Tools to Better Characterize the Stiffness Component of Knee Osteoarthritis

Request for Proposal

Purpose and Intent

Flexion Therapeutics, Inc. issues this RFP for a prospective clinical research study to further evaluate a tool(s) to better characterize the stiffness component of knee osteoarthritis (OA) and improved understanding of the treatment effect of triamcinolone acetonide extended release (TA-ER) on knee stiffness.

Target Audience

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

Timeline

The RFP application will remain open through 2021.

Background

Arthritis is a serious health crisis. CDC estimates that 1 in 4 (or 54.4 million) US adults have some form of doctor-diagnosed arthritis, a figure that is projected to reach 78 million by the year 2040.[1] While there are estimated to be more than 100 types of arthritis, osteoarthritis (OA) is the most common form of arthritis, affecting 32.5 million US adults.[2] People with OA experience greater pain, fatigue, levels of disability, and activity limitations than people of their comparable age.[3] While arthritis pain is extremely individualized,

severe joint pain is not uncommon. Recent estimates suggest that one-fourth of adults with arthritis experience severe joint pain, characterized by a score of 7 or greater on the 0-10 pain scale.[4]

Almost 44% of people with arthritis have "arthritis-attributable activity limitations," defined as self-reported limitations in "usual activities" because of arthritis symptoms.[1] By 2040, 11.4% of all adults will experience arthritis-attributable activity limitations.[5] Patients with OA also experience work limitations.[1]

Work Limitations[1]

- 33% of adults with arthritis find stooping, bending, or kneeling very difficult.
- 20% cannot or find it very difficult to walk 3 blocks or push/pull large objects.
- People with OA (working age) experience lower employment rates than those without OA. Research suggests that arthritis-related activity limitations might contribute to this lack of employment.

Pain and stiffness, the primary symptomatic manifestations of knee osteoarthritis (OA), contribute substantially to functional disability.[6] Persons with knee OA report reduced joint stability during activities of daily living, and this instability interferes with their ability to function. [7] To overcome instability and joint laxity with advancing osteoarthritis, persons with knee OA may utilize higher antagonistic muscle activity and develop higher dynamic joint stiffness during walking.[8]

While stiffness is a sensation of decreased ease in moving the joint, those with knee OA often describe vague muscle aches as "stiffness." Stiffness may be prominent even when joint pain is not. Mild morning stiffness is common in osteoarthritis and often goes away after just a few minutes of activity. A similar type of stiffness is sometimes experienced during the day, after resting the joint for an hour or so. There are various patient-reported outcome/PRO measures assessing stiffness, but the current PROs are limited in content and characterization as it relates to the different dimensions of stiffness. Most importantly, the role of stiffness and its impact on OA patients' lives and responsiveness to knee OA treatment remains elusive.

TA-ER is an extended-release synthetic corticosteroid indicated as an intra-articular injection for the management of osteoarthritis pain of the knee. FDA approved since 2017, TA-ER has been evaluated in patients with OA knee pain utilizing multiple patient-reported outcomes, including all three subscales of the Western Ontario and McMaster University (WOMAC) osteoarthritis index, including stiffness. In addition to the WOMAC scale, TA-ER effects on quality of life (QoL) have also been assessed via the KOOS-12, a knee-specific 12-item measure derived from the 42-item Knee injury and Osteoarthritis Outcome Score (KOOS). KOOS-12 contains four KOOS Pain items, four KOOS Function items, and four KOOS quality of life (QOL) items. The KOOS-12 PRO is intended to elicit people's opinions about the difficulties they experience due to problems with their knee.

TA-ER was evaluated in a pivotal 24-week, randomized, double-blind, phase III clinical trial (*n* = 484), and the primary endpoint was change from baseline at Month 3 in weekly mean average daily pain (ADP) intensity scores vs. placebo. Prespecified exploratory endpoints included WOMAC-B stiffness relative to placebo and conventional triamcinolone acetonide (TAcs). To review the results of this study, please see the Conaghan et al **publication**. [9] Clinical efficacy and safety of a single IA injection of TA-ER were also evaluated in a phase 2 study of primary efficacy (*n* = 228), and a phase 2b (*n* = 306) dose-confirmation study. To review the results of these studies, please see the Bodick et al **publication** and Conaghan et al **publication**, respectively. [10,11]

Furthermore, WOMAC-B stiffness was also evaluated as an exploratory efficacy endpoint in a 52-week, phase IIIb, single-arm, open-label safety trial of repeat administration of TA-ER in patients with knee OA pain. To review the results of this study, please see the Spitzer et al **publication**. [12]

Scope of Work

The successful applicant will prepare a research proposal that explores and further characterizes the stiffness component of knee OA and responsiveness to TA-ER within 6 months to 1 year. Study evaluations may include any of the following:

- Stiffness and its clinical dimensions in OA
- Impact of stiffness on OA patients' lives with respect to pain, function, psychosocial, quality of life, work and home productivity
- Characterize the stiffness component with knee OA with responsiveness to TA-ER in terms of overall improvement

The study proposal should include a focus on patients (≥ 40 yoa) with primary knee osteoarthritis. Proposals should clearly define the osteoarthritis patient population to be included (i.e. radiographic Kellgren-Lawrence grade of osteoarthritis, history of synovitis and/or effusion, etc.). Patients diagnosed with any other type of arthritis or other musculoskeletal conditions should be excluded from any study proposal.

