



iovera^o USE IN HEADACHE DISORDERS REQUEST FOR PROPOSAL

BACKGROUND

Pacira BioSciences, Inc. is committed to supporting independent research initiatives that foster the advancement of scientific and clinical information and improve patient care. To that end, Pacira extends a new grant opportunity by way of a request for proposal (RFP) focused on research trials that seek to result in optimized patient care. These research trials will provide valued information on the efficacy of the company's marketed products.

All proposals are reviewed for scientific merit, innovation, clinical impact on patients, and compliance with Pacira policy and requirements. If you are interested in applying for support of a research proposal, please review the submission process and apply online by clicking [here](#). Pacira will review and consider all relevant research proposals but is not obligated to provide support for any research proposals received.

While the Pacira Grant Review Committee (PGRC) reviews all research proposals, the principal investigator (and ultimately the grantee) is responsible for the design, implementation, and conduct of the independent initiative supported by the grant. Pacira will not be involved in the conduct or monitoring of the proposed trial, including drafting the research study protocol.

PURPOSE AND INTENT

Pacira issues this RFP for a prospective clinical research study evaluating the iovera^o system to treat headache disorders. This RFP is funded through the investigator-initiated trial (IIT) grant program at Pacira. Funding is available for the fiscal year 2022 and may be extended at the company's discretion.

ELIGIBILITY

To be eligible for consideration, the requestor must be an independent third party. Examples of appropriate requestors include, but are not limited to:

- Academic medical centers
- Healthcare institutions, including private practice settings and ambulatory care facilities

Note: If the research involves multiple departments within an institution and/or between different institutions/organizations/associations, please note each institution's role in the grant application.

TARGET AUDIENCE

Health care professionals involved in the care of patients with headache disorders.

TIMELINE

The RFP application will remain open until the grant has been awarded.

Note: The PGRC may award multiple awards at its discretion.

BURDEN

Epidemiology of headache disorders

Headache disorders are characterized as primary (i.e., headache with no known underlying cause) or secondary (ie, headache with a known underlying cause such as inflammation). According to the International Classification of Headache Disorders 3rd edition (ICHD-3), common types of primary headaches include migraine, tension-type headaches, and trigeminal autonomic cephalalgias (e.g., cluster headaches) (1).

The lifetime prevalence of headache disorders is reported to be 96%, with a female predominance and tension-type headache is approximately 40% and migraine 10% (2). Headache disorders are also among the most prevalent and disabling conditions worldwide (3, 4). Almost three billion individuals were estimated to have a migraine or tension-type headache with migraine headache causing 45.1 million years lived with disability (YLDs) and tension-type headaches 7.2 million YLDs globally in 2016 (4).

Economic impact of headache disorders

The economic impact of headache disorders are significant with total indirect costs estimated to exceed \$19.3 billion USD (5). The national burden of illness, mostly attributed to absenteeism was estimated to be \$12 billion USD (6). Consequently, those with headache disorder experience significantly reduced work productivity and greater health care costs when compared to the general population.

Management of headache disorders

Current treatment options for headache disorders include medications with the main drug classes including analgesics, anti-emetics, specific anti-migraine medications, and prophylactic medications. Non-drug therapies include biofeedback, relaxation therapies, cognitive behavioral therapy, physiotherapy, acupuncture, and electrostimulation (7).

Cryoneurolysis has been applied in a number of pain disorders including occipital and trigeminal neuralgia. Kim et al. (2015) reported outcomes of 38 patients who received local anesthetics in addition to cryoneurolysis to the occipital nerve (ON) to treat occipital neuralgia who experienced $\geq 50\%$ benefit following local anesthetic injections (8). The average improvement of pain relief with cryoneurolysis was 57.9% with an average duration of 6.1 months.

Stogicza et al. (2019) reported on the safety of an ultrasound-guided technique to target the greater ON with cryoneurolysis (9). The authors had performed this procedure more than 50 times in their clinic and reported no major complications and rare minor complications (post-procedure soreness), which resolved spontaneously in 1 to 3 weeks (9).

The results of a recently published randomized controlled trial comparing cryoneurolysis to steroid and local anesthetic block found that although not statically significant, cryoneurolysis provided a more prolonged effect (10). While there is a scarcity of evidence for cryoneurolysis for headache disorders, the reported outcomes are worth exploring further.

SCOPE OF WORK

The successful applicant will prepare a research proposal for a feasibility study that adequately addresses the management of headache disorders using the iovera^o system.

The study proposal should focus on patients with primary or secondary headaches (ie, cluster headache, migraine headache, tension headache, cervicogenic headache, occipital neuralgia). The study will be a case series evaluating patients before and after cryoneurolysis treatment for up to six months with a 3-month enrollment period. Outcomes may include pain (eg, NRS, VAS), pain medication consumption, headache recurrence, disability/impairment, and patient reported outcomes (eg, satisfaction, quality of life).

Grant recipients will receive training on proper use of the iovera^o system and agree to provide data to Pacira at the time of study completion.

The Pacira Grant Review Committee will consider funding awards inclusive of indirect costs for the conduct of the study based on a budget within fair market value.

PROPOSAL SUBMISSION REQUIREMENTS

All requestors must submit a written proposal that addresses the following topics and includes required supporting documentation including:

- Organization's contact information
- Primary contact name, title, address, phone, and email
- Describe the organization's current activities relevant to the proposal including current standard of care and patient volume
- Project description and specific proposal objectives
- Available data/information relevant to proposal submission (eg, pilot data)
- Describe how the proposal will improve patient care in alignment with grant objectives
- Proposed timeline for completion with associated deliverables. If possible, attach a flow chart outlining the operational steps of the proposed program.
- Proposed budget that is within fair market value and reflects the scope of responsibilities to accomplish the goals of this project. No funding match is required; however, requestors will need to identify any other sources of funding, both in-kind and monetary, that will be used.

