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Document:
Study Protocol with Statistical Analysis Plan

Brief Title:
Localized Injection of Lidocaine and Glucocorticoid for Headache Treatment Phase 1 (LIGHT 1)

Official Title:
Intra-Arterial Injection of Lidocaine and Glucocorticoid in the Treatment of Intractable Headaches: A Non-Randomized, Open-Label Phase 1 Clinical Trial

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Clinical Research Protocol

Intra-Arterial Injection of Lidocaine and Glucocorticoid in the Treatment of Intractable Headaches: A Non-Randomized, Open-Label Phase 1 Clinical Trial

Protocol Number:	0.1.4
Version Date:	02/21/2025
Investigational Drug(s):	Xylocaine®-MPF (lidocaine hydrochloride) SOLU-MEDROL® (methylprednisolone sodium succinate)
IND Number:	170099
Development Phase:	Phase 1
Sponsor-Investigator:	Daniel A Tonetti, MD, MS Cooper University Health Care 101 Haddon Avenue, Suite 407 Camden, New Jersey, USA 08103
Funding Organization:	Society of Vascular and Interventional Neurology
Principal Investigator:	Name: Daniel A Tonetti, MD, MS Telephone: 855-306-3876 Fax: 856-546-8527 E-mail: tonetti-daniel@cooperhealth.edu
Coordinating Center:	Cooper University Health Care

1. TABLE OF CONTENTS

2. PROTOCOL SUMMARY

Name of Drug(s)	Lidocaine hydrochloride (Xylocaine®-MPF); methylprednisolone sodium succinate (SOLU-MEDROL®)
Treatment Group/Sample Size	10 total subjects
Design	Open-label, non-randomized study
Estimated Length of Subject Involvement	90 days
Route of Administration	Intra-arterial
Regimen	40 mg lidocaine/20mg methylprednisolone co-administered into each middle meningeal artery (left and right side) once
Primary Objective	This study will evaluate the safety of a co-administration of intra-arterial lidocaine and methylprednisolone for patients with intractable migraine. In addition, an examination of pain-related symptomatic relief per pain score scales will be assessed.
Study Population	10 adults over the age of 18 with a diagnosis of intractable migraine without aura, defined as failure of four treatment trials, will be enrolled in the study if they meet inclusion and exclusion criteria and are willing to participate in the study.
Multicenter	No
Blinding	None/Open-label
Randomization	None/Non-randomized
Primary Safety Variable	Adverse Events
Primary Efficacy Variable	Difference in pre- and post-drug MIDAS, 4-point verbal pain scale, and 11-point numeric pain scale scores.

3. STUDY RATIONALE

3.1. Intractable Migraine

Treatment-refractory intractable migraine is a challenging clinical condition. The Refractory Headache Survey estimated intractable migraine prevalence to be on average between 5-10% of the neurologic specialists' patient consensus.[1] Failure of adequate control of symptoms under standard therapy causes significant pain burden, migraine-related disability, and impaired quality of life.[1] Consequently, new approaches to intractable migraine treatment have potential to improve patient outcomes.

Previous case reports describe positive clinical experiences from initial attempts at intra-arterial lidocaine administration into the middle meningeal artery, including reduced migraine-related disability, subjective reports of pain improvement, and reduced pain scores.[2,3] Two severe migraine patients received intra-arterial doses of 40 mg lidocaine and 20 mg methylprednisolone in the middle meningeal artery, and reported subjective improvement in headache intensity after 24 hours.[3] Qureshi et al. (2021) found that in a study of four patients, intra-arterial lidocaine administered in 2 mg/ml increments up until 50 mg to bilateral middle meningeal arteries resulted in large decrease in pain score (from greater than 5/10 to less than 5/10) and subjective reports of decreased headache intensity in four patients.[2] Moreover, these initial experiences have not reported any serious adverse effects associated with intra-arterial lidocaine administration. This is in concordance with the safety profile of intra-arterial lidocaine administration in the peripheral circulation.[4,5,6] However, the patient sample was limited, and a formal phase 1 trial is yet to be conducted.

Results of this study will demonstrate the safety profile of this drug co-administration, and it will serve as the basis for future larger-scale investigations to evaluate efficacy. Safety and efficacy of the administration will expand available treatment options for intractable migraine patients.

We propose to conduct a pilot, non-randomized, open-label phase 1 clinical trial to characterize the safety of intra-arterial injection of lidocaine and methylprednisolone into the middle meningeal artery for treatment of intractable migraine.

The primary objective is to evaluate the safety of intra-arterial co-administration of lidocaine and methylprednisolone into the middle meningeal artery for intractable migraine patients. The secondary objective is to evaluate the effectiveness of lidocaine and methylprednisolone administration for modifying migraine-related symptom burden in intractable migraine patients.