Proposals focused on the dynamic joint stiffness (DJS) associated with gait biomechanics will not be accepted.[8]

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 the research committee will provide support for your proposal.

TA-ER is marketed under the tradename ZILRETTA. Please see the next page for indication and Select Important Safety Information for ZILRETTA.

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.

Indication and Select Important Safety Information

Indication: ZILRETTA is indicated as an intra-articular injection for the management of osteoarthritis pain of the knee.
Limitation of Use: The efficacy and safety of repeat administration of ZILRETTA have not been demonstrated.

Contraindication: ZILRETTA is contraindicated in patients who are hypersensitive to triamcinolone acetonide, corticosteroids or any components of the product.

Warnings and Precautions:

- **Intra-articular Use Only:** ZILRETTA has not been evaluated and should not be administered by epidural, intrathecal, intravenous, intraocular, intramuscular, intradermal, or subcutaneous routes. ZILRETTA should not be considered safe for epidural or intrathecal administration.

- **Serious Neurologic Adverse Reactions with Epidural and Intrathecal Administration:** Serious neurologic events have been reported following epidural or intrathecal corticosteroid administration. Corticosteroids are not approved for this use.

- **Hypersensitivity reactions:** Serious reactions have been reported with triamcinolone acetonide injection. Institute appropriate care if an anaphylactic reaction occurs.

- **Joint infection and damage:** A marked increase in joint pain, joint swelling, restricted motion, fever and malaise may suggest septic arthritis. If this occurs, conduct appropriate evaluation and if confirmed, institute appropriate antimicrobial treatment.

- Other warnings and precautions for ZILRETTA and corticosteroids as a class include, **alterations in endocrine function, cardiovascular and renal effects, increased intraocular pressure, GI perforation, alterations in bone density** and **behavior and mood disturbances**.

Adverse Reactions: The most commonly reported adverse reactions (incidence ≥1%) in clinical studies included sinusitis, cough, and contusions.

Please see ZILRETTALabel.com for full Prescribing Information.

References

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2. Helmick CG and Watkins-Castillo SI. United States Bone and Joint Initiative. The Burden of Musculoskeletal Diseases in the United States (BMUS). In: In. Fourth ed. Rosemont, IL. 2018: Available at https://www.boneandjointburden.org/fourth-edition. Accessed November 21, 2020.
3. Osteoarthritis Research Society International. Osteoarthritis: A Serious Disease, submitted to the U.S. Food and Drug Administration. 2016. https://oarsi.org/sites/default/files/library/2018/pdf/oarsi_white_paper_oa_serious_disease121416_1.pdf Accessed November 21, 2020.
4. Barbour KE, Boring M, Helmick CG, Murphy LB, Qin J. Prevalence of Severe Joint Pain Among Adults with Doctor-Diagnosed Arthritis – United States, 2002-2014. *MMWR Morb Mortal Wkly Rep.* 2016;65(39):1052-1056.
5. Hootman JM, Helmick CG, Barbour KE, Theis KA, Boring MA. Updated projected prevalence of self-reported doctor-diagnosed arthritis and arthritis-attributable activity limitation among US adults, 2015-2040. *Arthritis Rheumatol*. 2016;68(7):1582–1587. doi: 10.1002/art.39692. PubMed PMID: 27015600.
6. Thakral M, Shi L, Shmerling RH, Bean JF, Leveille SG. A Stiff Price to Pay: Does Joint Stiffness Predict Disability in an Older Population? J Am Geriatr Soc. 2014 October; 62(10): 1891–1899.
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9. Conaghan PG, Hunter DJ, Cohen SB, et al. Effects of a single intra-articular injection of a microsphere formulation of triamcinolone acetonide on knee osteoarthritis pain: a double-blinded, randomized, placebo-controlled, multinational study. *J Bone Jt Surg Am*. 2018;100(8):666–677.
10. Bodick N, Lufkin J, Willwerth C, et al. An intra-articular, extended-release formulation of triamcinolone acetonide prolongs and amplifies analgesic effect in patients with osteoarthritis of the knee: a randomized clinical trial. *J Bone Jt Surg Am.* 2015;97(11):877–888.
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12. Spitzer AI, Richmond JC, Kraus VB, et al. Safety and efficacy of repeat administration of triamcinolone acetonide extended-release in osteoarthritis of the knee: a phase 3b, open-label study. *Rheumatol Ther.* 2019;6(1):109-124.