THOMAS JEFFERSON UNIVERSITY
JEFFERSON HEADACHE CENTER

PI: Stephen D. Silberstein, M.D. Protocol # SDS/IVIb/01
Version: 7/31/14

"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)

STUDY SITE:
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BACKGROUND AND RATIONALE:

Migraine is a chronic neurologic disorder characterized by episodic attacks of headache and associated symptoms such as nausea, vomiting, photophobia and phonophobia (Headache Classification Committee, 2004). Migraine is a headache disorder often with unilateral location, pulsating quality, moderate to severe intensity and aggravation by routine physical activity. Migraine prevalence is approximately 18% in women and 6% in men (Lipton and Silberstein, 2001; Lipton et al., 2001; Lipton et al., 2007). About 90%

of migraine sufferers have moderate or severe pain. Three quarters of migraineurs have a reduced ability to function and one third require bed rest during their migraine attacks (Lipton et al., 2001; Lipton et al., 2007). Therefore, effective treatments and treatment strategies play a critical part in reducing the disability, burden, and cost of care for these patients (Matchar et al., 2000).

Patients that present to an ambulatory acute care setting or emergency room with a severe migraine have a limited number of treatment options. NSAIDS, including ibuprofen, have been shown to be efficacious in the acute treatment of migraine. However, the use of oral NSAIDS is sometimes not an option, such as after abdominal surgery, or in a patient with a severe migraine, that may have emesis and digestion abnormalities such as gastroparesis. IV opioids provide pain relief, but have the risk of respiratory and CNS depression, as well as a high propensity for addiction. For those patients who receive treatment in the ER, opioids are used for approximately 64% of patients, despite recommendations from the American Academy of Neurology that physicians should limit the use of opioids in the treatment of migraine (Gupta et al., 2007).

NSAIDs are not addictive, do not cause urinary retention, constipation or ileus, in contrast to opioids. IV ibuprofen (Caldolor) has been approved by the FDA for the treatment of pain and fever. Besides ibuprofen, Ketorolac (Toradol) is the only other NSAID available in an injectable form. However, ketorolac may result in severe gastrointestinal side effects. Thus, IV ibuprofen may offer another option. This pilot study will assess the efficacy and tolerability of injectable ibuprofen for the treatment of migraine headache in the ambulatory acute care setting.

OBJECTIVE:

This is a pilot trial to collect and evaluate data on the use of intravenous ibuprofen (IVIb) in the treatment of an acute migraine attack. Data will be collected on the efficacy of IVIb in subjects who are treated with study medication between 2 and 72 hours from time of onset of headache.

Periodic safety and efficacy assessments will be performed prior to and after study drug administration.

STUDY DESIGN:

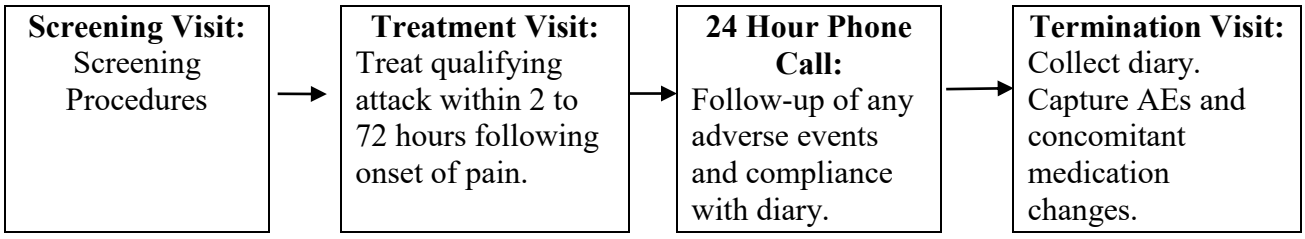
This is a 3 visit trial: screening visit, treatment visit, and final visit. Screening visit and a treatment visit may occur on the same day. Additionally, there will be one follow-up phone call at 24 hours post-dose. Subjects will be screened and the investigator will determine whether or not the subject experiences episodic migraine headaches. When a potential subject is seen as an office patient at the Jefferson Headache Center, has a headache, and is referred by the PI or co-investigator to this study, the referring study physician will document that the subject's cognition is intact and the subject is able to understand and sign the informed consent at that time. If the potential subject's cognition

is affected by the migraine, the subject must return to the Jefferson Headache Center for the research screening visit when the headache and cognitive difficulties have resolved. Subjects who are not being seen as an office patient on the day of screening must be headache-free at the time of screening.

