Study Protocol

UCI School of Medicine

Effectiveness of Onabotulinumtoxin A (Botox®) in Pediatric Patients Experiencing Migraines: A Randomized Double Blinded Placebo Crossover Study in the Pediatric Pain Population

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Institutional Review Board
Human Research Protections
Protocol Narrative ~ Expedited/Full Committee
Biomedical/Clinical Research
Version 2015

Upload this completed narrative and any supplemental documentation to the IRB Application.	**IRB USE ONLY –** **HS#: 2016-3108**
Lead Researcher Name: Shalini Shah, MD	
Study Title: Effectiveness of Onabotulinumtoxin A (Botox®) in Pediatric Patients Experiencing Migraines: A Randomized Double Blinded Placebo Crossover Study in the Pediatric pain population	

CLINICAL TRIAL MASTER PROTOCOL AND INVESTIGATIONAL BROCHURE INFORMATION *

	Master Protocol	**Investigator Brochure:** <Specify Drug/Device>	**Investigator Brochure:** <Specify Drug/Device>	**Sponsor Consent Form Template(s)**
Version #:				
Version Date:				

[ ] This study is investigator-authored (investigator developed the study and is conducting the study at UCI and/or with other non-UCI sites).

* Add columns as applicable

NON-TECHNICAL SUMMARY

Provide a brief non-technical summary or synopsis of the study that can be understood by IRB members with varied research backgrounds, including non-scientists and non-affiliated members.

Headaches are traditionally characterized as acute, frequent, severe or throbbing/dull pain localized to the face or neck. Analgesics can be prescribed or acquired over-the-counter, depending on the severity of the ailment, as a common remedy to relieve pain and associated symptoms. Currently, preventative measures have emerged as a means to improve the quality of life of patients affected by neurological pain such as migraines. Botulinum Toxin Type A (Botox®), or onabotulinumtoxinA, is an FDA-approved neurotoxin developed by Allergan Inc. for treating chronic headaches and migraines in adults, however there is limited scientific literature on the outcomes of pediatric patients aged 8-17 receiving onabotulinumtoxinA. The purpose of this study is to determine the effectiveness of Botox® injections in pediatric patients for the treatment of chronic headache and common migraine in the pediatric population. We want to examine the long-term outcomes of patients who received onabotulinumtoxinA injections at UC Irvine Health for migraines and determine its effectiveness for pediatric pain use.

SECTION 1: PURPOSE AND BACKGROUND OF THE RESEARCH

1. Provide the scientific or scholarly rationale for the research. Describe the relevant background information and the specific gaps in current knowledge that this study intends to address.

Background

Chronic headache and migraine are one of the most common pain complaints in children and adolescents, both to the primary care provider, as well as to the pain physician specializing in pediatric pain disorders. Prevalence of migraine in younger children is approximately 10%, and up to 28% of adolescents suffer from recurrent headaches, the majority of which have migrainous features. [3,4] Aydin et al reported the most common headache presentation in pediatric neurology practices was migraine type, comprising 57.1% of all headaches presenting for initial consultation.[5] Population studies have demonstrated that over 130,000 school days are missed every two weeks and 3 million bedridden days occur per month as a result of pediatric migraine.[6] Common migraine is a debilitating disorder that requires both a plan to reduce the severity of attacks, as well as a prophylactic plan that reduces the frequency of occurrence. Episodic syndromes associated with migraine include recurrent gastrointestinal disturbance, cyclic vomiting syndrome and abdominal migraine, benign paroxysmal vertigo, and benign paroxysmal torticollis.[7] Powers et al demonstrated the negative impact of having childhood migraine on overall quality of life is similar to pediatric cancer, heart disease and rheumatic disease [8] As the frequency of migraine attacks increase, so does proportionally the child's disability in lost school time and family and social interactions, all of which may lead in turn to economic disability. Compared with episodic migraine sufferers, patients with chronic migraine have a lower socioeconomic status, reduced health-related quality of life, greater psychiatric and medical comorbidities, and increased occupational disability. [9] Stang et al estimated the health care costs are 70% higher for a family with a migraine than a non-migraine affected family, and direct medical costs for children with migraine are reported to be similar to those for adults. [6]. A study published in JAMA 2003 found that health care costs, work-related disability for parents and lost educational opportunity for the child leads to an annual economic impact in the US of approximately $36 billion due to both direct medical costs and lost productivity into adulthood.[10]

OnabotulinumtoxinA

Botulinum neurotoxin-A is a purified neurotoxin complex produced by the anaerobic bacterium *Clostridium botulinum.* [11,12]. The main mechanism of action of botulinum toxin involved the targeting of the neuromuscular junctions by means of a specific cleavage of the soluble N-ethylmaleimide-sensitive factor (NSF)-attachment protein receptor complex (SNARE)-like synaptosomal-associated protein of 25kDa (SNAP-25) [11, 12]. The final outcome of this multi-step process is the inhibition of pain neurotransmission (i.e. Chemo denervation), including the inhibition of the release of migraine-related neuropeptides (eg CGRP and SP) and glutamate. [11,12,13]

OnabotulinumtoxinA was approved by the FDA in 2010 for adult patients with common migraine, with the indication of >15 headache days per month, with headache lasting 4 or more hours each day in people 18 years or older. BOTOX® prevents up to 9 headache days a month (versus up to 7 in placebo) and is injected every 3 months. [14,15]

While randomized, double blind, placebo-controlled trials evaluating OnabotulinumtoxinA efficacy in migraine prophylaxis in adult literature demonstrates statistically significant results towards safety and efficacy [14, 15], no such randomized, double blind placebo controlled data for safety or efficacy exists

in the pediatric population. In a retrospective case series by Ahmed et al to assess tolerability and efficacy of OnabotulinumtoxinA in 10 female patients aged 11-17years, four patient reported subjective but clinically relevant relief in headache intensity, and 2 patients noting both decrease in intensity and frequency. The four responders also reported improvements in quality of life. [16] Chan et al prospectively evaluated 12 adolescent females with migraine and chronic daily headache, 6 of which were long term patients. They reported all long term patients had improvement in headache symptoms, which decreased on average 33-75%, and improvement in quality of life. [17] Kabbouche et al also in another retrospective study found statistically significant improvement in monthly headache frequency in 45 pediatric chronic daily headache patients who participated in 252 OnabotulinumtoxinA injections (average dose 188.5 +/- 32 units) and an improvement in pediatric migraine disability. A 30 point improvement in pediatric disability scoring between first injection and follow-up injection was also observed with decreased calculated disability from severe to moderate on PedMIDAS. [18] In a 10-year follow up of case series of OnabotulinumtoxinA intervention in adolescents with chronic daily headache and cervicalgia, Schroeder et al demonstrated both short term efficacy on headache frequency and severity, and in the long term follow up (10 years post injection therapy), chronic daily headache was not existent in any of the patients. [19] Common adverse events of OnabotulinumtoxinA reported in literature in the pediatric population are redness or temporary swelling at injection site, temporary pain at injection site, ptosis, and blurred vision [17]. In all of these studies, completion of a prospective, randomized double blinded placebo controlled trial is highly recommended to demonstrate objective outcome parameters in efficacy and tolerability. In the PI's nearly 5 year experience of using OnabotulinumtoxinA in pediatric practice she has seen dramatic improvement in patient pain (both in intensity and frequency of migraine), duration of action of migraine, school attendance, social interaction, disability and reaching student's intellectual potential by prophylactically treating headache with Botox.

Applications of Botulinum toxin A appears to be generally safe in the pediatric population for other indications, such as localized or segmental spasticity disorders, bladder hypertonicity, vestibular migraine as young as 2 years of age, although the majority of the class I and II studies included abobotulinumtoxinA (Trade name *Dysport*). [21] With the encouraging data in adults with chronic migraine presented at the 14th Congress of the International Headache Society (Philadelphia, PA 2009) and with the experiences of the above cited retrospective case series, it certainly appears reasonable to further explore a potential role for OnabotulinumtoxinA in the management of chronic migraine in the pediatric population.