[1] D'Antona L, Matharu M. Identifying and managing refractory migraine: barriers and opportunities? J Headache Pain. 2019;20(1):89. Epub 20190823.
[2] Qureshi AI, Pfeiffer K, Babar S, Huang W, Lobanova I, Ishfaq MF, et al. Intra-arterial injection of lidocaine into middle meningeal artery to treat intractable headaches and severe migraine. J Neuroimaging. 2021;31(6):1126-34.
[3] Qureshi AI, Qureshi MH, Khan AA, Suri MF. Effect of intra-arterial injection of lidocaine and methyl-prednisolone into middle meningeal artery on intractable headaches. J Vasc Interv Neurol. 2014;7(5):69-72.
[4] Duvnjak S, Andersen PE. Intra-arterial lidocaine administration during uterine fibroid embolization to reduce the immediate postoperative pain: a prospective randomized study. CVIR Endovasc. 2020;3(1):10.
[5] Keyoung JA, Levy EB, Roth AR, Gomez-Jorge J, Chang TC, Spies JB. Intraarterial lidocaine for pain control after uterine artery embolization for leiomyomata. J Vasc Interv Radiol. 2001;12(9):1065-9.
[6] Lee SH, Hahn ST, Park SH. Intraarterial lidocaine administration for relief of pain resulting from transarterial chemoembolization of hepatocellular carcinoma: its effectiveness and optimal timing of administration. Cardiovasc Intervent Radiol. 2001;24(6):368-71.

3.2. Rationale of Evaluating Study Drug for Treatment Indication

Treatment-refractory intractable migraine is a challenging clinical condition, and causes severely impaired quality of life due to subpar control of symptoms.[7] Anesthetic agents, such as lidocaine, administered within the blood circulation have been shown in prior investigations to be beneficial for severe headache patients.[8,9] Steroidal agents, such as methylprednisolone, administered within the blood circulation have also been previously studied as viable agents for headache treatment, including as a stand-alone measure and in combination with anesthetic agents.[10,11]

Mechanistically, lidocaine inhibits ionic fluxes across the neuronal membrane necessary for initiating and propagating electrical impulses conducting pain signals.[12] Consequently, inhibited neuronal signaling blocks the pain sensation associated with migraines. Steroids exert a multi-organ anti-inflammatory response, including within the brain, through cell signaling inhibition of inflammatory markers.[13] Hence, steroids likely are therapeutic for migraines, since they counteract the neurogenic inflammation associated with migraines.[10,11]

Prior case reports in six patients describe initial clinical experiences following intra-arterial lidocaine and methylprednisolone administration into the middle meningeal artery.[14,15] These patients reported favorable symptomatic relief, including reduced disability and subjective pain improvement, following the drug co-administration. Moreover, there were no serious adverse events reported in both investigations.

Consequently, the co-administration of two commercially-available drugs demonstrates potential to provide patients relief for a clinically-challenging diagnosis. Although early experience suggests favorable safety and efficacy, formal analysis in this phase 1 study and other subsequent investigations will evaluate the drug as a potentially viable treatment option for patients with treatment-resistant migraines, and thus improve their pain and qualify of life. Additionally, this phase 1 study will facilitate global assessment of practices, research procedures, and recruitment practices, with the intention of use as the basis for multicenter support for future clinical trial phases.

3.3. Alternatives to Study Drug

The alternative for not taking part in this study is to continue current course of care, which may include continuing current medications (oral or infusion) for intractable migraine. Other medications are available for this condition, including antiepileptic drugs, beta-blockers, antidepressants, angiotensin receptor blockers/angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory agents (NSAIDS), ergots, triptans, analgesics (i.e., acetaminophen), botulinum toxin injections, or calcitonin gene-related peptide monoclonal antibodies.

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[7] D'Antona L, Matharu M. Identifying and managing refractory migraine: barriers and opportunities? J Headache Pain. 2019;20(1):89. Epub 20190823.

[8] Krusz JC, Scott V, Belanger J. Intravenous propofol: unique effectiveness in treating intractable migraine. *Headache.* 2000;40:224–30.

[9] Sheridan DC, Spiro DM, Nguyen T, Koch Tk, Meckler GD. Low-dose propofol for the abortive treatment of pediatric migraine in the emergency department. *Pediatric Emergency Care.* 2012;28:1293.

[10] Rowe BH, Colman I, Edmonds ML, Blitz S, Walker A, Wiens S. Randomized controlled trial of intravenous dexamethasone to prevent relapse in acute migraine headache. *Headache.* 2008;48:333–40.

[11] Fiesseler FW, Shih R, Szucs P, et al. Steroids for migraine headaches: a randomized double-blind, two-armed, placebo-controlled trial. *The Journal of Emergency Medicine.* 2011;40:463–8.

[12] NDA 006488 lidocaine hydrochloride injection, solution. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ba082c2f-64f4-419d-9c88-74f203316e17

[13] NDA 011856 methylprednisolone sodium succinate for injection, USP. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cd99be87-c8d9-48d6-a8e5-e081052e3f19

[14] Qureshi AI, Pfeiffer K, Babar S, Huang W, Lobanova I, Ishfaq MF, et al. Intra-arterial injection of lidocaine into middle meningeal artery to treat intractable headaches and severe migraine. J Neuroimaging. 2021;31(6):1126-34.

[15] Qureshi AI, Qureshi MH, Khan AA, Suri MF. Effect of intra-arterial injection of lidocaine and methyl-prednisolone into middle meningeal artery on intractable headaches. J Vasc Interv Neurol. 2014;7(5):69-72.

