Thomas Jefferson University
Informed Consent Document for Human Subjects Research

Department: Neurology / Jefferson Headache Center

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Medical Study Title: A Double-Blind, Placebo-Controlled Pilot Study to Collect and Evaluate Data on the Use of Intravenous Ibuprofen in the Treatment of an Acute Migraine Attack (Protocol Number: SDS/IVIb/01)

Lay Study Title: A Research Study to Evaluate the Safety and Effectiveness of Intravenous (IV) Ibuprofen for the Treatment of One Migraine Headache.

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What Is Informed Consent?

You are being asked to take part in a medical research study. As required by federal regulations, this research study has been reviewed and approved by an Institutional Review Board (IRB), a University committee that reviews, approves and monitors research involving humans. Before you can make a knowledgeable decision about whether to participate, you should understand the possible risks and benefits related to this study. This process of learning and thinking about a study before you make a decision is known as *informed consent* and includes:

- Receiving detailed information about this research study;
- Being asked to read, sign and date this consent form, once you understand the study and have decided to participate. If you don't understand something about the study or if you have questions, you should ask for an explanation before signing this form;
- Being given a copy of the signed and dated consent form to keep for your own records.

You should understand that your relationship with the study doctor is different than your relationship with your treating or personal doctor. The treating doctor treats a specific health problem with the goal of improving a medical condition. A study doctor treats all subjects according to a research plan to obtain information about the experimental drug, device or procedure being studied and with the understanding that you may or may not benefit from being in the study. You should ask questions of the study doctor if you want to know more about this.

The type of study you are being asked to join is known as a pilot study. A pilot study is a preliminary study involving a small number of subjects. Information from this small study may be used to help design future larger studies.

What is the purpose of this study?

Patients that present to an ambulatory acute care setting or emergency room with a severe migraine have a limited number of effective treatment options. Because patients with migraine often have nausea, vomiting or digestive disturbances, oral medications are often not effective. The purpose of this study is to evaluate the effectiveness of ibuprofen, given intravenously (through a vein in the arm or hand), for the treatment of a moderate or severe migraine headache.

Ibuprofen is the active ingredient in over the counter oral medications, such as Motrin and Advil. It is also available in oral form in a stronger, prescription strength. The intravenous form of ibuprofen has been approved by the FDA for the treatment of pain and for the treatment of fever. This study will specifically look at IV ibuprofen for the treatment of migraine pain.

How many individuals will participate in the study and how long will the study last?

This study will only take place at the Jefferson Headache Center. We plan to screen approximately 150 patients at Jefferson. Your involvement in the study will last about 6 months. The entire study will take about 12 months to complete.

What will I have to do during the study?

This study consists of 3 visits to the Jefferson Headache Center:

- Screening Visit (Visit #1)
- Treatment Visit (Visit #2)
- Final Visit (Visit #3)

It is possible that Visit #1 and Visit #2 will be combined and may occur as a single visit.

During the first visit (screening visit) you will be asked to read this informed consent form. You have the option to take this consent form home for review and discussion with other physicians and/or family members. You will be asked to sign and date this informed consent form, provided that all of your questions have been answered to your satisfaction and you agree to participate. In addition, the following procedures will be performed during your screening visit:

Screening: Visit 1

- Medical history
- Headache History
- Urine pregnancy test for women of childbearing potential
- Physical and neurological examination performed by study physician
- Blood pressure and pulse measurements
- Height and weight measurements
- Collection of blood for chemistry (salts and labs for kidney function), hematology (white blood cells, red blood cells and platelets) - (approximately 3 teaspoons of blood will be withdrawn.)
- Detailed medication history

It is important that you inform the study physician and study coordinator of all medications that you take, including over-the-counter vitamins and herbs, so that we can determine if you are eligible to participate in the study and to minimize the risk of a drug interaction with the study

drug. Additionally, if, during the course of your study participation, you start a new medication, it is important for you to inform the research staff of the change.

Treatment Visit: (visit may occur on same day as screening visit, but must occur within 6 months from screening visit)

If you qualify to continue in the treatment phase of the study, you will be asked to call the Jefferson Headache Center when you think that you have a headache that qualifies for study treatment: moderate or severe headache pain intensity, within 6 hours of the onset of headache pain, and you have not taken an analgesic (pain) medication, within 24 hours. The study coordinator will review your headache history with you by phone and determine if you should come to the headache center for treatment with study drug.