2. Provide relevant preliminary data (animal and/or human).

Significance

While most chronic pain conditions are manageable, migraine pain can be devastating. Recently, OnabotulinumtoxinA was approved for the prophylaxis of migraine symptoms by the US Food and Drug Administration (FDA), which has dramatically altered the way pain physicians approach migraine pain. Unfortunately, most adults who suffer with migraines have their first headache during childhood or adolescence [1]. Although it appears that many preventative agents are safe in children, none are currently FDA-approved for this age group. As a result, despite experiencing significant disability, the vast majority of children who present to their physician with migraine headache do not receive prophylactic therapy. [2]

Treatment for pediatric head pain is an extrapolation from all that we have learned about adult headache with the expertise of working with children in pain. Pediatric pain medicine historically has its

own challenges, largely suffering from under-assessment or treatment paradigms extrapolated from adult literature. Current clinical studies, while able to demonstrate efficacy, may not demonstrate safety, or vice versa.
The significance of this study is to evaluate the efficacy of OnabotulinumtoxinA (BOTOX®) for the treatment and prophylaxis of pediatric migraine in a randomized, double-blinded, placebo cross over study. No trials currently exist in literature studying OnabotulinumtoxinA for efficacy and/or safety for indication of pediatric migraine, although significant contributions have been made by retrospective case series over the last 10 years. The historical and longitudinal context of the interest to design this study comes from the Principal Investigator's (PI) extensive use of "off label" OnabotulinumtoxinA to treat refractory pediatric migraine over the last 5 years. Anecdotally, the results are so impressive and impactful in her patients' lives, that this therapeutic ought to be studied in a controlled setting to demonstrate clinical outcome to validate existing treatment strategies. Thus, this study seeks to fulfill ASRA's goal of identification of novel applications of existing therapeutics. Moreover, this trial may benefit an under-studied pain population with the long-term goal of new FDA indication to "on label" status. The proposal also caries policy and legislative impact as it fulfills the federal initiative to design and conduct trials in the pediatric pain population within confines of the Best Pharmaceuticals for Children Act (BPCA) of 2002. The goal of the BPCA Program is to improve pediatric therapeutics through preclinical and clinical drug trials that lead to drug labeling changes.

3. Describe the purpose, specific aims or objectives. Specify the hypotheses or research questions to be studied.

Specific Aims

The proposed research is intended to explore whether pediatric chronic migraine may benefit from OnabotulinumtoxinA treatment. The study is focused on a specific debilitating disorder of chronic pain in a well-defined population that is historically not well studied. The objectives are attainable within the proposed timeframe.

Hypothesis:
Aim 1: To test if OnabotulinumtoxinA is superior to placebo in reducing headache frequency, intensity and pediatric migraine-related disability (Efficacy)
Aim 2: To evaluate the incidence of adverse events of OnabotulinumtoxinA administration in children aged 8-17 (Safety, Tolerability)
Aim 3: To evaluate if OnabotulinumtoxinA can contribute to reduction in preventive and rescue medication, reduction in health care utilization via emergency room and hospital admissions and health care costs (Hospital and pharmacy resource utilization)

Study aims fit together in an overall framework such that primary and secondary outcomes are easily defined, measureable, and validated as an acceptable means to measure clinical success and to longitudinally assess response.

4. Describe the primary outcome variable(s), secondary outcome variables, and predictors and/or comparison groups as appropriate for the stated study objectives/specific aims.

Primary outcome: Absolute number of headache days per month.

Secondary outcomes

- Severity of headache episode
- Disability scoring (PedMIDAS)
- Duration of benefit assessed at every 6 week interval
- Change from baseline in the frequency of severe headache days
- Change from baseline in the total cumulative hours of headache on headache days Change from baseline in the total dose or interval of preventive migraine or rescue migraine medication
- Percentage of patients with ≥ 50% decrease from baseline in the frequency of headache days
- Percentage of patients who are prescribed oral rescue migraine prophylactic treatment
- Percentage of patients who reduce consumption of preventive migraine or rescue migraine treatment
- Change from baseline in the absolute ED visits and/or hospital admission during each treatment phase
- Percentage of patients experiencing associated adverse events, serious or non-serious. (Non-serious defined as injection site swelling, redness, temporary pain, ptosis, blurred vision, worsening of migraine, nausea, vomiting, head lag weakness, drooling.)

5. List up to ten relevant references/articles to support the rationale for the research. Do not append an extensive NIH-grant-style bibliography.

1. Aurora, S.K., et al., *OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program.* Headache, 2011. **51**(9): p. 1358-73.
2. Dodick, D.W., et al., *OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program.* Headache, 2010. **50**(6): p. 921-36.
3. Ahmed, K., et al., *Experience with botulinum toxin type A in medically intractable pediatric chronic daily headache.* Pediatr Neurol, 2010. **43**(5): p. 316-9.
4. Bonfert, M., et al., *Primary headache in children and adolescents: update on pharmacotherapy of migraine and tension-type headache.* Neuropediatrics, 2013. **44**(1): p. 3-19.
5. Brodsky, J.R., B.A. Cusick, and G. Zhou, *Evaluation and management of vestibular migraine in children: Experience from a pediatric vestibular clinic.* Eur J Paediatr Neurol, 2016. **20**(1): p. 85-92.
6. Chan, V.W., E.J. McCabe, and D.L. MacGregor, *Botox treatment for migraine and chronic daily headache in adolescents.* J Neurosci Nurs, 2009. **41**(5): p. 235-43.
7. Hermann, C., M. Kim, and E.B. Blanchard, *Behavioral and prophylactic pharmacological intervention studies of pediatric migraine: an exploratory meta-analysis.* Pain, 1995. **60**(3): p. 239-55.
8. Hershey, A.D., et al., *Childhood and Adolescent Migraine Prevention (CHAMP) study: a double-blinded, placebo-controlled, comparative effectiveness study of amitriptyline, topiramate, and placebo in the prevention of childhood and adolescent migraine.* Headache, 2013. **53**(5): p. 799-816.
9. Jacobs, H. and J. Gladstein, *Pediatric headache: a clinical review.* Headache, 2012. **52**(2): p. 333-9.
10. Kabbouche, M., H. O'Brien, and A.D. Hershey, *OnabotulinumtoxinA in pediatric chronic daily headache.* Curr Neurol Neurosci Rep, 2012. **12**(2): p. 114-7.
11. Kacperski, J. and A.D. Hershey, *Preventive drugs in childhood and adolescent migraine.* Curr Pain Headache Rep, 2014. **18**(6): p. 422.
12. Lewis, D.W. and SpringerLink (Online service), *Clinician’s Manual on Treatment of*

Pediatric Migraine. 2010, Springer Healthcare Ltd.: Tarporley.
13. Mack, K.J., *Management of chronic daily headache in children.* Expert Rev Neurother, 2010. **10**(9): p. 1479-86.
14. Robertson, C.E. and I. Garza, *Critical analysis of the use of onabotulinumtoxinA (botulinum toxin type A) in migraine.* Neuropsychiatr Dis Treat, 2012. **8**: p. 35-48.
15. Schroeder, A.S., et al., *Ten-year follow-up in a case series of integrative botulinum toxin intervention in adolescents with chronic daily headache and associated muscle pain.* Neuropediatrics, 2012. **43**(6): p. 339-45.
16. Seshia, S.S., *Chronic daily headache in children and adolescents.* Curr Pain Headache Rep, 2012. **16**(1): p. 60-72.
17. Tajti, J., et al., *Prophylactic Drug Treatment of Migraine in Children and Adolescents: An Update.* Curr Pain Headache Rep, 2016. **20**(1): p. 1.
18. Yonker, M. and T. Mangum, *Migraine management in children.* Curr Neurol Neurosci Rep, 2015. **15**(5): p. 20.