3.4. Risk / Benefit Assessment

Risks associated with intra-arterial administration route includes rare adverse events related to intravascular access, including allergic response to contrast agents, vessel injury, access site hematoma, and infection. Risks will be mitigated by implementation of institutional standard practices protocol, including standardized procedures in the event of an interventional access-related complication.

For example:

- Protocols are in place to obtain an ultrasound study if access site hematoma is suspected post-administration of the study drug.
- In case of unexpected, severe contrast allergy, a combination of intravenous fluids, diphenhydramine, hydrocortisone, and/or adrenaline will be administered.

Risks associated with sedative mediations used for "twilight anesthesia"/monitored anesthesia care (MAC) include the risk of excessive or prolonged sedation, potentially requiring intubation. Risks will be mitigated by using minimal sedation necessary to safely obtain interventional access.

Risks associated with methylprednisolone administration include teratogenic effect on unborn fetuses. Risks will be mitigated by pre-treatment urine pregnancy test to screen for pregnancy in patients of child-bearing age.

Risks associated with bilateral versus unilateral injection are present, including from catheterization and dose toxicity. Intra-arterial navigation to obtain access to the contralateral middle meningeal artery present similar risks associated with intravascular access, as described above. Although risk of contralateral access is present, this phase 1 protocol uses a bilateral injection approach, as unilateral treatment has only been shown to be effective in patients with migraine-related symptoms that are exclusively localized to one side.[1] Although risk of toxicity from dose quantity is present, the dosages outlined in this study are well below the threshold for toxicity per the Prescribing Information. Moreover, a prior case report using lidocaine hydrochloride/methylprednisolone sodium succinate administered intra-arterially into the middle meningeal artery bilaterally for the indication of migraine and headache, using the dosing approach described in Section 6.1.5/Amendment #2, demonstrated no safety concerns in two patients.[16] In a separate dose-escalation study in four patients, intra-arterial lidocaine was administered in 2mg/mL increments until 50 mg per middle meningeal artery (100mg lidocaine total), and there were no adverse effects reported.[17] Based on prior clinical experience in the same or greater dosing amount with the same route of administration for the same indication, the risk for toxicity is expected to be minimal.

Benefits to subjects for the research include potential resolution of intractable migraine symptoms following treatment. Potential benefit also includes presenting an alternative, minimally invasive pharmacologic approach to intractable migraine to substitute chronic, frequent treatment with oral medications.

3.4.1. Drug-Related Risks

No specific lidocaine-related risks are anticipated for the investigational dosing amount and route. The following are potential complications for lidocaine use per Section 5 (WARNINGS AND PRECAUTIONS) for the Prescription Drug Labeling of NDA 006488. Patients are contraindicated from use if they have a known history of hypersensitivity to lidocaine

[16] Qureshi AI, Pfeiffer K, Babar S, Huang W, Lobanova I, Ishfaq MF, et al. Intra-arterial injection of lidocaine into middle meningeal artery to treat intractable headaches and severe migraine. J Neuroimaging. 2021;31(6):1126-34.

[17] Qureshi AI, Qureshi MH, Khan AA, Suri MF. Effect of intra-arterial injection of lidocaine and methyl-prednisolone into middle meningeal artery on intractable headaches. J Vasc Interv Neurol. 2014;7(5):69-72.

and local anesthetics of the amide type. Lidocaine administration has been associated with cases of methemoglobinemia. Drugs within the anesthetic agent pharmacologic class may trigger familial malignant hyperthermia. Small doses injected percutaneously into the head and neck area for retrobulbar, dental, and stellate ganglion blocks, have been reported to rarely cause confusion, convulsions, respiratory depression and/or arrest, cardiovascular stimulation and/or depression, and thus, require close cardiopulmonary monitoring during medication administration.

No specific methylprednisolone-related risks are anticipated for the investigational dosing amount and route. The following are potential complications for methylprednisolone use per Section 5 (WARNINGS AND PRECAUTIONS) for the Prescription Drug Labeling of NDA 011856. Complications with methylprednisolone treatment are dependent on dosage size, duration, and route of administration. Methylprednisolone has been associated with rare serious neurological adverse events, including spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke, with epidural administration. There have been rare reports of anaphylactoid reactions. Large doses of corticosteroids have been associated with elevated blood pressure and increased potassium and calcium excretion. After recent myocardial infarction, there has been a suggested association between drugs within the corticosteroid pharmacologic class and left ventricular free wall rupture. Chronic methylprednisolone use is associated with hypothalamic-pituitary adrenal axis suppression, Cushing's syndrome, and hypoglycemia. High doses of cyclic, pulsed methylprednisolone administration are associated with toxic acute hepatitis. Corticosteroid use is associated with increased susceptibility to infections, including fungal infections.

Other risks of participation include very rare adverse events related to route of administration, including allergic response to agents, vessel injury, access site hematoma, and infection.

