCT Number:	NCT04589611
Unique Protocol ID:	201911366
Official Title:	Translating Metabolic Responses to Mechanical Insult Into Early Interventions to Prevent PTOA
Date of Document:	17/AUG/2022

PHASE 1
INFORMED CONSENT DOCUMENT

Project Title: A Single Dose Level Study to Assess the Safety and Tolerability, of Intra-Articular Injection of Amobarbital in a Formulation Containing Cross-linked Hyaluronate in Patients with Intra-articular Distal Tibial Fractures

Principal Investigator: J. Lawrence Marsh, MD

Research Team Contact: Darby Donovan
319-384-9643 or 319-356-1616 ask to page DDONVAN

This consent form describes the research study to help you decide if you want to participate. This form provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights as a research subject.

- If you have any questions about or do not understand something in this form, you should ask the research team for more information.
- You should discuss your participation with anyone you choose such as family or friends.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We are inviting you to participate in this research study because you have broken your ankle and will require one or two operations to repair your ankle.

The purpose of this research study is to study an investigational combination therapy to determine the safety and tolerability and how effective this combination is in preventing osteoarthritis from forming in your ankle. This combination is considered investigational, which means that it has not been approved by the United States Food and Drug Administration (FDA). The drug amobarbital will be combined with a type of hydrogel solution called Gel-One, and these two medicines will be injected into a joint.

Amobarbital is normally used for sedation, insomnia, preanesthetic medication or to prevent seizures. It is not normally given as a joint injection or as a treatment for arthritis. But studies in animals indicate that it may be beneficial to help prevent post-traumatic osteoarthritis, which you are at risk for because of your ankle fracture. Amobarbital has not been previously studied for this purpose in humans. We do not know how much Amobarbital will remain in the joint versus spreading through the body, nor do we know how severe its side effects will be.

Gel-One has been used for many years to treat arthritis in the knee of humans and is approved by the FDA for this purpose. There is some evidence that it is beneficial for post-traumatic ankle arthritis, but further research has been recommended.

This research study is studying the combination of amobarbital with Gel-One. Phase 1 of this study is studying the safety of this combination.

HOW MANY PEOPLE WILL PARTICIPATE?

There are three phases to this study, and you are being consented for the Phase 1 of the study.

Approximately 30 people will take part in either Phase 1, Phase 2 (single stage) or Phase 2 (two stage) of this study conducted by investigators at the University of Iowa. The study will enroll a total of approximately 70 people between Indiana University and the University of Iowa.

Approximately 6 out of the 30 subjects enrolled at the University of Iowa will participate in Phase 1 of this study.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, your involvement will last for approximately 24 months. You will have about 5 study visits while you are in the hospital and then you will have 4 study visits at the University of Iowa Hospitals and Clinics after you are discharged. Those follow up visits will last approximately 2 hours.

WHAT WILL HAPPEN DURING THIS STUDY?

Day of Injury: If you consent to be in this study, the study team will collect information about your age, the type of ankle break you have, any ankle arthritis you already have, and any other injuries that you have had. The study team will also collect a copy of any standard of care (SOC) CT scan(s) or any x-ray(s) that you had when your ankle was evaluated for this injury.

The external and internal fixation of your ankle will be done as Standard of Care (SOC). The research study will have additional procedures that are outlined below.

You will have the amobarbital/Gel-One combination injected into your ankle joint during the Internal Fixation surgery to repair your ankle break.

External Fixation: If done, this will be done as SOC.

Internal Fixation: Done as SOC but this is when the research procedures will take place.

Baseline: Prior to your surgery, you will have a blood sample taken. This blood sample will be collected to evaluate your liver, kidney, and white/red blood cell health prior to your surgery for the research study.

Post Internal Fixation: You will have the research blood tests you had taken prior to surgery repeated (at 30 min, 1, 2, 4 and 8 hour). You will also have a urine sample for the research study collected (at 30 min, 1, 2, 4 and 8 hour).

Day 1: You will have the research blood and urine tests you had taken after your surgery repeated, if still hospitalized.

Day 2: You will have the research blood and urine tests you had taken after your surgery repeated, if

still hospitalized.

Day 7: You will have the research blood and urine tests you had taken after your surgery repeated, if still hospitalized.