SECTION 2: ROLES AND EXPERTISE OF THE STUDY TEAM

1. List all research team members who will interact or intervene with human subjects or will have access to identifiable private information about human subjects. *Include additional rows for Co-researchers and Research Personnel, as needed.*
2. For each research team member, indicate all applicable research activities the individual will perform. *Finalizing informed consent is reviewing, answering/asking questions, confirming competency, as necessary, and signing/confirming the informed consent.*
3. If applicable, list the Faculty Sponsor as a Co-Researcher who will have research oversight responsibilities.

Lead Researcher:

Name and Degree: **Shalini Shah**, **MD**

Position/Title and Department: Associate Program Director, Pain Medicine Fellowship and an Assistant Clinical Professor in the Department of Anesthesiology & Perioperative Care Division of Pain Management at UC Irvine Health / UC Irvine Health Center for Comprehensive Pain Management, and Director of Pediatric Pain Medicine at UC Irvine Health.

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Shah's duties include: performing investigational study treatment injections, research procedures, access to identifiable data, data collection, data analysis, and publication drafting.

Co-Researcher:

Name and Degree: **Joseph Rinehart, MD**

Position/Title and Department: Associate Clinical Professor and Vice Chair of Research in the Department of Anesthesiology and Perioperative Care at UC Irvine Health

Team Member will: **[ ]** serve as Faculty Sponsor with research oversight responsibilities

[X] Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Rinehart's duties include: access to identifiable data, data collection, data analysis, and publication drafting.

Research Personnel:

Name and Degree: **Michael-David Calderon, BS**

Position/Title and Department: Clinical Research Coordinator in the Department of Anesthesiology and Perioperative Care at UCI Health

Team Member will: **[ ]** Screen/Recruit **[ ]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): He will assist with the necessary support to coordinate, develop, implement, and evaluate project procedures and materials. He has two plus years of experience conducting clinical research (including FDA regulated) studies as a research coordinator. He has vast experience in data collection and data analysis during this time. He has been involved in His duties include: access to identifiable data, data collection, data analysis, and publication drafting.

Research Personnel:

Name and Degree: **Michael Ma, BS**

Position/Title and Department: Clinical Research Coordinator in the Department of Anesthesiology and Perioperative Care at UCI Health

Team Member will: **[ ]** Screen/Recruit **[ ]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): He will assist with the necessary support to coordinate, develop, implement, and evaluate project procedures and materials. He has two plus years of experience conducting clinical research (including FDA regulated) studies as a research coordinator. He has vast experience in data collection and data analysis during this time. His duties include: access to identifiable data, data collection, data analysis, and publication drafting.

Research Personnel:

Name and Degree: **Paulette Mensah, BA**

Position/Title and Department: Clinical Research Coordinator in the Department of Anesthesiology and Perioperative Care at UCI Health

Team Member will: **[ ]** Screen/Recruit **[ ]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): She will assist with the necessary support to coordinate, develop, implement, and evaluate project procedures and materials. She has vast experience in data collection and data analysis. Her duties include: access to identifiable data, data collection, data analysis, and publication drafting.

SECTION 3: SUBJECT POPULATION(S) (INDIVIDUALS/RECORDS/SPECIMENS)

A. Subjects To Be Enrolled on this UCI protocol (Persons/Records/Biospecimens)

1. Complete the table of subject enrollments below. *Include additional rows for subject category/group, as needed.*
2. If the study involves the use of existing records or biological specimens, specify the maximum number to be reviewed/collected and the number needed to address the research question.

Category/Group (e.g., adults, controls, parents, children)	**Age Range** (e.g., 7-12, 13–17, adults)	**Maximum Number to be Consented or Reviewed/Collected** (include withdrawals and screen failures)	**Number Expected to Complete the Study *or Needed to Address the Research Question***
Children/Adolescents	8-17	35	26
		Total: 35	

B. Overall Study Sample Size

If this is a multi-site study, provide the total number of subjects to be enrolled from all sites.

[X] Not applicable: This study will only take place at UCI, and does not involve other sites.

Total number of subjects across all sites: <Type here>

C. Eligibility Criteria

1. Identify the criteria for inclusion and exclusion.

Patients will provide at least 28-day baseline data in the form a daily diary and must have at least 15 days of reported headache during this period, with at least 4 distinct episodes lasting at least 4 hours each.

Inclusion Criteria

- Children aged 8-17
- Medical history of chronic migraine for at least 6 months
- 15 or more headache days during a 4 week period

Exclusion criteria

- Previous use of any botulinum toxin of any serotype for any reason
- Diagnosis of Myasthenia gravis, Eaton-Lambert Syndrome, Amyotrophic Lateral Sclerosis
- Treatment of headache using acupuncture, transcutaneous electrical stimulation (TENS), cranial traction, dental splints, or injection of anesthetics/steroids within 4 weeks prior to the week -4 screening visit
- Pregnancy
- Hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation and Infection at the proposed injection site" or added as "applicable contraindications to Botox

2. If eligibility is based on age, gender, pregnancy/childbearing potential, social/ethnic group, or language spoken (e.g., English Speakers only), provide a scientific rationale.

[ ] Not applicable: Subject eligibility is not based on these factors.

Patients who are younger than 18 years of age are physiologically different compared to the general population. Historically, Botox® has been utilized for a reduction in frequency of headaches in adult patients aged 18 or greater [14.15]. We are investigating the outcomes of this specific patient population aged 8-17 years to receive Botulinum toxin type A (Botox ®) for the treatment of neurological pain (migraine, chronic daily or tension-type headaches).

SECTION 4: RECRUITMENT METHODS

Check any of the following methods that will be used to recruit subjects for this study:

[ ] This study involves no direct contact with subjects (i.e., use of existing records, charts, specimens).

Specify database or IRB-approved protocol number (HS#), if applicable: <Type here>

[X] Advertisements, flyers, brochures, email, Facebook, and/or other media.

Specify where recruitment materials will be posted: Subject Recruitment Flyer will be sent to colleagues for the purpose of referring individuals/patients interested in the study.

If subjects will be recruited by mail, e-mail, or phone, specify how their contact information will be obtained: <Type here>

Submit recruitment materials for IRB approval.

[X] The study will be listed on Clinicaltrials.gov. *All clinical research must be registered.*

[ ] The study will be listed on the UC Irvine Health Clinical Trials web page.

Submit the UCIMC Standard Research Recruitment Advertisement for IRB approval.

[ ] The UCI Social Sciences Human Subjects Lab/Sona Systems will be used.

Submit the Social Science Human Subject Pool Recruitment Advertisement for IRB approval.

[ ] Referral from colleagues

- Study team will provide colleagues with UCI IRB-approved recruitment materials for distribution to potential subjects (e.g., recruitment flyer, introductory letter);
- An IRB-approved recruitment letter will be sent by the treating physician. The letter will be signed by the treating physician and sent to his/her patients to inform them about how to contact study team members; and/or
- Colleagues obtain permission from interested patient to release contact information to researchers.
- Study team does not have access to patient names and addresses for mailing.
- If colleagues will screen their patients' medical records to determine subject eligibility and approach patients directly about study participation: *Complete Appendix T to request a partial waiver of HIPAA Authorization.*

Submit recruitment materials for IRB approval.

[ ] Study team will contact potential subjects who *have given prior permission to be contacted* for research studies.

Specify when and how these individuals granted permission for future contact: <Type here>

Specify database or IRB-approved protocol number (HS#): <Type here>

[ ] Study team members will approach their own patients, students, employees for participation in the study.

[X] Study team will screen UCIMC medical records to which they have access to determine subject eligibility. The patients' physicians will approach patients directly about study participation.

Complete Appendix T to request a partial waiver of HIPAA Authorization.

[ ] Other Recruitment Methods: <Indicate the recruitment method(s) here>

SECTION 5: INFORMED CONSENT PROCESS

A. Methods of Informed Consent

1. Indicate all applicable informed consent methods for this study. *Submit the consent/assent document(s) with your e-IRB Application (e.g., Study Information Sheet, Recruitment script, Consent Form, etc.). Only IRB approved consent forms (containing the IRB approval footer) may be used to consent human subjects at UCI.*

[X] Written (signed) informed consent will be obtained from subjects. Signed informed consent, parental permission, and/or child assent will be obtained from subjects, as applicable.