4. STUDY OBJECTIVES

4.1. Primary Objective

Primary outcome is safety of the lidocaine and methylprednisolone co-administration intra-arterially into the middle meningeal arteries. The endpoints that will be analyzed to examine this outcome include: incidence of all adverse events; incidence of adverse events attributed to the study drug; and incidence of any serious adverse events.

4.2. Secondary Objectives

Efficacy is a secondary outcome that will be examined. The endpoints for evaluation include difference in MIDAS, 4-point verbal pain scale, and 11-point numeric pain scale scores prior to drug administration and 1 week, 6 weeks, and 3 months after drug administration.

5. STUDY DESIGN

5.1. General Approach for Evaluation of Treatment

This study will be a non-randomized, open-label phase 1 clinical trial. Participants above the age of 18 years who have an established diagnosis of intractable migraine (defined as failure of four other pharmacologic agents) and are active patients at our institution (i.e., have an appointment with a neurologic care provider during the enrollment period) will be offered enrollment. Either intolerance or side effects requiring early discontinuation or adequate trial at therapeutic dose without relief constitutes failure of therapy.

A neurological provider will perform a baseline assessment of enrolled patient's medical history and symptom scale scores, including MIDAS, 4-point verbal pain scale, and 11-point

numeric pain scales (Appendix G). An experienced neurointerventional co-investigator will inject 20 mg methylprednisolone and 40 mg lidocaine into the middle meningeal artery bilaterally. Each patient will receive a total of two doses of the 40mg lidocaine/20mg methylprednisolone co-administration of drugs (i.e., one dose administered within the left middle meningeal artery, and the other dose in the right middle meningeal artery). Immediate post-operative clinical evaluation, and evaluation at subsequent follow-up appointments with a neurological provider will involve assessment of neurological functional status, symptom scores, and occurrence of any associated adverse event at 1 week, 6 weeks, and 3 months. To evaluate the primary safety outcome, data will be analyzed to yield the prevalence of any adverse event, treatment-related adverse events, and serious and/or fatal adverse events. Data comparing pairwise differences in pre- and post-drug changes in symptom scores at 1-week, 6-week, and 3-month follow-up clinical encounters will be analyzed to assess secondary efficacy outcome.

5.2. Description of First Year Trial(s)

This study will be a non-randomized, open-label phase 1 clinical trial. Qualifying patients as described in Section 4.3 will be offered the option to be enrolled within the clinical trial, including explanation of study-related components and a pre-specified 3-month clinical follow-up duration.

5.3. Number of Subjects to be Evaluated

Up to 10 patients will be evaluated. Sample size was determined off of norms for phase 1 trials, as there lacks sufficient data to conduct a power analysis. Patients who are lost to follow-up and/or withdraw early from the study will not be replaced.

5.4. Duration of Trial and Subject Involvement

The duration of the clinical investigation will be 1 year, with patient involvement lasting approximately 4 months from enrollment to completion of clinical trial-related follow-up.

5.5. Administrative Organization

Participating Units: Cooper University Health Care is the only study site participating in this study. The clinical laboratory core within Cooper University Health Care will be utilized per protocol. Data management and coordination will be within a validated database within Cooper University Health Care maintained by the study team subject to approval by the Cooper University Institutional Review Board.

Principal Investigator: Dr. Daniel A. Tonetti, MD, Assistant Professor of Neurosurgical Surgery at Cooper University Health Care. Dr. Tonetti is a highly qualified open and endovascular neurosurgery who will lead this trial, given his prior experience in leading and coordinating early-stage clinical trials. His contributions to the field of Cerebrovascular Neurosurgery and Endovascular Neurosurgery are notable, as evidenced by his experience with over 100 peer-reviewed publications, numerous abstracts, and international/national presentations. Within the Cooper Neurological Institute, a prominent institution with a specialized South Jersey Headache clinic, Dr. Tonetti works alongside a team of skilled neurologists and advanced practices providers who actively treat patients suffering from intractable migraine headaches.

Additional Personnel: The following sub-investigators comprise of the core study team.

Dr. Hamza A. Shaikh, MD, Scientific Advisor, is an Assistant Professor of Neurological Surgery and Radiology at Cooper University Health Care. He has been actively working as a Neurointerventional Radiologist and senior Neuroradiologist at Cooper University Health Care, and has founded and developed the Neurointerventional program to its current standing. He has extensive expertise in neurointerventional approaches to intracranial pathology. He will be responsible for overseeing development, coordination, and completion of the project aims. He will serve as an advisor and mentor for the principal investigator. Dr. Shaikh and Dr. Tonetti will work closely together to implement the research program as a team, along with their senior colleagues.

Dr. Ajith J. Thomas, MD, Sub-Investigator, is a Professor of Neurological Surgery and Chairman/Chief for the Department of Neurosurgery at Cooper University Health Care. He is a neurointerventional physician that will participate in clinical care including enrolling candidates, performing investigational procedures, and providing follow-up care for enrolled patients.

Dr. Tudor G. Jovin, MD, Sub-Investigator, is a Professor of Neurology and Neurological Surgery and Chairman/Chief of Neurology at Cooper University Health Care. He is a neurointerventional physician that will participate in clinical care including enrolling candidates, performing investigational procedures, and providing follow-up care for enrolled patients.