If you qualify to come into the headache center for treatment of your headache, we update your health and medication history, take your pulse and blood pressure before treatment, perform a urine pregnancy test if you are a woman of childbearing potential, and teach you how to complete your paper headache diary. You will then be randomized (assigned by chance, like the flip of a coin) to either ibuprofen or placebo (placebo is saline - salt water without active drug). You have a 50% chance of receiving either ibuprofen or placebo.

Since this is a double-blind study, neither you nor the research staff will know if you are on placebo or study drug. However, in the event of an emergency, the medication code can be broken to identify what medication you have taken.

Both the ibuprofen and placebo will be administered to you intravenously (IV) through a vein in your hand or arm. A small needle will be inserted into a vein in your hand or arm. The needle will be attached to a long, narrow tube, which, in turn, attaches to a plastic container. Either placebo or active medication will be slowly infused (flow from the container, through the tube, and into your vein.)

Your pulse and blood pressure will be checked every 30 minutes, after the administration of study medication, until you are discharged to home. You also will be asked to complete your diary, which assess the intensity of your headache pain, the presence of associated migraine symptoms, and your ability to function at the time points listed below.

If you still have a moderate to severe headache at 2 hours after the study drug dose (either ibuprofen or placebo), you can receive a dose of active drug as a rescue. (Everyone can receive ibuprofen; no one will receive placebo as rescue). If you receive IV ibuprofen rescue medication, you will remain at the Jefferson Headache Center for additional monitoring (pulse, blood pressure) every 30 minutes for an additional 2 hours and assessment of your headache symptoms.

Summary of steps for treatment visit:

- If eligible headache occurs after the screening visit has been completed, call the Jefferson Headache Center at the onset of qualifying migraine attack. Study coordinator will determine whether you can treat this attack.
- Blood pressure and pulse measurements pre-dose

- Urine pregnancy test for women of childbearing potential
- Inform study staff of any changes in concomitant medications and/or medical conditions since screening visit
- Review of headache diary
- Migraine pain and associated symptoms assessments at pre-dose, 15 minutes, 30 minutes, 1 hour, 1 ½ hours, 2 hours. The 4 hours, 8 hours and 24 hours post-dosing assessments will be performed at home. (*However, if you received rescue IV ibuprofen at 2 hours after study drug, you will still be at the Jefferson Headache Center at the 4 hour time point, and will complete the 4 hour diary in the clinic.)*
- Administration of study drug 800 mg. (ibuprofen/placebo) in 250 ml of normal saline over 7-10 minutes. (Infusion time may be increased up to 1 hour if necessary).
- Vital signs (pulse and blood pressure) 30 minutes, 1-hour and 2-hours post-dosing.
- If you still have a moderate to severe headache at 2 hours after receiving double-blind study drug, you will receive a rescue dose of 800 mg. IV Ibuprofen and will be monitored for an additional 2 hours.
- Inform research staff of any adverse events experienced.
- You will be discharged from the headache center at 2 hours after your dose of double-blind study medication if you have headache relief, or when it is clinically indicated. If you do not have headache relief at 2 hours after study medication administration, you may receive IV ibuprofen rescue and will be observed at the Jefferson Headache Center for an additional 2 hours.

It is possible that you may receive up to 1600 mg of IV Ibuprofen in a 24 hour period (800 mg. as double-blind treatment and 800 mg. as optional rescue), but this is not standard treatment and has not been extensively studied.

At approximately 24 hours after your dose of IV study medication, the study coordinator will contact you by telephone. The coordinator will ask you if you have had any side effects and if you have properly completed your headache diary. You must return to the headache center for your Study Termination Visit (Visit 3), within 7 days of your treatment with study drug.

Termination Visit: Visit to occur within 7 days from Treatment Visit

- Coordinator will collect and review your take-home diary
- Coordinator will ask you about any changes in your medications and/or medical conditions since your last visit
- Coordinator will ask you about any adverse events that you may have experienced.

What are the risks or discomforts involved?

IV ibuprofen has been well tolerated. There is a risk that your headache pain may not improve or may even worsen. Additional risks include the following:

Cardiac (heart) and circulatory problems:

Ibuprofen is a non-steroidal anti-inflammatory (NSAID) drug. This class of drugs has been associated with heart and circulation problems, as serious as heart attack and stroke, which can be fatal. Patients with known cardiovascular disease may be at increased risk, although it is possible that these problems could occur in someone who does not have a history of heart

disease. Our study will not include subjects with known cardiovascular disease or risk factors for cardiovascular disease that the investigator feels should prohibit study participation. It is important to inform the study personnel if you have any history of heart failure, heart attack, stroke, or TIAs.