[ ] Requesting a waiver of written (signed) informed consent. Signed consent will not be obtained; consent will be obtained verbally or via the web. Informed consent, parental permission and/or child assent will be obtained from subjects, as applicable.

Complete Appendix P.

[ ] Requesting to seek surrogate consent from a legally authorized individual. Surrogate consent may be considered only in research studies relating to the cognitive impairment, lack of capacity or serious or life-threatening disease and conditions of the research subjects.

Complete Appendix E.

[ ] Requesting a waiver of informed consent. (i.e., consent will not be obtained). *Skip to Section 5.B.*

Complete Appendix O.

2. Indicate where the consent process will take place.

[X] In a private room
[ ] In a waiting room
[ ] In an open unit
[ ] In a group setting
[ ] The internet
[ ] In public setting
[ ] Over the phone
[ ] Other (specify): <Type here>

3. Specify how the research team will assure that subjects have sufficient time to consider whether to participate in the research.

[ ] Subjects will be allowed to take home the unsigned consent form for review prior to signing it.

[ ] Subjects will be allowed <Type here> hours to consider whether to consent.

[X] Other (specify): We will avoid coercion by emphasizing that participation is completely voluntary. Whether or not the patient chooses to participate will not affect the care that they would receive. We will use a private room to obtain consent and the patient will be given adequate time to decide if they would

like to participate. We are requesting to consent the subjects on the day of their visit since we do not anticipate that the study will cause additional stress to the subjects.

4. If children are enrolled in this study, describe the parental permission process and the child assent process.

[ ] Not applicable: Children are not enrolled in this study.

The study investigator will explain the study in detail to the parents and child to answer any questions that they may have. The research team will emphasize confidentiality and rights of study subjects when obtaining consent. The patient will be enrolled in the study only after at least one of the investigators reviews the consent form with the patient, ensuring that the patient understands the study. All questions will be answered and written consent obtained.

5. Some subjects may be vulnerable to coercion or undue influence, such as those who are economically or educationally disadvantaged, mentally disabled, or students (undergraduate, graduate, and medical students) and employees of UCI (administrative, clerical, nursing, lab technicians, post-doctoral fellows and house staff, etc.), describe the procedures to ensure the voluntary participation of these individuals.

[ ] Not applicable: Subjects are not vulnerable to coercion or undue influence.

[X] Other (specify): The study team will make every effort to minimize undue influence. Procedures to ensure voluntary participation includes: allowing the subject adequate time during the consent process. We will only disclose the details of the studies in a private room. No member of the study team has any disclosable conflicts of interests. All subjects will be encouraged to discuss study participation with family and friends before consenting. No matter what the patient will decide regarding participation, patient care received from their physician will not be affected.

B. Health Insurance Portability and Accountability Act (HIPAA) Authorization

Indicate all applicable HIPAA authorization methods for this study.

[ ] Not applicable: Study does not involve the creation, use, or disclosure of Protected or Personal Health Information (PHI).

[ ] Requesting a Total waiver of HIPAA Authorization. HIPAA authorization will not be obtained at all for the study.


Complete Appendix T.

[X] Requesting a Partial waiver of HIPAA Authorization. HIPAA authorization will not be obtained for screening/recruitment purposes. However, written (signed) HIPAA research authorization is obtained for further access to personal health information.


Complete Appendix T.

[X] Written (signed) HIPAA Research Authorization will be obtained from subjects. Signed authorization, parental authorization, and/or child assent will be obtained from subjects, as applicable.


Complete the HIPAA Research Authorization form.

C. Methods of Informed Consent for non-English Speakers

1. Indicate the applicable informed consent method for non-English speakers.

[ ] Not applicable: Only individuals who can read and speak English are eligible for this study. *Scientific justification must be provided in Section 3.C.2.*

[X] The English version of the consent form will be translated into appropriate languages for non-English speaking subjects once IRB approval is granted. *The translated consent form must be submitted to the IRB for review prior to use with human subjects. Only IRB approved consent forms (containing the IRB approval stamp) may be used to consent human subjects at UCI.*

[ ] Requesting a short form consent process.


Complete Appendix Q.

The short form process will be used for the following occasional and unexpected languages: **[ ]** All non-English languages

[ ] All non-English languages except Spanish

[ ] Other languages (specify): <Type here>

2. Explain how non-English speaking subjects will be consented in their language and who will be responsible for interpreting and facilitating the informed consent discussion for the non-English speaking subjects.

[ ] At least one member of the study team is fluent in the language that will be used for communication, and that study team member(s) will be available during emergencies.


For all members of the study team responsible for obtaining informed consent from non-English speaking subjects, provide their qualifications to serve in this capacity (i.e. language fluency) in Section 2.

[X] The study team has 24-hour access to a translation service with sufficient medical expertise to discuss the research in this study.

[ ] Other (explain): <Type here>

SECTION 6: RESEARCH METHODOLOGY/STUDY PROCEDURES

A. Study Location

Specify where the research procedures will take place (e.g. UCI Douglas Hospital – Cardiac Care Unit, UCI Main Campus Hewitt Hall, UCI Health – Pavilion II, UCI Family Health Center, Anaheim, Irvine High School).


If research activities will also be conducted at non-UCI locations (e.g., educational institutions, businesses, organizations, etc.), Complete Appendix A. Letters of Permission or other documentation may be required (e.g. Off-site Research Agreements or IRB Authorization Agreements).

The research procedures will take place at UC Irvine Medical Center in the Medical Specialties facility and Gottschalk Medical Plaza on UCI main campus. Any data obtained for the study will be stored in a secure, locked facility in the UCI Anesthesia Research Department for the duration of the study.

B. Study Design

1. Include an explanation of the study design (e.g., randomized placebo-controlled, cross-over, cross-sectional, longitudinal, etc.) and, if appropriate, describe stratification/ randomization/blinding scheme.

Study Protocol

After enrollment, each subject will begin with a 28 day baseline screening phase followed by a 24 week double-blind, placebo-controlled, randomized AB|BA crossover period as the primary study protocol, followed by a second 24-week open-label period where all subjects will receive treatment with OnabotulinumtoxinA as follow-on treatment. There will be one treatment every 12 weeks, meaning 4 treatment blocks over the 48 week study period total. Those assigned to the AB group will receive OnabotulinumtoxinA in the first treatment and saline placebo in the second, while those in the BA group will receive saline and then OnabotulinumtoxinA. Both groups will then receive OnabotulinumtoxinA in the last two treatments. Progress check-ups will occur every 6 weeks during the study. Twelve week blocks were specifically selected in order to minimize carry-over effects from treatment periods, as the clinical efficacy of OnabotulinumtoxinA is nearly gone after twelve weeks in the PI's experience and reported literature.

Randomization will be via selection of sealed envelope. Injections will be performed at fixed-site, fixed-dose locations at 31 sites recommended by the PREEMPT 1 and 2 studies, including procerus, corrugators, frontalis, temporalis, occipitalis, splenius capitis, and trapezius muscle beds. At the

investigator's discretion, an additional 40U may be administered using a follow-the-pain strategy. The maximum dose will be **155 U across 31 sites**. All treatments will be performed by the PI.

2. Provide precise definitions of the study endpoints and criteria for evaluation; if the primary outcomes are derived from several measurements (i.e., composite variables) or if endpoints are based composite variables, then describe precisely how the composite variables are derived.