Dr. Larisa Syrow, MD, Sub-Investigator, is an Associate Professor of Clinical Neurology at Cooper University Health Care. She is a headache specialist who will be participating in the enrollment process and follow-up care for patients.

Dr. Jane Khalife, MD, MS, Sub-Investigator, is an Attending Neurologist at Cooper University Health Care. She is a neurointerventional physician that will participate in clinical care including enrolling candidates, performing investigational procedures, and providing follow-up care for enrolled patients.

Dr. Pratit D. Patel, MD, Sub-Investigator, is an Assistant Professor of Neurology at Cooper University Health Care. He is a neurointerventional physician that will participate in clinical care including enrolling candidates, performing investigational procedures, and providing follow-up care for enrolled patients.

Manisha C. Koneru, MS, Graduate Research Assistant, has education and training in statistical methods and clinical trial design. She will be assisting in report generation, data collection, and statistical analyses.

Lindsay Colman, MS, Clinical Coordinator, will assist with administrative responsibilities, including maintaining records of enrollees, generating compliance reports for oversight committees, and continued compliance with regulatory requirements.

6. SUBJECT SELECTION

6.1. Inclusion Criteria

1. Male or female ≥18 years of age.

2. Documentation of a diagnosis of intractable migraine without aura, including failure of at least four classes of preventative drugs. Either intolerance or side effects requiring early discontinuation or adequate trial at therapeutic dose without relief constitutes failure of therapy.
3. Written informed consent obtained from subject and ability for subject to comply with the requirements of the study.

6.2. Exclusion Criteria

1. Pregnant, breastfeeding, or unwilling to practice contraception during participation in the study. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD).
2. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.
3. Patients with concomitant intracranial pathology (e.g., intracranial malignancy).
4. Blood glucose level on screening complete metabolic blood panel > 400 mg/dL.
5. Patients with known hypersensitivity and/or contraindication to either lidocaine hydrochloride or methylprednisolone sodium succinate, including:
    - Patients with known history of hypersensitivity to local anesthetics of the amide type.
    - Patients with systemic fungal infections.
    - Patients with known or suspected hypersensitivity to cow's milk or its components or other dairy products (SOLU-MEDROL® 40mg presentation includes lactose monohydrate, and may contain trace amounts of milk ingredients).
6. Patients taking chronic medications that, when co-administered with lidocaine and other local anesthetics, are at increased risk of developing methemoglobinemia: nitrates/nitrites, local anesthetics, antineoplastic agents, antibiotics, antimalarials, anticonvulsants, acetaminophen, metoclopramide, quinine, sulfasalazine.
7. Patients taking chronic medications that, when co-administered with methylprednisolone, are at increased risk for hypokalemia, altered drug levels, convulsions, or altered clearance: amphotericin B, diuretics, aminoglutethimide, macrolide antibiotics, anticholinesterases, antitubercular drugs, cholestyramine, cyclosporine, digitalis glycosides, estrogens (including oral contraceptives), hepatic enzyme inducers/inhibitors, and ketoconazole.
8. Patients have known contraindications for angiography. Patients with contrast allergy will be premedicated with diphenhydramine and steroids.
9. Patient has known active systemic infection or sepsis.
10. Patient has contraindication to anesthetic agents used for conscious sedation/monitored anesthesia care (MAC).
11. Concurrent participation in another research protocol for investigation of an experimental therapy.
12. Known or suspected inability to adhere to study protocol or protocol requirements, as per the discretion of the Investigator or treating provider.

6.3. Recruitment

Patients meeting inclusion/exclusion criteria and have an existing clinical encounter with a Cooper University Health Care neurological provider during the enrollment period will be offered enrollment. Recruitment will include explanation of the study using standardized language by a subinvestigator and written information about the study using simple language. The patient will have an opportunity to deny enrollment, proceed with providing consent, or opt for a follow-up phone outreach by a subinvestigator within 1-2 weeks. The purpose of the follow-up phone outreach is to provide a standardized approach for when the patient expresses that they need more time to make a decision regarding participation, and thus are deferring making a decision to consent or decline. The 2-week period will provide the opportunity for the patient to review the informed consent document and discuss their participation with other supportive individuals (i.e., family members, friends, primary care provider, etc.). This also provides the patient with an opportunity to deliberate any questions they may have. The follow-up phone outreach with physician study personnel is to a) address any questions that have arisen during the deliberation process and b) ascertain whether the patient has decided to consent to participate or not. No further advertising will be performed.

6.4. Screening

Upon enrollment, the neurological provider will be asked to verify past medical history (i.e., tobacco use, obesity status, past traumatic brain injury, diabetes mellitus, hypertension, hyperlipidemia) and current medications during the clinical encounter. Patients would undergo a pre-treatment serum metabolic blood panel to document baseline serum glucose levels, which is a routine biomarker to assess prior to administering glucocorticoid medications. Specific for research purposes only, patients would also be asked to score baseline MIDAS, 4-point verbal rating scale, and 11-point numeric pain scores (Appendix G). Patients will be instructed to keep a Study Diary, and will be instructed to record migraine episodes and any adverse events with date of onset, duration, and description for four weeks before and three months after treatment.

