



## **Opioid-Sparing Approaches in the Management of Knee OA Pain**

### *Request for Proposal*

#### **Purpose and Intent**

Flexion Therapeutics, Inc. issues this RFP for a prospective clinical research study evaluating whether the use of triamcinolone acetonide extended-release (TA-ER) has the potential to diminish, delay or avoid opioid use (broader termed “opioid-sparing”) in patients with painful knee osteoarthritis (OA).

#### **Target Audience**

Healthcare professionals involved in the care of patients with knee osteoarthritis.

#### **Timeline**

The RFP application will remain open through 2021.

#### **Background**

Despite mounting evidence suggesting opioids are minimally effective in the management of knee OA pain, coupled with the well-established evidence concerning the risks associated with opioid use, the rates of long-term use of opioids in the setting of OA remain high.<sup>1</sup> In 2019, Desai et al., published opioid utilization results from a large observational cohort study of Medicare enrollees with osteoarthritis undergoing Total Joint Replacement (TJR) of knee or hip.<sup>2</sup> The authors reported that one in six patients used long-term prescription opioids ( $\geq 90$  days) for pain management in the year leading up to the TJR, with an average duration of approximately 7 months. Further, nearly 20% of the long-term users consumed an average daily dose of

≥50 MME, a range that is identified by the recent CDC guidelines as potentially imparting a high risk of opioid-related harms.<sup>3</sup>

The 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee<sup>4</sup> echoes concerns over the use of non-tramadol opioid use noting that “...evidence suggests very modest benefits of long-term opioid therapy and a high risk of toxicity and dependence. Use of the lowest possible doses for the shortest possible length of time is prudent, particularly since a recent systematic review and meta-analysis suggests that less pain relief occurs during longer trials in the treatment of non-cancer chronic pain.<sup>5</sup>”

Based on the above, there remains an unmet need with respect to finding non-opioid analgesic treatment strategies as a means of eliminating and/or shorting the time and/or dose associated with opioid use in management of osteoarthritis pain.

### **Scope of Work**

The successful applicant will prepare a research proposal that explores one or more approaches to developing and studying opioid-sparing outcomes in the setting of painful knee osteoarthritis (OA). The proposal should consider how the incorporation of TA-ER into the management of painful knee OA could potentially aid in achieving defined opioid-sparing outcome(s). The opioid-sparing outcome(s) could include potential for reducing, delaying and/or avoiding opioids for purposes of managing knee OA pain. The study proposal should include a focus on patients with primary knee osteoarthritis who are either receiving opioids and/or considering initiating opioids to manage their knee OA pain. However, patients currently receiving opioids or those planned to receive opioids for a chronic pain condition related to another comorbidity and/or injury should be excluded from any study proposal. As any opioid-sparing intervention should not result in unacceptable increases in pain or decreases in health-related quality of life (HRQoL) to the patient, the applicant must therefore include adequate measures of pain, patient-reported outcome measures (PROMs), and to be taken at clinically reasonable time intervals.

Flexion’s IIR review committee will consider funding awards inclusive of indirect costs for the conduct of the study based on a budget within fair market value.

Your concept proposal will be considered by Flexion’s cross-functional research committee that meets routinely to review IIR proposals. Flexion may make suggestions to improve the scientific merit of the proposal and enhance consistency with Flexion’s support approval criteria. The principal investigator will have full and final discretion and responsibility for all aspects of the study design, implementation, data analysis, and data dissemination, including compliance with all laws and regulations applicable to research sponsors. The terms under which Flexion will provide support must be contained in a written agreement. Flexion provides no guarantees that research committee will provide support for your proposal.

TA-ER is marketed under the tradename ZILRETTA. Please see full Prescribing Information at [ZILRETTALabel.com](http://ZILRETTALabel.com)

The information within this RFP is not intended to promote any use of the product that is inconsistent with its approved labeling, nor does this RFP provide comprehensive information regarding TA-ER.

## References

1. Krebs EE, Gravely A, Nugent S, et al. Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial. *JAMA : the journal of the American Medical Association* 2018;319:872-882.
2. Desai RJ, Jin Y, Franklin PD, Lee YC, Bateman BT, Lii J, Solomon DH, Katz JN, Kim SC. Association of Geography and Access to Health Care Providers With Long-Term Prescription Opioid Use in Medicare Patients With Severe Osteoarthritis: A Cohort Study. *Arthritis Rheumatol*. 2019 May;71(5):712-721. doi: 10.1002/art.40834. Epub 2019 Apr 2. PMID: 30688044; PMCID: PMC6483834.
3. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. *JAMA*. 2016;315(15):1624-45. [PubMed: 26977696]
4. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, Callahan L, Copenhaver C, Dodge C, Felson D, Gellar K, Harvey WF, Hawker G, Herzig E, Kwoh CK, Nelson AE, Samuels J, Scanzello C, White D, Wise B, Altman RD, DiRenzo D, Fontanarosa J, Giradi G, Ishimori M, Misra D, Shah AA, Shmagel AK, Thoma LM, Turgunbaev M, Turner AS, Reston J. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Care Res (Hoboken)*. 2020 Feb;72(2):149-162. doi: 10.1002/acr.24131. Epub 2020 Jan 6. PMID: 31908149.
5. Busse JW, Wang L, Kamaleldin M, Craigie S, Riva JJ, Montoya L, et al. Opioids for chronic noncancer pain: a systematic review and meta-analysis. *JAMA* 2018;320:2448-60.