Primary outcome variables:

- Pain scores: as a standard part of the procedure, patients are asked to record their pain scores before and after their procedure. The principal endpoints are intensity on a 10 point NRS scale (VAS where needed), and frequency of migraine episodes in a 30 day period. This will be compared to baseline data pre-injection. For the study, pain score data will be collected up until the last follow up of the last injection of each patients' Botox ® injection series.
- Duration of benefit from the Botox ® injections: reduction in pain score by greater than or equal to 30%
- Functionality: the extent of normal activity able to be performed by a patient
- Disability: inability to function normally, physically or mentally
- Opioid consumption: amount of opioid medication consumed
- Neuropathic/migraine medication consumed including immediate release NSAID

Secondary outcome variables:

- Quality of pain: continuous, intermittent, throbbing, etc.
- Associated side effects: nausea, vomiting, food intake, diarrhea, constipation, anxiety, depression and/or adverse events associated with study drug
- Psychological history i.e. anxiety, depression
- Neuropathy: any weakness, numbness, and pain from nerve damage, usually in the hands and feet
- Type of analgesia/anesthesia: analgesic/anesthetic medication(s) used during procedure ・ Incidence of hospital admissions
- Incidence of ER visits
- Current medication use

Other variables:

- Neurological workup: Neurological medical evaluation, including medical history, physical examination, medical tests, survey of the patient's medical record for any information regarding Neurological disease
- Diagnosis: identification of chronic migraine head pain
- Indications: reason for Botox ® injections, number of injections in the Botox ® injection series ・ Procedure: specific procedure including location of procedure, imaging information, and other specific procedure information
- Block medications: medications and dosage used for the Botox ® injections
- Disposition: notes regarding patient's state during procedure

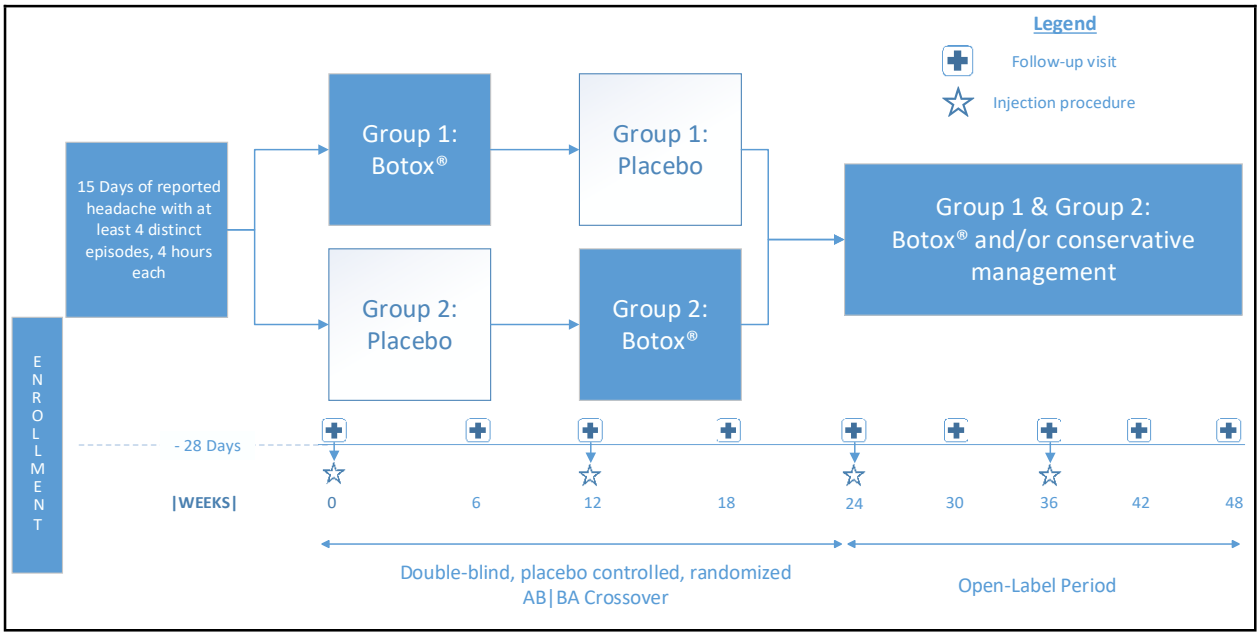
C. Research Procedures

1. Provide a detailed chronological description of all research procedures.

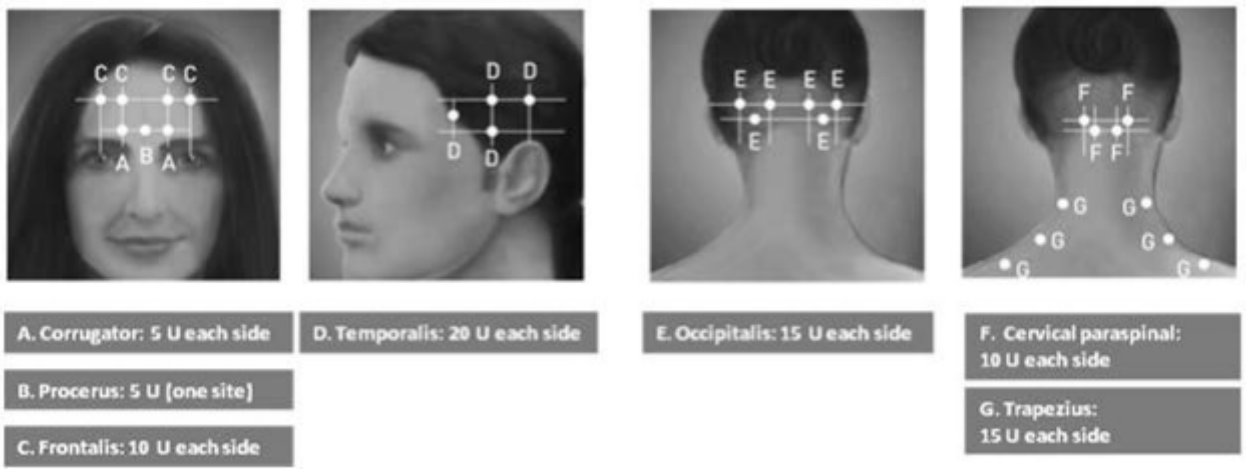
Methods

Given the existing evidence of efficacy in the available scientific data (adult and retrospective pediatric) and the PI's extensive personal experience in the pediatric population (where use of the study drug has

been found to be transformative), prolonged withholding of OnabotulinumtoxinA for the purpose of study was not considered reasonable by the PI. Thus, a study design minimizing the placebo control period while still allowing for comparison of OnabotulinumtoxinA to a control group, was desirable. An AB|BA cross-over design (which uses each patient has his/her own control, both minimizing recruitment numbers and the need for a control group which never receives treatment with OnabotulinumtoxinA), was selected as the best option after consultation. The influence of confounding covariates is reduced because each crossover patient serves as his or her own control. A four week baseline prior to treatment will act as a no-treatment control to compare to both the treatment and placebo. The study does not exclude patients on preventive or abortive migraine medication, in an attempt to demonstrate superiority on study drug over conservative medical management.



Diagrams 1-4: Recommended Injection Sites (A through G) for Chronic Migraine



(From BOTOX® Prescribing Information) Total of 31 Sites with a **maximum dose will be 155 U**

All data collection will follow Good Clinical Practices and HIPPA. This study has been submitted to the Institutional Review Board. Parent/guardian and/or child will sign an informed consent and assent (child) approving enrollment in study.

Patient Population

Children aged 8 – 17 years of age with a history of migraine meeting the criteria established in ICHD-II (2004), Section 1. Patients will provide at least 28-days (4 week) baseline data in the form a daily diary and must have at least 15 days of reported headache during this period, with at least 4 distinct episodes lasting at least 4 hours each. (Patients with continuous headache will thus be excluded as this may represent non-migraine symptoms). A total of 26 patients will be enrolled.

Data Collection

Our primary endpoint will be the same as that used in the PREEMPT trials which examined the efficacy of OnabotulinumtoxinA in adult patients aged 18 or greater [14, 15] Specifically, we will look for a reduction in frequency of headache days per month. In that trial, at baseline, patients reported 19.9 ± 3.6 headache days per month. The treatment group showed a reduction of 8.4 days, and the placebo group a reduction of 6.6 days (standard deviations on these reductions were not reported). Interpretation of the data was complicated by the varied medication regimens the patients were on at baseline (which frequently included over-use of opioid medications).