Patients with baseline serum glucose of above 400 mg/dL will fail screening procedures and not be included within the study due to elevated risk of acute exacerbation of steroid hyperglycemia during methylprednisolone administration.

7. STUDY TREATMENT, PROCEDURES, AND GUIDELINES

7.1. Study Intervention

After baseline screening assessment, patients will be scheduled within one month for investigational drug administration. Xylocaine®-MPF will be prepared for administration of 40 mg of active lidocaine hydrochloride per dose as described in Section 3.1.4. A total of two doses (40 mg lidocaine hydrochloride per dose; 80 mg total) of lidocaine hydrochloride will be prepared for the injection of each dose into each middle meningeal artery (left and right). SOLU-MEDROL® will be prepared for administration of 20 mg of active methylprednisolone sodium succinate as described in Section 3.1.4. A total of two doses (20 mg methylprednisolone sodium succinate per dose; 40 mg total) of methylprednisolone sodium succinate will be prepared for the injection of each dose into each middle meningeal artery (left and right). No placebo agents will be used during the study. Agents will not be blinded. Agents will be prepared and stored per instructions contained within Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) of the Prescribing Information and manufactures' guidelines contained within the packaging insert.

The treatment will be administered in the Acute Stroke and NeuroInterventional Suite at Cooper University Health Care. The care team will include an experienced neurointerventional physician with extensive experience in proper catheter placement and technical specifications

necessary for the procedure below, certified and licensed angiography technicians, a dedicated anesthesiology care team, pharmacy team, and nursing team comprised of neurocritical care certified nurses (including post-procedural recovery and observation). Within the immediate treatment area, availability to resuscitative equipment and continuous vital sign monitoring, including rapid cycling continuous blood pressure monitoring (with measurements at least every 5 minutes), continuous pulse oximetry, respiratory rate, continuous heart rate monitor, and electrocardiographic monitoring, will be ensured. For safety, patients may be sedated using institutional monitored anesthesia care (MAC) protocol under the care of a licensed anesthesiologist, and thus will not require intubation. Patients will be monitored continuously throughout the procedure and for four hours post-operatively in a dedicated post-angiography care unit.

The following steps will be performed interprocedurally:

1. Intra-arterial access will be obtained under ultrasound guidance via femoral or radial artery.
2. Fluoroscopic-guided catheterization and intracranial vascular access to the middle meningeal artery will be obtained using devices per neurointerventional provider discretion.
3. Manual infusion of 40 mg lidocaine bolus will occur over 5 minutes.
4. The provider will wait 2 minutes before administering active medications to assess for toxicity or acute adverse reactions.
5. Manual infusion of 20 mg methylprednisolone bolus will occur over 5 minutes.
6. The provider will wait at least 5 minutes before administering active medications to the contralateral side to assess for toxicity or acute adverse reactions.
7. The intravascular access will be retracted from intracranial circulation and navigated to the contralateral middle meningeal artery.
8. As described in Steps 3-5, infusion of lidocaine and methylprednisolone will occur.
9. Intravascular catheters will be retracted and access site will be sealed with appropriate closure device.

The following intra-procedural protocol adjustment is allowed: in the event of concern for overdose or other toxicity, the protocol permits administering half-strength dosages prior to completing administration of full dosage amounts (for example, administering 20 mg of lidocaine over the 2-5 min, waiting 2 minutes, and then subsequently administering the remaining 20 mg of lidocaine over another 2-5 min interval to result in a complete administration of a full dose). If this protocol adjustment is enacted, the Investigator must document this variation from standard protocol in procedural documentation.

Following study drug administration, patient will be monitored for post-procedure recovery by a nursing staff member for at least 4 hours. During this time, the patient's vital signs will be monitored, including continuous electrocardiogram, pulse oximetry, cyclic blood pressure monitoring (with measurements obtained at least every 15 minutes), respiratory rate, and heart rate monitoring. The catheterization access site will be assessed 2 hours following administration to ensure adequate closure and absence of access site hematoma.

7.2. Study Assessment and Activities

Summary of all study-related visits and activities are described in Table 1, including screening procedures and study drug administration.

Table 1. Schedule of Study Visits

	Visit 1 (Screening)	**Visit 2** (Administration) (Week 0)[a]	**Visit 3** (Week 1)[b]	**Visit 4** (Week 6)[b]	**Visit 5** (Week 12)[b]
Informed Consent	X				
Medical History	X				
Concomitant Medication Review	X	X	X	X	X
Complete Neurological Physical Exam	X	X	X	X	X
Vital Signs	X	X	X	X	X
Comprehensive Metabolic Blood Panel	X	X			
Pregnancy Test (Urine or Serum)	X				
MIDAS Score (Appendix A)	X	X	X	X	X
4-point Verbal Rating Scale (Appendix B)	X	X	X	X	X
11-point Numeric Pain Rating Scale (Appendix C)	X	X	X	X	X
Subject Diary Review	X	X	X	X	X
Study Drug Administration		X			