Those subjects who meet the qualifying criteria will be eligible for treatment in the study. Subjects who qualify will be asked to come to the Jefferson Headache Center within 2 to 72 hours following the onset of pain.

IVIb or placebo will be administered intravenously as the study treatment. For active treatment, 800 mg of injectable ibuprofen will be placed in 250 ml of normal saline, and infused over 7-10 minutes. (Infusion time may be increased up to 1 hour if necessary due to possible anatomical restrictions). The placebo group will receive 250 ml of normal saline, infused over 7-10 minutes. (Infusion time may be increased up to 1 hour if necessary due to possible anatomical restrictions). Safety and efficacy assessments will be made periodically just prior to and after administration of study drug. Migraine pain and associated symptom assessments will be measured by the subjects for 24 hours from the administration of study drug for the treated attack. If subjects still have a moderate to severe headache at 2 hours after receiving double-blind study drug, they will receive a rescue dose of 800 mg. IV Ibuprofen. Subjects will be discharged at 4 hours post study drug dose, or when clinically indicated.

Diagram Study Design



Study Procedure Flow Sheet

	Screening Visit	Treatment Visit	Phone Follow-up	Termination Visit
Informed Consent Administration	X			
Inclusion/ Exclusion assessment	X			
Medical History Intake	X			
Headache History Intake	X			
Urine HCG test	X	X		X
Physical Examination	X			
LABS: CBC, Chemistry	X			
Update medical history and concomitant medications		X		

Study Drug Administration		X		
Migraine pain and associated symptoms measurements		X (predose, 15 mins, 30 mins, 1 hr, 1.5 hrs 2 hrs, 4hrs, 8 hrs, and 24 hrs post-dose)		
Study Drug Administration		X		
Vital Signs	X	X (pre-dose, 30 mins, 1 hr and 2 hrs post-dose)		X
2 hour in-clinic monitoring		X		
IV ibuprofen rescue if mod-severe HA at 2 hours		X		
Additional in-clinic 2 hr. monitoring if received IV ibuprofen rescue		X		
Height/ Weight measurement	X			
Concomitant Medications Capture	X	X	X	X
Adverse Events Capture		X	X	X
Take home materials collected and reviewed (e.g. paper diary)		X		X

STUDY PROCEDURES:

Screening: Visit 1

- Informed Consent administration; assess qualification criteria
- Medical history intake
- Headache History Intake
- Urine pregnancy test for women of childbearing potential
- Physical examination performed by study investigator
- Blood pressure and pulse measurements
- Height and weight measurements
- Obtain chemistry, hematology studies
- Collect and record concomitant medications

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

- Subject to contact site at onset of qualifying migraine attack. Determine whether subject will be treating this attack. Schedule subject to come to site accordingly.
- Blood pressure and pulse measurements
- Urine pregnancy test for women of childbearing potential
- Capture any changes in concomitant medications and/or medical conditions since screening visit

- Review diary with subject
- Migraine pain and associated symptoms assessments at pre-dose, 15 minutes, 30 minutes, 1 hour, 1 ½ hours, 2 hours, 4 hours. The 8 hours and 24 hours post-dosing assessments will be performed by the subject at home. However, if the subject received rescue IV ibuprofen at 2 hours after double-blind dosing, subjects will still be at the Jefferson Headache Center for observation at the 4 hour time point, and will complete the 4 hour diary in the clinic.
- Administer study drug (800 mg IV Ibuprofen or placebo)
- Measure vitals pre-dose, 30 minutes, 1-hour and 2-hours post-dosing.
- If subjects still have a moderate to severe headache at 2 hours after receiving double-blind study drug, they will receive a rescue dose of 800 mg. IV Ibuprofen.
- Capture and record any adverse events experienced. Investigator to determine relatedness and reportability
- Subjects will be discharged from the headache center at 2 hours after dose of double-blind study medication if they have had headache relief, or when it is clinically indicated. If subjects do not have headache relief at 2 hours after study medication administration, they may receive IV ibuprofen rescue and will be observed at the Jefferson Headache Center for an additional 2 hours.