In 1999 the Migraine Disability Score (MIDAS) was developed by Stewart et al. [10] which is an easy-to use 5 item questionnaire accepted as a means to diagnose and follow adult headache. Hershey et al developed the pediMIDAS based on MIDAS but utilizes 6 questions, 3 addressing school attendance and functioning, and 3 evaluating participation in events outside of school. [22]. The questionnaire is based on the patient's recall of previous 3 months and can be used longitudinally to asses response. [1] In the clinical setting, the PedMIDAS can be helpful in assessing a patient's migraine burden and response to therapy. Some researchers advocate its use as an outcome measure in clinical trials. The Pediatric Migraine Disability Assessment (PedMIDAS) is the only validated clinical tool available to estimate migraine disability in the school-aged child,aged 4-18. [22]
Each data point will be collected at baseline, 6 weeks, 12 weeks, 18 weeks, 24 weeks, 30 weeks, 36 weeks, 42 weeks, and 48 weeks

2. Describe the duration of a subject's participation in the study. If there are sub-studies, include duration of participation in each sub-study.

After enrollment, each subject will begin with a 28 day baseline screening phase followed by a 24 week double-blind, placebo-controlled, randomized AB|BA crossover period, followed by a second 24-week open-label period where all subjects will receive treatment with OnabotulinumtoxinA. There will be one treatment at the beginning of each 12 week block, meaning 4 treatments over the 48 week study period total. Those assigned to the AB group will receive OnabotulinumtoxinA in the first treatment and saline placebo in the second, those in the BA group will receive saline and then OnabotulinumtoxinA. Both groups will then receive OnabotulinumtoxinA in the last two treatments. Progress check-ups will occur every 6 weeks during the study; participants will be asked to complete the Pediatric Migraine Disability Assessment (PedMIDAS) survey.

3. List data collection instruments (e.g., measures, questionnaires, interview questions, observational tool, etc.).

Investigator-authored, non-standardized, or un-validated measures must be submitted for review.

Data will be collected using a diary provided to the subject enrolled in the study. The participants will be asked to record the frequency and intensity of any neurological pain that occurs for the duration of the study. Progress check-ups will occur every 6 weeks during the study; participants will be asked to complete the Pediatric Migraine Disability Assessment (PedMIDAS) survey.

D. UCIMC Supplementary Clinical Services

If a UCIMC clinical unit/department (e.g., phlebotomy for blood draws, pharmacy for dispensing study drug(s), radiation services for X-rays, MRIs, CT scans, and Neurology for lumbar punctures) will perform research-related procedures:

1. List the research procedure (e.g. lumbar puncture, MRI, CT Scan), and
2. Identify the unit/department that will perform the procedure.

[X] Not applicable: This study does not involve the services of a UCIMC clinical unit/department.

E. Privacy

Privacy is about the subject's ability to control how much others see, touch, or collect information about the subject. Indicate all of the following methods that will be used to assure subject privacy. *Violations of privacy include accessing a subject's private information without consent, asking personal sensitive information in a public setting, being audio recorded or photographed without consent.*

[ ] Research procedures (including recruitment) are conducted in a private room.

[ ] Use of drapes or other barriers for subjects who are required to disrobe.

[X] Only sensitive information directly related to the research is collected about subjects.

[ ] When information is collected from internet sources, the internet site's privacy statement will be reviewed and followed.

Provide a copy of the Data Use Policy to the IRB.

[ ] Other (specify): <Type here>

F. Use of Existing Biological Specimens and/or Existing Information/Data

1. For studies that involve use of existing (i.e. on the shelf; currently available) specimens:
   a. Indicate the source of the specimens and whether the specimens were originally collected for research purposes.
   b. Explain how the existing specimens will be obtained.

[X] Not applicable: This study does not involve use of existing biological specimens.

Source: Indicate <u>all</u> that apply:

[ ] UCI/UCIMC

Originally collected for research purposes: **[ ]** YES; UCI IRB number (i.e. HS#): <Type here>

[ ] NO; explain: <Type here>

[ ] UCIMC Pathology Biorepository will provide specimens.

[ ] Non-UCI Entity; specify: <Type here>

Originally collected for research purposes: **[ ]** YES

Submit a copy of the IRB Approval Notice and Consent Form for the original collection.

[ ] NO; explain: <Type here>

[ ] Other; explain: <Type here>

2. For studies that involve use of existing (i.e. on the shelf; currently available) clinical data:
   a. Specify the source of the clinical data.
   b. Explain how the study team will access the clinical data. *Access to UCI Medical Center medical records for research purposes outside the capacity of the Honest Broker Services, such as access to physician notes, must be obtained from the Health Information Management Services*.

For investigator initiated/authored studies <u>only,</u> submit a data abstraction sheet that includes a complete list of data elements/information that will be collected from (existing) records or submit the case report form (CRF; eCRF).

[ ] Not applicable: This study does not involve use of existing clinical data. *Skip to Section 6.G.*

Source: Indicate <u>all</u> that apply:
[X] UCI/UCIMC.
[ ] non-UCI Entity; specify: <Type here>

How Obtained: Indicate <u>all</u> that apply:
[X] The study team will request specific patient information/data from UCIMC Health Information Management Services.

[X] The study team will review their patients' records and abstract data directly from those records.

[ ] The study team will request specific patient information/data from UCI Health Honest Broker Services. Describe the following:

Cohort selection criteria (e.g., use the available Clinical Terms from the Cohort Discovery Tool such as Demographics: Gender, Diagnoses: Asthma, Procedures: Operations on digestive system): <Type here>

Expected cohort size/patient count: <Type here>

Cohort attributes or data elements (e.g., lab test values, medication, etc.): <Type here>

[ ] Other; explain: <Type here>

3. For studies that involve use of existing (i.e. on the shelf; currently available) clinical data, specify the time frame of the clinical data to be accessed (e.g. records from January 2002 to initial IRB approval).

Existing medical records are checked for the duration of the study.

G. Collection of Photographs, or Audio/Video Recording

1. Describe all procedures involving the use and/or collection of photographs, or audio/video recording.

[X] Not applicable: This study does not involve photographs or audio/video recording. *Skip to Section 6.H.*

2. Specify if photographs or audio/video recording will include subject identifiable information (e.g., name, facial image). If so, indicate which identifiers will be collected.

N/A

3. Explain whether the photographs or audio/video recording will be included in subsequent presentations and/or publications and, if so, whether subject identifiers will be included.

N/A

H. Sharing Results with Subjects

1. Describe whether individual results (results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subject or others (e.g., the subject's primary care physician). *Only tests ordered by a physician and conducted in a CLIA certified lab may be shared.*
2. Explain what information will be shared and how the results will be shared.

[X] Not applicable: Individual results will not be shared with subjects.

3. Describe whether overall study results will be shared with subjects.
4. Explain how results will be shared.

[X] Not applicable: Final study results will not be shared with subjects.

I. Statistical Considerations *(This section is required for Investigator-Authored Research)*

1. Statistical Analysis Plan: Describe the statistical method(s) for the stated specific aims and hypotheses. *Your analysis plans should match the stated study specific aims and hypotheses in Section 1.*

1. **[ ]** Not applicable: A statistical analysis plan is not appropriate for this qualitative study design. Plan for assessing study results:

Our primary endpoint will be the same as that used in the PREEMPT trial which examined the efficacy of OnabotulinumtoxinA in adult patients [1, 2]. Specifically, we will look for a reduction in frequency of headache days per month, as well as decrease in intensity utilizing a 10 point NRS scale (VAS when appropriate). In that trial, at baseline, patients reported 19.9 ± 3.6 headache days per month. The treatment group showed a reduction of 8.4 days, and the placebo group a reduction of 6.6 days (standard deviations on these reductions were not reported). Interpretation of the data was complicated by the medication regimens the patients were on at baseline (which frequently included over-use of opioid medications).