[a]Approximately 4 weeks of Visit 1
[b]± 2 days

7.2.1. Visit 1 (Screening)

1. Review the study with the subject and obtain written informed consent and HIPAA authorization.
2. Assign the subject a unique screening number.
3. Record demographics data.
4. Record medical history, including history of tobacco use, obesity status, past traumatic brain injury, diabetes mellitus, hypertension, hyperlipidemia, migraines), diagnosis date, and prior preventative medications trialed for migraine treatment.
5. Record current, concomitant medications.
6. Perform a complete neurological physical exam, including visual field assessment, fundoscopic exam, cranial nerve exam, peripheral motor and sensory fields, and reflexes.
7. Perform and record vital signs, including blood pressure monitoring.
8. Perform clinical laboratory tests (i.e., complete metabolic blood panel and pregnancy test as applicable).
9. Administer migraine-related symptom scores (i.e., MIDAS, 4-point Verbal Rating Scale, 11-point Numeric Pain Rating Scale).
10. Initiate Subject Diary, including instructions to record migraine episodes and any adverse events with date of onset, duration, and description.
11. Schedule subject for Visit 2 (study drug administration).

7.2.2. Visit 2 (Administration)

(Week 0 – Approximately 4 weeks after Visit 1).

1. Record any changes to concomitant medications.
2. Perform a complete neurological physical exam, including visual field assessment, fundoscopic exam, cranial nerve exam, peripheral motor and sensory fields, and reflexes.
3. Perform and record vital signs, including blood pressure monitoring.
4. Administer study drug (lidocaine hydrochloride and methylprednisolone serially).
5. Perform clinical laboratory tests (i.e., complete metabolic blood panel) following study drug administration.
6. Administer migraine-related symptom scores (i.e., MIDAS, 4-point Verbal Rating Scale, 11-point Numeric Pain Rating Scale).
7. Review Subject Diary, including details of any migraine episodes.
8. Schedule subject for Visit 3.

7.2.3. Visit 3 (Week 1 ± 2 days)

1. Record any changes to concomitant medications.
2. Perform a complete neurological physical exam, including visual field assessment, fundoscopic exam, cranial nerve exam, peripheral motor and sensory fields, and reflexes.
3. Perform and record vital signs, including blood pressure monitoring.
4. Administer migraine-related symptom scores (i.e., MIDAS, 4-point Verbal Rating Scale, 11-point Numeric Pain Rating Scale).
5. Review Subject Diary, including any incidence of adverse events.
6. Schedule subject for Visit 4.

7.2.4. Visit 4 (Week 6 ± 2 days)

1. Record any changes to concomitant medications.
2. Perform a complete neurological physical exam, including visual field assessment, fundoscopic exam, cranial nerve exam, peripheral motor and sensory fields, and reflexes.
3. Perform and record vital signs, including blood pressure monitoring.
4. Administer migraine-related symptom scores (i.e., MIDAS, 4-point Verbal Rating Scale, 11-point Numeric Pain Rating Scale).
5. Review Subject Diary, including any incidence of adverse events.
6. Schedule subject for Visit 5.

7.2.5. Visit 5 (Week 12 ± 2 days)

1. Record any changes to concomitant medications.
2. Perform a complete neurological physical exam, including visual field assessment, fundoscopic exam, cranial nerve exam, peripheral motor and sensory fields, and reflexes.
3. Perform and record vital signs, including blood pressure monitoring.
4. Administer migraine-related symptom scores (i.e., MIDAS, 4-point Verbal Rating Scale, 11-point Numeric Pain Rating Scale).
5. Review Subject Diary, including any incidence of adverse events.

8. DATA SAFETY MONITORING

8.1. Safety Monitoring Plan

Data safety monitoring will be undertaken jointly by the Institutional Review Board and Investigator, including training all co-investigators to report research-related adverse events to Investigator within 12 hours. A safety report to the Institutional Review Board after either

reaching half of anticipated enrollment (10 subjects) or eight months following trial start, whichever event occurs first, will be prepared.

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Prescribing Information or of greater severity or frequency than expected based on the information in the Prescribing Information.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient study records. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 will be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 2 below should be used to grade severity.

Table 2. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug will be assessed using the following the guidelines in Table 3.

Table 3. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.

Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

All personnel will document all SAEs that occur (whether or not related to study drug). The collection period for all SAEs will begin after study drug administration and end after the final study visit have been completed.

Consistent with federal regulations and in accordance with standard operating procedures and policies of the Cooper University Health Care Institutional Review Board (IRB), all potential unanticipated problems that are 1) unforeseen and 2) indicate that participants are at increased risk of harm will be promptly reported to the Cooper University Health Care IRB. The Investigator will report internal and external AEs to the Cooper University Health Care IRB within 7 days of discovery that meet above criteria for an unanticipated problem requiring prompt reporting to the IRB. SAEs meeting prompt reporting criteria will be reported to the Cooper University Health Care IRB within 1 day of discovery by telephone, fax, or email, with a full report submitted within 7 days of notification. Full reports will include: a) whether the occurrence of the adverse event alters the risk-benefit relationship of study participation, b) whether the protocol and/or consent form require modification, and c) whether any additional information needs to be given to the subjects who are already enrolled. Per federal regulations, SAEs meeting prompt reporting criteria will be reported within 7 calendar days if life-threatening or fatal or within 15 calendar days for all other types of qualifying reportable events to the appropriate regulatory body (i.e., FDA).