3 Month Follow-Up Visit: You will have three different x-ray images taken of your ankle as standard of care (x-rays are SOC). A physical examination and 2 questionnaires will also be done at this visit for research, except the x-rays.

6 Month Follow-Up Visit: You will have a CT scan and three different x-ray images (x-rays are SOC) taken of your ankle. A physical examination and 5 questionnaires will also be done at this visit. All of these procedures are for research, except the x-rays.

12 Month Follow-Up Visit: You will have a CT scan and three different x-ray images (x-rays are SOC) taken of your ankle. A physical examination and 5 questionnaires will also be done at this visit. All of these procedures are for research, except the x-rays.

24 Month Follow-Up Visit: You will have a CT scan and three different x-ray images taken of your ankle. A physical examination and 5 questionnaires will also be done at this visit. All of these procedures are for research.

Data and Image Storage for Future Use

As part of this study, we are obtaining data and images from you. We would like to study your data and images in the future, after this study is over.

The research and tests we might want to use to study your data and images may not even exist at this time. Therefore, we are asking for your permission to store your data and images so that we can study them in the future. These future studies may provide additional information that will be helpful in understanding osteoarthritis and other diseases, but it is unlikely that what we learn from these studies will have a direct benefit to you. It is possible that your data and images might be used to develop products or tests that could be patented and licensed. In some instances, these may have potential commercial value and may be developed by the Investigators, University of Iowa, commercial companies, organizations funding this research, or others that may not be working directly with this research team. However, donors of data and images do not retain any property rights to the materials. Therefore, there are no plans to provide financial compensation to you should this occur.

This research will not include whole genome sequencing as part of this research.

Your data and images will be stored *with a code which may be linked to* your name, date of birth and medical record number. If you agree now to future use of your data and images but decide in the future that you would like to have it removed from future research, you should contact:

J. Lawrence Marsh, MD
University of Iowa
200 Hawkins Drive
Iowa City, Iowa 52242

However, if some research with your data and images has already been completed, the information from that research may still be used.

Please place your initials in the blank next to Yes or No for each of the questions below:

You do not have to agree to data and images future research to participate in this study.

My data and images may be stored/shared for future research in osteoarthritis.

_____ Yes _____ No

My data and images may be stored/shared for future research for other health problems (such as cancer, heart disease, etc.).

_____ Yes _____ No

WILL I BE NOTIFIED IF MY DATA, IMAGES, AND SAMPLES RESULT(S) IN AN UNEXPECTED FINDING?

The blood/urine tests and the research only CT and x-rays will be reviewed by a physician who normally reads such results and they will inform us if there are any unexpected findings. We will provide you with this information so that you may discuss it with your primary care physician. However, if you believe you are having symptoms that may require care prior to receiving any information from this study, you should contact your primary care physician. The study team/study will not cover the costs of any follow-up consultations or actions.

Possible Future Research:

In the future we may have other studies we would like to contact you about that you may qualify for. We would like to keep your contact information including your phone number and address in order to contact you about these studies. We would also like to keep your CT and x-ray images so that we can see if you would qualify for these studies prior to calling you. By agreeing to be in the current study you are not agreeing to be in these future studies, and it would require you to sign a separate consent document in order to participate in these studies. Saying no to being contacted in the future for other studies does not exclude you from participating in this study.

Do you agree for your CT and x-ray imaging results to be stored for future studies you may qualify for?

Please initial _____ Yes _____ No

Do you agree to be contacted for future studies you may qualify for?

Please initial _____ **Yes** _____ **No**

WHAT ARE THE RISKS OF THIS STUDY?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

Risk of receiving study the injection of amobarbital/Gel-One combination: Amobarbital and Gel-One are commonly used but this combination has not been used in this manner. Amobarbital is normally used for sedation, insomnia, preanesthetic or anticonvulsant. It is not approved to be used in combination with Gel-One or in the manner that the study team is using it in this study. The amount of amobarbital used in this study is smaller than when it is used as a standard of care (SOC) medication and it is injected into your joint. This is different than how it is administered as standard of care (SOC), which is in pill, injection in a muscle or through an IV.

You may have side effects from this investigational treatment that are unknown at this time.

Patients, who receive Amobarbital as a standard of care (SOC) medication orally, by injection in their muscle or by IV, report these side effects: excessive and persistent drowsiness, insomnia, anxiety, depression, headache, and diminished concentration. There is also a risk of bradycardia (slower heart rate), hypotension (low blood pressure) and respiratory depression (slow and ineffective breathing).