Gastrointestinal Effects: Risk of Ulceration, Bleeding, and Perforation

NSAIDs, including ibuprofen, can cause serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine. Upper gastrointestinal ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for one year. Longer duration of NSAID use increases the likelihood of developing a serious gastrointestinal event at some time during the course of therapy. However, even short-term therapy is not without risk. Subjects participating in this study will only be treating one headache with the IV ibuprofen. It is important to inform your study coordinator or physician if you have a history of peptic ulcer or gastrointestinal bleed, or if you are using oral corticosteroids or anticoagulants, since this could place you at greater risk.

Hepatic (Liver) Effects

Small elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, including ibuprofen. Significant elevations of liver function tests (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions have been reported, including jaundice (skin and membranes [such as the whites of the eyes] turn a yellowish or a yellow-brown color), fulminant (overwhelming) hepatitis, liver necrosis (destruction of liver tissue), and hepatic (liver) failure, some with fatal outcomes. Our study will not include subjects with a history of liver disease. Additionally, we will be obtaining serum chemistry at the screening visit, to ensure that our subjects have normal baseline liver function tests and are eligible to participate.

Hypertension (high blood pressure)

NSAIDs, including ibuprofen, can lead to onset of new hypertension or worsening of pre-existing hypertension. Patients taking certain anti-hypertensive medications may have impaired response to these therapies when taking NSAIDs. Our study will exclude subjects with uncontrolled hypertension and subjects taking any of the following classes of medications for high blood pressure: angiotensin-converting enzyme inhibitors (ACE inhibitors), thiazides, or loop diuretics. It, therefore, is important that you inform your research physician or coordinator of all medications that you are taking. If you qualify for study participation, your vital signs, including BP will be assessed at baseline, then every 30 minutes through 2 hours after dosing with study medication and for 2 hours after receiving IV ibuprofen rescue.

Congestive Heart Failure and Edema (fluid retention)

Fluid retention and edema have been observed in some patients taking NSAIDs. Subjects with a history of heart failure will be excluded from the study.

Renal (Kidney) Effects

Long-term administration of NSAIDs has resulted in kidney damage, such as renal papillary necrosis and other renal injury. Patients at greatest risk of renal toxicity include those with impaired kidney function, heart failure, liver disease, those taking certain blood pressure medications, such as diuretics or ACE inhibitors, and the elderly. This study will exclude subjects with impaired hepatic (liver) or renal (kidney) function. As part of the study, we will obtain serum chemistry, including liver function tests and tests of kidney function (blood urea nitrogen and creatinine levels).

Anaphylactoid Reactions

As with other NSAIDs, anaphylaxis (severe, life-threatening allergic reaction) may occur in patients without known prior exposure to ibuprofen. It is also possible that a less severe allergic reaction could occur. Our study will exclude subjects with a history of allergy or hypersensitivity to any component of IV ibuprofen, aspirin (or aspirin related products), NSAIDs.

Serious Skin Reactions

NSAIDs, including ibuprofen, can cause rare but very serious skin adverse reactions such as exfoliative dermatitis (rash characterized by redness, scaling and pealing), Stevens-Johnson Syndrome (a severe, potentially life-threatening disorder of the skin and mucous membranes), and toxic epidermal necrolysis (a very rare, but very severe skin disorder related to Stevens-Johnson Syndrome), which can be fatal. These rare, but serious events may occur without warning.

Hematological Effects

Anemia may occur in patients receiving NSAIDs, including ibuprofen. This may be due to fluid retention, gastrointestinal blood loss, or an effect on erythropoiesis (the formation of red blood cells in the body). NSAIDs can also inhibit platelet (a type of blood cell important in clotting) function. Subjects with clinically significant anemia, bleeding problems or platelet problems will be excluded from the study. Additionally, we will obtain blood to check hematology (white blood cells, red blood cells and platelets) at screening.

Pre-existing Asthma

Patients with asthma may have aspirin-sensitive asthma. Our study will exclude subjects with a history of asthma.

Ophthalmological Effects

Blurred or diminished vision and changes in color vision have been reported with oral ibuprofen.