Monitoring visits will be conducted by representatives of the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). The Investigator grants permission to appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

9. STATISTICAL METHODS AND CONSIDERATIONS

9.1. Analysis Plan

An intention to treat analysis will be performed. Prevalence of any adverse event, treatment-related adverse events, and serious and/or fatal adverse events will be calculated. Secondary analyses assessing pairwise differences in pre- and post-interventional changes in symptom scores will also be performed to identify trends and as the basis for future power analyses. Categorical variable data will be summarized as frequencies with Agresti-Coull intervals as applicable. Quantitative variable data will be summarized as medians with interquartile ranges. Spearman's rank correlation coefficient, two-sided Student's t-test, chi-square tests, and nonparametric equivalences may be conducted at 0.05 significance level.

9.2. Interim Analysis

One interim analysis is planned for formal evaluation of safety during phase 1. Interim analysis will be performed when a total of 10 patients (50%) have completed Study Visit 3 (1 week follow-up after study treatment).

10. ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

10.1. Informed Consent

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form and HIPAA authorization and provide the documents to submit to the IRB/IEC. The consent form generated by the Investigator must be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects must be given ample opportunity to inquire about details of the study. A copy of the signed consent form will be given to the subject and the original will be maintained with the subject's records.

10.2. Investigator and Facilities Data

The Principal Investigator is Dr. Daniel A. Tonetti, MD, Assistant Professor of Neurosurgical Surgery at Cooper University Health Care. Please refer to FDA Form 1572 (Appendix H) for further contact information. Dr. Tonetti is a highly qualified open and endovascular neurosurgery who will lead this trial, given his prior experience in leading and coordinating early-stage clinical trials. His contributions to the field of Cerebrovascular Neurosurgery and Endovascular Neurosurgery are notable, as evidenced by his experience with over 100 peer-reviewed publications, numerous abstracts, and international/national presentations. Within the Cooper Neurological Institute, a prominent institution with a specialized South Jersey Headache clinic, Dr. Tonetti works alongside a team of skilled neurologists and

advanced practices providers who actively treat patients suffering from intractable migraine headaches.

Investigation is to be conducted at Cooper University Health Care in Camden, New Jersey, USA. Please refer to FDA Form 1572 (Appendix H) for further details on facility data.

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312). The protocol will be reviewed and approved by:

Name: Cooper University Health Care Institutional Review Board
Address: 1 Cooper Plaza, Camden, NJ, 08103, USA

Serious adverse experiences regardless of causality will be reported to the institutional review board in accordance with the standard operating procedures and policies of the institutional review board, and the Investigator will keep the institutional review board informed as to the progress of the study. The Investigator will obtain assurance institutional review board compliance with regulations.

Any documents that the institutional review board may need to fulfill its responsibilities (such as protocol, protocol amendments, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the institutional review board. The institutional review board's written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written institutional review board approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the institutional review board and written verification that the modification was submitted and subsequently approved should be obtained. The institutional review board must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the institutional review board; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

11. APPENDICES

11.1. Appendix A: The Migraine Disability Assessment Test (MIDAS)

Over the past _____, please answer the following questions about ALL headaches you have had.

___ 1. On how many days in the last _____ did you miss work or school because of your headache?

___ 2. How many days in the last _____ was your productivity in work or school reduced by half or more because of your headaches? (Exclude days that were counted in question #1 where you missed work or school)

___ 3. How many days in the last _____ did you not do household work (such as housework, repairs, maintenance, shopping, caring for yourself, children, relatives) because of your headaches?

___ 4. How many days in the last _____ was your productivity in household work reduced by half or more because of your headaches? (Exclude days that were counted in question #1 where you did not do any household work)

___ 5. How many days in the last _____ did you miss family, social, or leisure activities because of your headaches?

Add the total number of days from questions 1-5:

MIDAS Grade	Definition	MIDAS Score
I	Little of No Disability	0-5
II	Mid Disability	6-10
III	Moderate Disability	11-20
IV	Severe Disability	21+

11.2. Appendix B: 4-Point Verbal Pain Scale

Provider, please ask: “How would you describe your pain?”

Score	Pain Descriptor	Severity of Pain
0	None	No pain
1	Mild	Pain reported in response to questioning only, without any behavioral signs
2	Moderate	Pain reported in response to questioning and accompanied by behavioral signs, or pain reported spontaneously without questioning
3	Severe	Strong verbal response accompanied by facial grimacing, withdrawal of the hand, or tears

Grade is determined based on patient descriptor and provider interpretation based on criteria in “Severity of Pain” column

11.3. Appendix C: 11-Point Numeric Pain Scale

Provider, please ask: "On a scale of 0-10, with 10 being the worst pain imaginable, how would you rate your headache-related pain?"

Score	Pain
0	No Pain
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	Worst Pain Imaginable