System toxicity: changes in the blood and urine levels of amobarbital that may affect liver, renal and central nervous system function.

Risks from Gel-One: joint swelling, fluid building up around your ankle joint, or ankle joint pain.

Injection Risk: injection site pain or an infection in your ankle joint.

Allergic reactions – all drugs have a potential risk of an allergic reaction, which if not treated promptly, could become life-threatening. Signs of an allergic reaction could include the following: itchy red spots on the skin, nasal congestion, rash, scratchy throat, watery or itchy eyes, pain or tightness in the chest, difficulty swallowing or breathing, dizziness.

Blood samples – You may have discomfort or pain when your blood is collected, or you may feel faint or pass out. There is also a slight possibility of infection, bruising, or bleeding at the puncture site.

Radiation Risk: The maximum amount of radiation from the research-related radiation procedures in this study is about equal to the average environmental radiation everyone experiences in 7 days. Although there are no proven harmful effects from this amount of radiation, long term effects on your health such as cancer cannot be ruled out with certainty. This dose estimate takes into account only the exposure to research procedures in this project. If you have participated in other research studies involving radiation exposure, you should be aware that the risk of effects from radiation is believed to increase with each exposure you receive (including studies performed as part of your medical care)

Radiation Exposure in Women Capable of Becoming Pregnant: You may not participate in this study if you are pregnant. If you are capable of becoming pregnant, we will perform a pregnancy test before each exposure to research-related radiation. You must tell us if you may have become pregnant within the previous 14 days because the pregnancy test is unreliable during that time.

Risk of questionnaires: You may be asked questions you find uncomfortable.

Loss of confidentiality: As this study involves the use of your identifiable, personal information, there is a slight chance that a loss of confidentiality will occur. The researchers have procedures in place to lessen the possibility of this happening (see “WHAT ABOUT CONFIDENTIALITY?” section below).

There are no known financial, legal or social risks to you.

WHAT ARE THE BENEFITS OF THIS STUDY?

We don't know if you will benefit from being in this study.

However, we hope that, in the future, information learned from this study may benefit other people with this injury in the future.

WHAT OTHER TREATMENT OPTIONS ARE THERE?

Before you decide whether or not to be in this study, your doctor will discuss the other options that may be available to you. You do not have to be in this study to have surgery to repair your ankle.

*****Specify what tests and procedures are covered by the study***|WILL IT COST ME ANYTHING TO BE IN THIS STUDY?**

You will not have any additional costs for being in this research study. The study will cover the costs of the following tests and procedures performed for research only:

- The study medications used for the study
- The blood and urine tests done for this study
- The x-rays and CT scan that is done at your 24 month visit

You and/or your medical/hospital insurance carrier will remain responsible for your regular medical care expenses.

WILL I BE PAID FOR PARTICIPATING?

You will be paid for being in this research study. You will receive \$75.00 when you complete the study (Month 24 visit).

WHO IS FUNDING THIS STUDY?

The Department of Defense is funding this research study. This means that the University of Iowa is receiving payments from Department of Defense to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary from the Department of Defense for conducting this study.

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?

- If you are injured or become ill from taking part in this study, medical treatment is available at the University of Iowa Hospitals and Clinics.
- The University of Iowa does not plan to provide free medical care or payment for treatment of any illness or injury resulting from this study unless it is the direct result of proven negligence by a University employee.
- If you experience a research-related illness or injury, you and/or your medical or hospital insurance carrier will be responsible for the cost of treatment.

WHAT ABOUT CONFIDENTIALITY?

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- federal government regulatory agencies,
- the U.S. Food and Drug Administration (FDA)
- The Department of Defense may also inspect any part of your medical record for the purposes of auditing the conduct of the study.
- auditing departments of the University of Iowa, and
- the University of Iowa Institutional Review Board (a committee that reviews and approves research studies)

To help protect your confidentiality, we will store all the data we gather from you in locked files and in a secure database that can only be accessed by the study team. You will be assigned a unique study identification (ID) number and all of your data and images collected from you will be stored under this unique study ID. All electronic files are stored on password protected computers that are connected to a secured shared drive. All members of the team have an individual log-on and secure password.