2. Describe the primary statistical method(s) that will be used to analyze the primary outcome(s) or endpoints.

Design considerations: Given the evidence of efficacy in the available scientific data and the PI's extensive personal experience in the pediatric population (where it has been found to be life-changing), prolonged withholding of OnabotulinumtoxinA for the purpose of study was not considered reasonable by the PI. Thus, a study design minimizing the placebo control period while still allowing for comparison of OnabotulinumtoxinA to a control group was desirable. An AB|BA cross-over design (which uses each patient has his/her own control, both minimizing recruitment numbers and the need for a control group which never receives treatment with OnabotulinumtoxinA), was selected as the best option. A four week baseline prior to treatment will act as a no-treatment control to compare to both the treatment and placebo.

The primary outcome will be the difference between treatment and placebo injections on headache frequency. The difference will be calculated as

$$(\beta_A - \beta_B) - \frac{1}{2}(\lambda_A - \lambda_B)$$

Where λ represents possible carry-over effects from the previous treatment period. Because the cross-over period is uniform and balanced, we will assume that period effects and sequence effects are aliased out. The treatment and placebo effects will be calculated as:

$$\hat{\mu}_A = \frac{1}{2}(\bar{Y}_{AB,1} + \bar{Y}_{BA,2}) \text{ and } \hat{\mu}_B = \frac{1}{2}(\bar{Y}_{AB,2} + \bar{Y}_{BA,1})$$

Where $\bar{Y}_{AB,1}$ represents the group mean of the respective cross over group periods. Given the adult baseline of 19.9 ± 3.6 headache days per month, the treatment reducing this to 6.6 days and the placebo to 8.4 days and assuming a concomitant reduction in SD since these numbers were not reported in the source manuscript, we find that the effect size for this difference (8.4 vs 6.6 with SD 1.35 for both groups) is 0.554, a Cohen's d of 1.33. A power analysis using a significance level of 0.05 and a power of 0.9 shows that 13 subjects per group will be needed for this study, or a total of 26 subjects (13 per group) if comparison were to be made by direct groupwise testing.

3. Describe the secondary statistical method(s) that will be used to analyze the secondary outcome(s) or endpoints.

N/A

4. If appropriate describe secondary or post hoc analyses of primary outcome(s) or other exploratory analysis.

N/A

5. Sample Size Determination**:** Explain how the overall target sample size was determined (e.g., power analysis; precision estimation), providing justification of the effect size for the primary outcome based on preliminary data, current knowledge/literature and/or cost consideration; if appropriate, provide sample size justification for secondary outcomes. Power analysis should (at least) match the primary outcome/endpoint.

Given the adult baseline of 19.9 ± 3.6 headache days per month, the treatment reducing this to 6.6 days and the placebo to 8.4 days and assuming a concomitant reduction in SD since these numbers were not reported in the manuscript, we find that the effect size for this difference (8.4 vs 6.6 with SD 1.35 for both groups) is 0.554, a Cohen's d of 1.33. A power analysis using a significance level of 0.05 and a power of 0.9 shows that 13 subjects per group will be needed for this study, or a total of 26.

SECTION 7: RISK ASSESSMENT AND POSSIBLE BENEFITS

A. Risk Assessment

1. Indicate the appropriate level of review of this study, based upon your risk assessment.

[X] This study involves greater than minimal risk to subjects and requires Full Committee review. *Skip to Section 7.B.*

[ ] This study involves no more than minimal risk and qualifies as **Expedited research**.

2. If this study involves no more than minimal risk, provide justification for the level of review and for all applicable Expedited Categories you have chosen.

B. Risks and Discomforts

1. Describe and assess any reasonably foreseeable risks and discomforts — physical, psychological, social, legal or other. Include an assessment of their expected frequency (e.g., common – 65%, less common – 40%, unlikely – 5%, rare - <1%) and the seriousness (mild, moderate, severe). *A bullet point list is recommended. If this study will involve the collection of identifiable private information, even temporarily, for which the disclosure of the data outside of the research could reasonably place the subjects at risk, include the risk of a potential breach of confidentiality.*

As listed in the Risks section of the Informed Consent.

2. Discuss what steps have been taken and/or will be taken to prevent and minimize any risks/ potential discomforts to subjects. *Examples include: designing the study to make use of procedures involving less risk when appropriate; minimizing study procedures by taking advantage of clinical procedures conducted on the subjects; mitigating risks by planning special monitoring or conducting supportive inventions for the study; implement security provisions to protect confidential information.*

All extracted data will be de-identified immediately and save on a secured database for research purposes only. Study team members will follow strictly the reporting guideline by IRB in case of a breach of confidentiality, which is nearly impossible since all data are de-identified. Regardless, all collected information will be securely stored on a password-protected server.

Subjects for this study will be closely monitored for any potential adverse events. Subjects will be able to call the Lead Researcher 24 hours a day for any potential issues.

C. Potential Benefits

1. Describe the potential benefits subjects may expect to receive from participation in this study. *Compensation is not a benefit; do not include it in this section.*

[ ] There is no direct benefit anticipated for the subjects.

There is a prospect of direct benefit to children participating in the study. Taking part in this study may or may not make your health better with the first two treatments. While researchers hope Botox® will be more effective than the standard (usual) treatment, there is limited proof of this yet.

2. Specify the expected potential societal/scientific benefit(s) of this study.

Overriding Rationale

OnabotulinumtoxinA (Botox ®) injections have been shown to provide chronic pain relief in patients aged >18 with migraine pain. However, there is limited literature on pain relief in pediatric patients receiving Botox ® injections for chronic migraine pain [15,16]. A PubMed search displays very few results on publications involving the study of the effectiveness of Botox ® injections in pediatric patients. The studies that are published involve Botox ® injections done for the treatment of migraines and chronic headaches in adults [17,19,23,24] or are largely retrospective reviews. Moreover, the results of these studies vary and have not established whether or not the procedure is beneficial by prospective randomized trials. Chronic headache pain is one of the most common presenting complaint to a multi-disciplinary pain center specializing in pediatric pain, and the most common

presenting complaint to a pediatric neurology practice. It results in a global health concern both in terms of economic and functional disability to patient and family, but also in skyrocketing health care utilization and pharmacy costs to the US healthcare system. If migraines can be prophylaxed by the BOTOX ® modality in children, these upstream and downstream costs and disability can be curtailed.

With the encouraging data in adults with chronic migraine presented at the 14th Congress of the International Headache Society (Philadelphia, PA 2009) and the PREEMPT trials, and with the experiences of the above cited retrospective case series, it certainly appears reasonable to further explore a potential role for OnabotulinumtoxinA in the management of chronic migraine in the pediatric population [14,15]. **The overriding rationale is to demonstrate efficacy, tolerability and safety of OnabotulinumtoxinA for pediatric migraine and thereby potentially hasten the lengthy process to evaluate Botox® for approval in the pediatric population.** The most urgent goals as concerns pharmaceutical innovation is the development of pathomechanism-based antimigraine drugs and personalized therapy tailored to the children and adolescents suffering with migraine. [13]

SECTION 8: ALTERNATIVES TO PARTICIPATION

Describe the alternatives to participation in the study available to prospective subjects. Include routine (standard of care) options as well as other experimental options, as applicable.

[ ] No alternatives exist. The only alternative to study participation is not to participate in the study.

[X] There are routine standard of care alternatives available; specify:

- Getting no treatment
- Getting standard treatment for your condition without being in a study.
- Getting a different experimental treatment/taking part in another study.

[ ] There are other alternatives to study participation; specify: <Type here>

SECTION 9: SUBJECT COSTS

1. Indicate below if subjects or their insurers will be charged for study procedures. Identify and describe those costs**.**

[ ] Not applicable: This study involves no interaction/intervention with research subjects. *Skip to Section 10.*

[X] This study involves interaction/intervention with research subjects; however there are no costs to subjects/insurers.

[ ] This study involves interaction/intervention with research subjects, and there are costs to subjects/insurers:

2. If subjects or their insurers will be responsible for study-related costs, explain why it is appropriate to charge those costs to the subjects or their insurers. Provide supporting documentation as applicable (e.g., study procedures include routine (standard of care) procedures; FDA IDE/HDE/IND letter that supports billing to subjects).

[X] Not applicable: The study involves no costs to subjects for study participation.