24 hour post-dose phone follow-up: (Phone follow-up window: 20-28 hours)
- Coordinator to contact subject within 24 hours of treatment
- Capture any adverse events. Investigator to determine relatedness and reportability
- Ensure diary entries completed by subject at appropriate time points

Termination Visit: Visit to occur within 7 days from Treatment Visit
(Visit Window: 5-9 days)
- Collect and review subjects take-home materials
- Capture any changes in concomitant medications and/or medical conditions since last visit
- Capture and record any adverse events experienced. Investigator to determine relatedness and reportability

NUMBER OF SUBJECTS:

This is a single-site trial. 150 subjects will be screened in order to obtain 120 completers (60 subjects for each treatment group, placebo: active drug 1:1). This should provide a power of 0.8, assuming an alpha of 0.05, a placebo response rate of 43%, and a response rate difference of 25% between placebo and active treatment.

INCLUSION CRITERIA:

To be considered eligible to participate in this study, a patient must meet the following inclusion criteria:

- Male and female subjects between the ages of 18 and 65, inclusive

- Subject diagnosed with episodic migraine, with or without aura according to ICHD-2 criteria for at least one-year prior to screening
- Subject experiences between 2-10 migraine attacks per month (during the previous 6 months) with no more than 15 days of headache per month.
- Subject is using or agrees to use for the duration of participation a medically acceptable form of contraception (as determined by investigator), if female and of child-bearing potential
- Subject is able to come for 4 hour in-clinic treatment of an acute migraine attack
- Subjects are able to understand and comply with all study procedures.
- Subject provides written informed consent prior to any screening procedures being conducted
- If subject is on an allowable migraine preventive medication, the dose has been stable for at least 4 weeks prior to screening and the dose will remain stable throughout study participation.

EXCLUSION CRITERIA:

To be eligible for entry into the study, the patient must not meet any of the following exclusion criteria:

- Unable to make a reliable self-report of pain intensity to pain relief
- Use of analgesic or opioid within 24 hours of onset of headache to be treated with study medication. (If subject has an eligible headache and has taken a triptan or DHE within 24 hours, but greater than 2 hours before study drug dosing, they can be treated with study medication.)
- Patients taking the following medications on a regular basis: warfarin, lithium, angiotensin converting enzyme inhibitors, loop diuretics, thiazide diuretics, and angiotensin II receptor blockers, methotrexate.
- Patients with active, clinically significant anemia
- Patients with a history or evidence of asthma
- Patients with a history heart failure
- Subjects with severely impaired hepatic or renal function, as determined by the investigator
- Patients with a history of allergy or hypersensitivity to any component of IVIb, aspirin (or aspirin related products), NSAIDs, or COX-2 inhibitors
- Pregnant or nursing women
- Patients who have a history of congenital bleeding diathesis (e.g., hemophilia) or any active clinically significant bleeding, or have underlying platelet dysfunction including (but not limited to) idiopathic thrombocytopenic purpura, disseminated intravascular coagulation, or congenital platelet dysfunction
- Patients who have GI bleeding that required medical intervention within the previous 6 weeks (unless definitive surgery has been performed.)
- Patients who have a platelet count less than 100,000, as determined within the 28 days prior to treatment
- Pre-existing or current dependence on opioids.

- Subjects who have participated in an investigational drug trial in the 30 days prior to the screening visit
- Subjects with uncontrolled hypertension

PERMITTED RESCUE MEDICATION / PARAMETERS:

Subjects that have a moderate to severe headache at 2 hours after the administration of study medication will receive 800 mg. of IV ibuprofen as rescue. If the headache persists after IV rescue mediation or returns during the 24 hours of follow-up, subjects may take their usual migraine rescue medication, if needed. Rescue medication may be taken at a minimum of 2 hours following IV study drug or IV rescue treatment. Permitted rescue medications include: DHE-45, triptans, antiemetics and opioids. NSAIDS are excluded as rescue medication.

STATISTICAL CONSIDERATIONS:

150 subjects will be screened in order to obtain 120 completers (60 subjects for each treatment group, placebo: active drug 1:1). This should provide a power of 0.8, assuming an alpha of 0.05, a placebo response rate of 43%, and a response rate difference of 25% between placebo and active treatment.