Aseptic Meningitis

Aseptic meningitis (inflammation of the lining of the brain and spinal cord) with fever and coma has been observed in patients on oral ibuprofen therapy. Although it is probably more likely to occur in patients with a disease called lupus (SLE) and related connective tissue diseases, it has been reported in patients who do not have underlying chronic disease.

Drug interactions

Drug interactions can occur between ibuprofen and medications such as the following: aspirin, anticoagulants, certain medications to treat high blood pressure, and lithium. Our study excludes subjects taking the above medications. It is very important that you tell your study physician and/or coordinator of all medications (including over the counter medications) that you are taking.

There may be risks to IV ibuprofen that are not now known. You will be notified of any new significant findings that might affect your willingness to continue in the study.

Blood Collection and IV placement

Risks from blood collection and IV placement include the possibility of bruising, swelling, bleeding, and infection. Additionally, dizziness and fainting can be associated with the blood collection. There is a risk that infusing too quickly can cause pain at the IV injection site.

You should call the study doctor as soon as possible at 215-955-2243 if, during the course of this study, you develop any of these side effects or symptoms. The study doctor has told you that if your condition worsens, if side effects become very severe, or if it turns out that being in this study is not in your best interest, you will be taken out of the study.

What are the risks to fetuses, infants and pregnant women?

Pregnant women or women who are breast feeding should not be in this study because exposure to investigational drugs may be hazardous to an embryo, fetus or nursing infant. Even medications that are well known and prescribed may have adverse effects on an embryo or fetus. As with any medication, there are unknown risks. To be in this study you and your partner must practice adequate birth control measures. The study doctor will discuss acceptable methods of birth control with you. If you are a woman of childbearing potential, you will have a pregnancy test before making a decision about being in this study. This requires a urine test prior to the start of the study. The results of this pregnancy test will be made available to you prior to the start of the study.

If you become pregnant during the course of this study, you should notify the study doctor as soon as possible.

If you are a person in a same sex relationship, it is not necessary for you to practice birth control. However, if you are female, you will still have to have pregnancy tests according to the study protocol.

Are there alternatives to being in the study?

You do not have to participate in this study. There may be other alternatives that could be considered. These alternative treatments may include drugs such as;

- Triptans (such as sumatriptan)
- Dihydroergotamine (DHE)
- Other non-steroidal anti-inflammatory drugs (NSAIDs) (such as Aleve®, Motrin®®), or injectable Ketorolac (Toradol)
- Opioids (such as Vicodin®).

The study doctor will provide information about the study and any alternative treatments available to you.

How will privacy and confidentiality (identity) be protected?

Federal regulations require that certain information about individuals be kept confidential. This information is called "protected health information" (PHI). PHI includes information that identifies you personally such as name, address and social security number, or any medical or mental health record, or test result, that may have this sort of information on it. The laws state that you may see and review your/his/her TJU medical records at any time. However, in a research study, you may not see the study results or other data about the study until after the research is completed unless the study doctor decides otherwise.

If you join this study, the following individuals or entities may have access to your PHI and by law must protect it. These include investigators listed on this consent form and other personnel involved in this specific study, the University's Division of Human Subjects Protection and the Institutional Review Board (IRB), your health insurance company (if necessary for billing for standard medical care).

Your PHI may also be shared with the following entities that, while not obligated by law to protect PHI, will protect it to the best of their ability:

- The Food and Drug Administration (FDA)
- With any person or agency required by law.
- Cumberland Pharmaceuticals which is funding Thomas Jefferson University to conduct this study.

The following information will be provided to the study sponsor (Dr. Silberstein) and other entities noted above:

Study data for analysis:

Headache diaries, headache diagnoses, history, and responses to headache questionnaires will be used for data analysis. Your blood work (chemistry, hematology, and clotting studies) and urine pregnancy test results will *not* be used in data analysis, but are performed for safety reasons.

Demographic data: Your age, sex, race, employment status, education level and income will be used in data analysis. Your name, social security number, address will *not* be used for data analysis. This information will be used for payment purposes.

If you develop an illness or injury during the course of your participation in this study, other PHI about treating and following the condition may be generated and disclosed as it relates to this study. Your PHI may be used/disclosed indefinitely.

You may quit the study and revoke permission to use and share your PHI at any time by contacting the principal investigator, in writing, at: **Stephen D. Silberstein, M.D., Jefferson Headache Center, 900 Walnut Street, 2nd Floor, Suite 200, Philadelphia, PA 19107**. If you quit the study further collection of PHI will be stopped, but PHI that has already been collected may still be used.