[ ] Study related costs will be billed to subjects or their insurers for the following reasons:

SECTION 10: SUBJECT COMPENSATION AND REIMBURSEMENT

1. If subjects will be compensated for their participation, explain the method/terms of payment (e.g., money; check; extra credit; gift certificate).

[ ] Not applicable: This study involves no interaction/intervention with research subjects. *Skip to Section 11.*

[X] No compensation will be provided to subjects.

[ ] Compensation will be provided to subjects in the form of cash/gift certificate.

[ ] Compensation will be provided to subjects in the form of a check issued to the subjects through the UCI Accounting Office. The subject's name, address, and social security number, will be released to the UCI Accounting Office for the purpose of payment and for tax reporting to the Internal Revenue Service (IRS).

[ ] Other

2. Specify the schedule and amounts of compensation (e.g., at end of study; after each session/visit) including the total amount subjects can receive for completing the study. *Compensation should be offered on a prorated basis when the research involves multiple visits.*

   For compensation ≥ $600, subject names and social security numbers must be collected. This information must be reported to UCI Accounting for tax-reporting purposes.

[X] Not applicable: This study involves no compensation to subjects.

Subjects will be compensated with the following schedule and amounts:

3. Specify whether subjects will be reimbursed for out-of pocket expenses. If so, describe any requirements for reimbursement (e.g., receipt).

[X] Not applicable: This study involves no reimbursement to subjects.

Subjects will be reimbursed; specify:

SECTION 11: CONFIDENTIALITY OF RESEARCH BIOSPECIMENS/DATA

A. Biospecimens/Data Storage

1. Indicate all subject identifiers that may be included with the biospecimens or collected for the research study. *If any study-related data will be derived from a medical record, added to a medical record, created or collected as part of health care, or used to make health care decisions the HIPAA policy applies. The subject's HIPAA Research Authorization is required or a waiver of HIPAA Research Authorization must be requested by completing Appendix T.*

[ ] This study does not involve the collection of subject identifiers.

Check all the following subject identifiers will be used, created, collected, disclosed as part of the research:

[X] Names	**[ ]** Social Security Numbers	**[ ]** Device identifiers/Serial numbers
[X] Dates*	**[X]** Medical record numbers	**[ ]** Web URLs
[ ] Postal address	**[ ]** Health plan numbers	**[ ]** IP address numbers
[X] Phone numbers	**[ ]** Account numbers	**[ ]** Biometric identifiers
[ ] Fax numbers	**[ ]** License/Certificate numbers	**[ ]** Facial Photos/Images
[ ] Email address	**[ ]** Vehicle id numbers	**[ ]** Any other unique identifier

[ ] Other (Specify all): <Type here>

* *birth date, treatment/hospitalization dates*

Indicate how data will be stored and secured, including electronic data as well as hardcopy data paper records, electronic files, audio/video tapes, biospecimens, etc. *If the research data includes subject identifiable data and/or Protected Health Information, the storage devices or the electronic research files must be encrypted. [For guidance on the use of cloud services, please review the UCI OIT policy.]*

Electronic Data/Files (check all that apply):

[ ] Anonymous data will be maintained; no subject identifiers

[X] Coded data; code key is kept separate from data in secure location.

[ ] Data includes subject identifiable information. Provide rationale for maintaining subject identifiable info)**:** <Type here>

[X] Data will be stored on secure network server.

[ ] Data will be stored on standalone desktop computer (not connected to network/internet)

[ ] Other (specify here): <Type here>

Hardcopy Data (Records, Recordings, Photographs) and Biospecimens (check all that apply):

[ ] Anonymous biospecimens/data will be maintained; no subject identifiers

[X] Coded data; code key is kept separate from biospecimens/data in secure location.

[ ] Biospecimens/Data includes subject identifiable information (Provide rationale for maintaining subject identifiable info)**:** <Type here>

[X] Data will be stored in locked file cabinet or locked room.

[ ] Biospecimens will be stored in locked lab/refrigerator/freezer.

[ ] Other (specify here): <Type here>

2. List the location(s) where the data and/or biological specimens will be stored**.**

The data will be stored in a secure, locked facility in the UCI Anesthesia Research Department for the duration of the study approval. Only, the investigators and study personnel will have access to the data. Any data collected on the computer will only be stored on a secure, encrypted server. Data will be retained for six years as this research involves Protected Health Information.

3. If subject identifiable data will be transported or maintained on portable devices, explain why it is necessary use these devices. *Only the "minimum data necessary" should be stored on portable devices as these devices are particularly susceptible to loss or theft. If there is a necessity to use a portable device for the initial collection of identifiable private information, the research files must be encrypted, and subject identifiers transferred to a secure system as soon as possible.*

[X] Not applicable: Research data will not be transported or maintained on portable devices.

Research data will need to be maintained on the following portable device(s) for the following reason(s): <Type here>

B. Data and/or Biological Specimens Access

Specify who will have access to subject identifiable data and/or biological specimens as part of this study.

[ ] Not applicable: No subject identifiers will be collected.

[X] Authorized UCI personnel such as the research team and appropriate institutional officials, the study sponsor or the sponsor's agents (if applicable), and regulatory entities such as the Food and Drug Administration (FDA), the Office of Human Research Protections (OHRP), and the National Institutes of Health (NIH).

[ ] Other: <Type here>

C. Data and/or Biological Specimens Retention

Indicate how long subject identifiable data and/or biological specimens, including the subject code key will be retained. *If more than one of the options below is applicable (e.g., the study involves children), records must be kept for the longer period.*

[ ] Not applicable: No subject identifiable research data will be retained.

[X] Separate code key will be destroyed or subject identifiable information will be removed from the biospecimens and/or data at the earliest convenience, consistent with the conduct of this research. Specify timeframe: <Type here>

[ ] Destroyed once research data is analyzed.

[ ] Destroyed after publication/presentation.

[ ] Will be maintained; specify time frame and provide the rationale: <Type here>

[ ] Will be stored and maintained in a repository for future research purposes.

Complete Appendix M

[X] Will be retained for six years as this research involves Protected Health Information (PHI) (e.g., IRB documentation, consent/assent forms – NOT the actual PHI). *Investigators must destroy PHI at the earliest opportunity, consistent with the conduct of this study, unless there is an appropriate justification for retaining the identifiers or as required by law.*

[X] Will be retained for seven years after all children enrolled in the study reach the age of majority [age 18 in California] as this study includes children.

[ ] Will be retained 25 years after study closure as this study involves in vitro fertilization studies or research involving pregnant women.

[ ] Will be retained for two years after an approved marketing application, as this is a FDA regulated study. If approval is not received, the research records will be kept for 2 years after the investigation is discontinued and the FDA is notified.

[ ] Other: <Type here>

D. Photographs, Audio/Video Recordings Retention

1. If subject identifiable audio or video recordings will be collected, specify the timeframe for the transcription and describe retention/destruction plans.

[X] Not applicable: Subject identifiable audio/video recordings will not be collected.

[ ] Audio or video recordings transcribed; specify time frame: <Type here>

[ ] Audio or video recordings will be maintained; specify time frame: <Type here>

[ ] Audio or video recordings maintained indefinitely; provide the rationale: <Type here>

[ ] Audio or video recordings destroyed; specify time frame: <Type here>

2. If subject identifiable photographs will be collected, describe retention/destruction plans**.**

[X] Not applicable: Subject identifiable photographs will not be collected.

[ ] Photographs will be maintained; specify time frame: <Type here>

[ ] Photographs maintained indefinitely; provide the rationale: <Type here>

[ ] Photographs destroyed; specify time frame: <Type here>

E. Certificate of Confidentiality

1. Indicate whether a Certificate of Confidentiality (COC) has been or will be requested.

[X] Not applicable: No COC has been requested for this study.

[ ] A COC will be or has been requested for this study. *The COC application must be submitted to the IRB staff for review after IRB approval.*

[ ] A COC has been obtained for this study. The expiration date of this COC is: <Type here>

Provide a copy of the COC Approval Letter.

2. Explain in what situations the UCI study team will disclose identifiable private information protected by a COC.

<Type here>