Primary end-point:

- Comparison of proportion of subjects in each treatment group (active treatment and placebo) who have pain relief at 2 hours after the completion of the double-blind treatment infusion. Pain relief is defined as a reduction in headache pain level from severe or moderate decreased to mild or headache-free, respectively.

Secondary end-points:

- Comparison of the proportion of subjects in each treatment group (active treatment and placebo) who are pain-free after the completion of the double-blind treatment infusion.
- Pain and associated symptom assessments as measured at pre-dose, 15 minutes, 30 minutes, 1 hour, 1 ½ hours, 2 hours, 4 hours, 8 hours and 24 hours post-dosing for each attack treated per subject in both treatment groups.
- Sustained pain relief over 24 hours.
- Subject's historical response to NSAID therapy compared to response to IV ibuprofen.
- Occurrence of adverse events.
- Use of rescue therapy.

INTERRUPTION OR DISCONTINUATION OF TREATMENT:

A subject may be withdrawn from the study because of an adverse event, unsatisfactory therapeutic effect, protocol violation, subject's withdrawal of consent, lost to follow-up, or other reason deemed medically indicated by study physician.

TREATMENT COMPLIANCE:

Detailed records of study medication used by each subject will be maintained. Compliance to treatment will be checked by the investigator based on the subject's diary. The investigator and the study coordinator will also review drug accountability on a regular basis, as each vial is dispensed and at the completion of the trial. The investigator and the clinical coordinator must maintain an accurate record of the dispensing and return of the study drug in a drug accountability ledger. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time.

SAFETY MEASURES:

- Physical Examinations:
  Physical and neurological examinations will be performed by a study physician at the Screening Visit. Weight and height will be recorded at Visit 1. Subjects with clinically significant medical/psychological abnormalities, as determined by the investigator, will be excluded from the study.
- Vital Signs:
  Blood Pressure and pulse rate will be recorded at Screening Visit, Treatment Visit, and Final Visit. During Treatment Visit, vital signs will be monitored prior to study drug administration, 30 minutes, 1 hour and 2 hours post-dosing. Additional vital signs will be taken if clinically indicated.
- Urine Pregnancy Tests:
  All women of childbearing potential will have pregnancy tests done at the Screening Visit. A negative result is required for participation. Additional urine pregnancy tests will be performed at each follow-up visit.
- Adverse Events:
  Throughout the course of the study, subjects will monitor any adverse effects or events experienced. They will record start and stop times, intensity, and characteristics of these events. This information will be collected at follow-up visits and Final Visit. Subjects will be provided a number that they may contact 24 hours a day to report any serious adverse events. All adverse effects or events will be monitored and appropriate intervention will be applied as deemed necessary by the investigator. Adverse events will be collected following signing of informed consent.

Reporting of Adverse Events:

Reporting of all adverse events will be in accordance with Good Clinical Practice. Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the Adverse Event Form and followed up as appropriate. An adverse event is any undesirable sign, symptom, or medical condition occurring after starting study drug, even if the event is not considered to be related to

study drug. Study drug includes the drug under evaluation given during any phase of the trial.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, or indicate underlying pathology or require therapy. These will be recorded on the Adverse Events Form.

As far as possible, each adverse event will also be described by:

1. duration (start and end dates),
2. severity grade (mild, moderate, severe)
3. relationship to the study drug (suspected/not suspected),
4. action(s) taken and, as relevant, the outcome.

Serious Adverse Events:

A serious adverse event is an undesirable sign, symptom, or medical condition that:

- is fatal or life-threatening
- requires or prolongs hospitalization
- is significantly or permanently disabling or incapacitating
- constitutes a congenital anomaly or a birth defect
- is medically significant, may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed above.

Events not considered to be serious adverse events are hospitalizations for the following:

- treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen;
- treatment on an emergency, out subject basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

The Jefferson Headache Center will notify Thomas Jefferson University Institutional Review Board immediately in the event of a serious adverse event. Additionally, the Jefferson Headache Center will notify Cumberland Pharmaceutical of any SAE deemed by the principal investigator to be related to study drug within 24 hours of awareness.

Cumberland Pharmaceutical SAE Notification Contact Person:
Anita Hays or Amy Rock for SAE reporting within 7 days of occurrence:
Phone: 615-255-0068/fax 866-438-2372.