Your blood and urine samples and images that are processed or evaluated at the University of Iowa Hospitals and Clinics will have your name and medical record number on them so that they may be processed, and the results will be stored in your medical record. If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

The University of Iowa Hospitals and Clinics generally requires that we document your participation in research occurring in a University of Iowa Health Care facility. This documentation will be in either your medical record or a database maintained on behalf of the institution reflecting that you are

participating in this study. The information included will provide contact information for the research team as well as information about the risks associated with this study. We will keep this Informed Consent Document in our research files; it will not be placed in your medical record chart.

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

WILL MY HEALTH INFORMATION BE USED DURING THIS STUDY?

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires your health care provider to obtain your permission for the research team to access or create “protected health information” about you for purposes of this research study. Protected health information is information that personally identifies you and relates to your past, present, or future physical or mental health condition or care. We will access or create health information about you, as described in this document, for purposes of this research study and for your treatment. Once your health care provider has disclosed your protected health information to us, it may no longer be protected by the Federal HIPAA privacy regulations, but we will continue to protect your confidentiality as described under “Confidentiality.”

We may share your health information related to this study with other parties including federal government regulatory agencies, the University of Iowa Institutional Review Boards and support staff, and the Department of Defense.

You cannot participate in this study unless you permit us to use your protected health information. If you choose *not* to allow us to use your protected health information, we will discuss any non-research alternatives available to you. Your decision will not affect your right to medical care that is not research-related. Your signature on this Consent Document authorizes your health care provider to give us permission to use or create health information about you.

Although you may not be allowed to see study information until after this study is over, you may be given access to your health care records by contacting your health care provider. Your permission for us to access or create protected health information about you for purposes of this study has no expiration date. You may withdraw your permission for us to use your health information for this research study by sending a written notice to:

J. Lawrence Marsh, M.D.
200 Hawkins Drive
Iowa City, Iowa 52242

However, we may still use your health information that was collected before withdrawing your permission. Also, if we have sent your health information to a third party, such as the study sponsor, or we have removed your identifying information, it may not be possible to prevent its future use. You will receive a copy of this signed document

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If

you decide to be in this study, you may stop participating at any time. If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

What if I Decide to Drop Out of the Study?

If you leave this study, you will still receive your normal medical care.

If you decide to leave the study early, you will be asked to make one final visit so that you can complete the testing planned for the final visit.

Will I Receive New Information About the Study while Participating?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

Can Someone Else End my Participation in this Study?

Under certain circumstances, the researchers might decide to end your participation in this research study earlier than planned. This might happen because, in our judgment, it would not be safe for you to continue, because your condition has become worse, or because you are or become pregnant.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact:

J. Lawrence Marsh, MD
319-356-0430 or 319-356-1616 pager # 7417

If you experience a research-related injury, please contact:

J. Lawrence Marsh, MD
319-356-0430 or 319-356-1616 pager # 7417

If you have questions, concerns, or complaints about your rights as a research subject or about research related injury, please contact the Human Subjects Office, 105 Hardin Library for the Health Sciences, 600 Newton Rd, The University of Iowa, Iowa City, IA 52242-1098, (319) 335-6564, or e-mail irb@uiowa.edu. General information about being a research subject can be found by clicking "Info for Public" on the Human Subjects Office web site, <http://hso.research.uiowa.edu/>. To offer input about your experiences as a research subject or to speak to someone other than the research staff, call the Human Subjects Office at the number above.

This Informed Consent Document is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by signing this Informed Consent Document. Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a copy of this form.

Subject's Name (printed): _____

(Signature of Subject)	(Date)
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Legally Authorized Representative's Name and Relationship to Subject:

(Name - printed) (Relationship to Subject - printed)

(Signature of Parent/Guardian or Legally Authorized Representative)	(Date)
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Legally Authorized Representative:

In studies conducted in the state of Iowa, the first person on the list below who is reasonably available and competent must sign as the legally authorized representative even if another person on the list is more conveniently available.

1. The designated proxy (such as a Durable Power of Attorney for Health Care)
2. Court-appointed guardian
3. Spouse (does not include "Common-law" spouse)
4. Adult child
5. Parent
6. Adult sibling

Statement of Person Who Obtained Consent

I have discussed the above points with the subject or, where appropriate, with the subject's legally authorized representative. It is my opinion that the subject understands the risks, benefits, and procedures involved with participation in this research study.

(Signature of Person who Obtained Consent)

(Date)