The results of clinical tests and procedures performed as part of this research may be included in your medical records. The information from this study may be published in scientific journals or presented at scientific meetings but you will not be personally identified in these publications and presentations.

What if I am injured as a result of being in this study?

In the event that you experience a research-related injury, necessary and available medical care (including hospitalization) will be provided. However, Thomas Jefferson University cannot assure that this comprehensive medical and/or surgical care will be provided without charge. The costs may be billed to your insurance carrier but they may ultimately be your responsibility. A research-related injury is a physical injury or illness resulting to you that is directly caused by any procedure or treatment used in this study that is different from the treatment you would receive if you were not participating in a research study. No other financial compensation is available.

If you receive a bill related to a research-related injury that seems wrong, please discuss it with the study doctor or research coordinator.

Will I benefit from being in this study?

You may not benefit from being in this research, but we hope that what we learn may be helpful to future patients or society in general. Possible benefits from being in the study may include: relief from your headache pain.

Will I be paid for being in this study?

You will receive payment for your participation in this study. You will be paid $175 if you complete all visits required for the study to cover your [transportation, parking, or other] expenses related to your participation in this study. If you do not finish the study, you will be paid for the part of the study that you did complete. You will receive $25 for Visit 1, $100 for Visit 2 (Treatment Visit) and $50 for Visit 3 (final visit). If Visit 1 and Visit 2 are combined, you will receive $125 for that combined visit. Your payment will be issued in the form of a check after your last study visit.

Will I be told about any new findings?

Anything learned during the study, beneficial or not, that may affect your health or your willingness to continue in the study, will be told to you and explained.

Disclosure of Financial Interest

The Cumberland Pharmaceuticals is paying Thomas Jefferson University to conduct this study.

Are there costs related to being in this study?

The study drug and testing required by this research will be provided free of charge.
You may have to pay for some expenses related to this study, such as transportation, parking, meals, or other expenses.

Research Procedures

The history, physical examination and blood work to ensure that you qualify for the study are research procedures. The administration of study drug (IV ibuprofen or placebo), administration of rescue medication (IV ibuprofen) if needed, completion of headache diary and monitoring of vital signs (pulse and blood pressure) during study drug administration are all considered research procedures. You will not be charged for these research procedures.

Standard Testing Procedures

Procedures, tests and doctor's charges resulting from being in the study that are considered standard of care will be billed to your health insurance carrier. These are charges that you would have whether or not you were participating in a research study. It is possible that your insurance company may deny payment. If that happens you may be responsible for some or all of these charges. The study doctor will explain to you which procedures, tests and doctor visits are considered standard of care.

If you receive a bill that you think is wrong, please discuss it with the study doctor or research coordinator.

Can I be removed from the study or quit the study?

Your decision to participate in this research study is entirely voluntary. You have been told what being in this study will involve, including the possible risks and benefits.

Your participation in this research project may be terminated by the study doctor without your consent for any reason that he/she feels is appropriate.

You may refuse to participate in this investigation or withdraw consent and quit this study without penalty and without affecting your ability to receive medical care at Thomas Jefferson University.

If you withdraw from this study, you may continue treatment with your Jefferson doctor, or you may seek treatment from another doctor of your choice.

Should you decide to withdraw from the study, please be sure to inform the study doctor. Additional tests or procedures may be needed to ensure your safety. The study doctor will explain why these tests or procedures are necessary.

CONTACT INFORMATION

Telephone number for questions about your rights as a research participant	The Jefferson Institutional Review Board	215-503-8966
For questions, concerns or complaints about the research, or if you suspect a research-related injury	The Principal Investigator, Dr. Silberstein, or any co-investigator listed at the beginning of this form	215-955-2243
If you have difficulty contacting the study staff	Call the Jefferson Office of Human Research during working hours	215-503-0203

Non-Waiver of Legal Rights Statement

By your agreement to participate in this study, and by signing this consent form, you are not waiving any of your legal rights.

In order to be in this research study, you must sign this consent form.

You affirm that you have read this consent form. You have been told that you will receive a copy.

Signatures:

_____
Your Name *(please print or type)*

_____(Date)
Your Signature

_____
Name of Person Conducting Consent Interview

_____(Date)
Signature of Person Conducting Consent Interview

_____(Date)
Signature of Principal Investigator or
Co-Investigator

As Per University Counsel - Do Not Sign
This Consent Form After 5-31-18