Disclosure and Confidentiality:

All subject information will be maintained in strict confidence. Study documents provided by the Jefferson Headache Center (protocols, source documents, case report forms and other material) will be stored appropriately to ensure their confidentiality and safety. However, all study documents and subject records may be reviewed by the FDA or institution regulatory agencies

Clinical Monitoring:

Dr. Silberstein, the Principal Investigator, is responsible for ensuring that the clinical trial is conducted according to Good Clinical Practices, protecting the rights, safety and welfare of subjects. During the course of the study trial, Dr. Silberstein will periodically review the progress of the trial. He will maintain contact with study coordinator as well as ensure that annual and continuing reports are submitted to the appropriate regulatory agencies. In summary, Dr. Silberstein will oversee and be responsible for all clinical aspects of the trial, as detailed in 21 CFR 312.50 through 312.70.

The co-investigators and clinical coordinators at the site will also ensure that Good Clinical Practices are followed, and will assure that that the protocol is adhered to strictly. All modifications to the protocol will receive approval from the Thomas Jefferson University Institutional Review Board, before modifications to the protocol are implemented. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval, but the IRB will be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB approval that can be treated as administrative amendments include, for example, a change in study personnel (excluding investigators).

Safety reports and annual reports will be submitted to the IRB, according to established guidelines.

Role of Study Monitor:

The study monitor will be a representative from the Jefferson Headache Center who is not involved with the clinical trial. The monitor will conduct periodic reviews of the study progress and performance. The monitor's role will include the following:

- Ensuring that all eligibility inclusion criteria and no eligibility exclusion criteria are met for all subjects.
- Ensuring that consent forms are appropriately signed and dated.
- Reviewing subject study records to ensure that study protocol has been strictly adhered to.
- Ensuring accuracy and completeness of study records. Ensuring accuracy of data entry from source documents and case report forms into electronic database.
- Reviewing IRB study records to ensure that all modifications to protocol were submitted and received approval prior to institution of protocol changes.

- Ensuring that adverse events are appropriately reported.

The study monitor will maintain a record of site visits. The monitor will verbally review results of the site evaluation with the PI and submit written copies of the evaluation to the PI, which will be forwarded to the primary site IRB.

IND STATUS:

We propose this pilot trial to collect/evaluate data is exempt from IND status according to the following:

21 CFR 312.2(b) (1), the clinical investigation of a marketed drug or biologic does not require submission of an IND if all six of the following conditions are met:

i. it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
ii. it is not intended to support a significant change in the advertising for the product;
iii. it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
iv. it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
v. it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and
vi. it does not intend to invoke 21 CFR 50.24.

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APPENDIX A:
International Classification of Headache Disorders-II (ICHD-II)

1.1 Migraine without aura

Diagnostic criteria:

A. At least 5 attacks1 fulfilling criteria B–D
B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
    1. unilateral location
    2. pulsating quality
    3. moderate or severe pain intensity
    4. aggravation by or causing avoidance of routine physical activity (*eg*, walking or climbing stairs)
D. During headache at least one of the following:
    1. nausea and/or vomiting
    2. photophobia and phonophobia
E. Not attributed to another disorder

1.2.1 Typical aura with migraine headache

Description:

Typical aura consisting of visual and/or sensory and/or speech symptoms. Gradual development, duration no longer than one hour, a mix of positive and negative features and complete reversibility characterize the aura which is associated with a headache fulfilling criteria for 1.1 *Migraine without aura*.

Diagnostic criteria:

A. At least 2 attacks fulfilling criteria B–D
B. Aura consisting of at least one of the following, but no motor weakness:
    1. fully reversible visual symptoms including positive features (*eg*, flickering lights, spots or lines) and/or negative features (*ie*, loss of vision)
    2. fully reversible sensory symptoms including positive features (*ie*, pins and needles) and/or negative features (*ie*, numbness)
    3. fully reversible dysphasic speech disturbance
C. At least two of the following:
    1. homonymous visual symptoms and/or unilateral sensory symptoms
    2. at least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
    3. each symptom lasts ≥5 and ≤60 minutes
D. Headache fulfilling criteria B–D for 1.1 *Migraine without aura* begins during the aura or follows aura within 60 minutes
E. Not attributed to another disorder.

APPENDIX B:
Caldolor Infusion Rate

APPENDIX C
Caldolor Monograph and Package Insert