To apply for a grant, please click [here](#).

A letter of intent on organizational letterhead should be included. The letter of intent should be single-spaced and not exceed four pages (not including the reference page).

The RFP process

Pacira maintains a stepwise process for review of RFPs. In brief, after registering on the online grant portal, the principal investigator submits a brief concept proposal and if accepted after a review by the PGRC, will be invited to submit a full proposal. Details on brief and full proposal contents are below.

Brief concept proposal:

A brief concept proposal must contain an adequate amount of information for the PGRC to determine interest in requesting a full study proposal. When submitting a brief concept proposal, the following information will be requested (if applicable):

- Principal investigator contact information
- Brief background for the study
- Method of administration of the marketed product
- Primary study objectives/endpoints
- Estimated study timelines
- Estimated total study budget
- Estimated study drug or device(s)
- Preliminary grant request: funding, drug, device, or a combination thereof
- Experience as sponsor-investigator
- Letter of intent on the requesting institution's letterhead
- Curriculum vitae from the principal investigator dated within the last calendar year

The PGRC will review all concept proposals for scientific merit, innovation, clinical importance/potential impact on patients, and compliance with company policy and requirements. The PGRC will extend contingent approval to individual applicants to proceed to the second step of the process, which is the submission of a full study proposal. Applicants will be notified of the PGRC's decision via email, and the status will also be available on the portal. Please note that an invitation to submit a full study proposal does not guarantee the approval of funding.

Full study proposal:

A full study proposal submission must contain enough detail about the research study to enable the PGRC to make an evaluation on support. When submitting a full study proposal, the following information will be requested (if applicable):

- Principal investigator contact information
- Study type: non-clinical or clinical
- Objectives: primary and secondary
- Key inclusion and exclusion criteria
- Study design
- Efficacy variables/measures
- Safety variables/measures
- Adverse event/Serious adverse event reporting
- Decision points/statistical methods/interim analysis
- Study product regimens
- Ethical rationale for the study



- Study deliverables
- Value of the study
- Applicable scientific references
- Publication plan
- Research Setting: single-site or multi-site
- Detailed budget
- Grant request: funding, product, or a combination thereof

Pacira reserves the right to reconsider its support if the research objectives outlined in the final protocol are materially different from the approved full study proposal. Pacira will not compensate for any work performed before the execution of a final contract or for impermissible costs, which include:

- Construction funds to build new facilities
- General education and training activities
- Hiring of staff that are not dedicated to the proposed research study
- Study to involve new investigational products or devices
- Studies that are designed to generate business for Pacira
- Purchase of capital equipment unrelated to the study or that would generate revenue
- Requests for support for ongoing or new research without an associated research study protocol
- Start-up funds to establish new clinical or research programs or to expand existing programs
- Support for ongoing clinical programs that are part of an organization's routine operations

PACIRA CONTACT INFORMATION

If you have questions regarding this RFP, please email grants@pacira.com and include in the subject line *headache RFP*.

CONFIDENTIALITY

This Request for Proposal constitutes the confidential and proprietary information of Pacira BioSciences Inc. and its respective subsidiaries and may not, in whole or in part, be copied, reproduced, or otherwise used in any manner whatsoever without the prior express written permission of Pacira. All information provided herein is proprietary to Pacira and is to be used only by your company in its response hereto. Any other use or communication of this information is prohibited.

REFERENCES

1. Yang S, Orlova Y, Lipe A, Boren M, Hincapie-Castillo JM, Park H, et al. Trends in the Management of Headache Disorders in US Emergency Departments: Analysis of 2007-2018 National Hospital Ambulatory Medical Care Survey Data. *J Clin Med.* 2022;11(5).
2. Rizzoli P, Mullally WJ. Headache. *The American journal of medicine.* 2018;131(1):17-24.
3. Stovner LJ, Hagen K, Linde M, Steiner TJ. The global prevalence of headache: an update, with analysis of the influences of methodological factors on prevalence estimates. *The journal of headache and pain.* 2022;23(1):34.
4. Collaborators GBDH. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology.* 2018;17(11):954-76.
5. Yucel A, Thach A, Kumar S, Loden C, Bensink M, Goldfarb N. Estimating the economic burden of migraine on US employers. *Am J Manag Care.* 2020;26(12):e403-e8.
6. Hawkins K, Wang S, Rupnow MF. Indirect cost burden of migraine in the United States. *Journal of occupational and environmental medicine.* 2007;49(4):368-74.
7. Steiner TJ, Jensen R, Katsarava Z, Linde M, MacGregor EA, Osipova V, et al. Aids to management of headache disorders in primary care (2nd edition) : on behalf of the European Headache Federation and Lifting The Burden: the Global Campaign against Headache. *The journal of headache and pain.* 2019;20(1):57.
8. Kim CH, Hu W, Gao J, Dragan K, Whealton T, Julian C. Cryoablation for the treatment of occipital neuralgia. *Pain physician.* 2015;18(3):E363-8.
9. Stogicza A, Trescot A, Rabago D. New Technique for Cryoneuroablation of the Proximal Greater Occipital Nerve. *Pain Pract.* 2019;19(6):594-601.
10. Kvarstein G, Hogstrom H, Allen SM, Rosland JH. Cryoneurolysis for cervicogenic headache - a double blinded randomized controlled study. *Scand J Pain.* 2019.