Treating Knee Osteoarthritis with TA-ER in People with Type 2 Diabetes Mellitus

Request for Proposal

Purpose and Intent

Flexion Therapeutics, Inc. issues this request for proposals (RFP) for a prospective clinical research study to adequately address the impact of triamcinolone acetonide-extended release (TA-ER) on the management of symptomatic osteoarthritis (OA) in patients with Type 2 Diabetes Mellitus (T2DM).

Target Audience

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

Timeline

The RFP application will remain open through 2021.

Background

People with type 2 diabetes (T2DM) have an overall increased prevalence of osteoarthritis (OA) and this has been well described in the literature.[1,2,3] OA is the leading cause of disability worldwide.[4] As OA is a chronic, progressive and painful condition, it can lead to a decrease in physical activity which can worsen T2DM and its associated comorbidities.[3,5]

The management of OA is multifactorial and can include non-pharmacological therapies such as physical activity and weight loss, in addition to medications like NSAIDs, acetaminophen, and/or intra-articular corticosteroid (IACS) injection therapy.[6] Intra-articular (IA) injection of corticosteroids is used to manage pain and inflammation associated with OA of the knee. However, systemic absorption of corticosteroids like triamcinolone acetonide (TA) following administration may lead to side effects such as blood glucose elevation in diabetic patients. [7] One study has demonstrated that 1 to 2 days after an IACS injection, the mean glucose peak can climb to 300mg/ml and remain elevated for up to 5 to 7 days in individuals with well-controlled T2DM (HbA1C < 7%).[7] There is an unmet need to find safe and effective treatments of OA in patients with T2DM.

TA-ER is an extended-release formulation of triamcinolone acetonide delivering 32 mg. TA-ER has been studied in multiple phase 2 and 3 studies. An evaluation of pharmacokinetics in patients with OA of the knee demonstrated that a single IA injection of TA-ER reduced systemic exposure to TA relative to TAcs (triamcinolone acetonide crystalline suspension).[8] The clinical relevance of this plasma exposure information is unknown.

A phase 2, double-blind, randomized (1:1) parallel-group, single-dose, multicenter, pharmacodynamic study was conducted in which patients (n= 33) with controlled T2DM (HbA1C 6.5-9% and managed with 1-2 oral hypoglycemic agents- no injectable therapy) and knee OA were randomized to either a single intra-articular injection of TA-ER 32 mg or TAcs 40 mg.[9] This study was designed to assess the effects of a single intra-articular/IA injection on average blood glucose levels measured with continuous glucose monitoring over a 6-day period (72 hours prior to dosing through 72 hours after dosing).[9] To review the results of this study, please see the Russell et al publication.[9]

While TA-ER has been evaluated in patients with T2DM, the efficacy of TA-ER in this patient population has not been evaluated.

Scope of Work

The study proposal should focus on adults > 40 years of age with primary knee osteoarthritis and Type 2 diabetes mellitus with an HbA1C $\leq$ 9.0%. Evaluation may include any of the following, in ranked order of priority:

- assessment of pain, stiffness and/or function post TA-ER treatment
- performance improvement post-TA-ER injection
- patient reported outcomes such as quality of life, sleep, or activity level
- impact of treatment on T2D measures or co-morbidity measure
- additional biomarkers and/or patient characteristics distinguishing OA phenotypes in patients with Type 2 diabetes

Proposals with assessments of TA-ER treatment in patients with Type 1, Type 1.5 or Gestational Diabetes will not be accepted.

Study proposals assessing outcomes beyond six months will not be considered.

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 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

1. Louati K, Vidal C, Berenbaum F, Sellam J. Association between diabetes mellitus and osteoarthritis: systematic literature review and meta-analysis. *RMD Open*. 2015;1(1):e000077.
2. Vina ER, Kwoh CK. Epidemiology of osteoarthritis: literature update. *Curr Opin Rheumatol.* 2018;30(2):160-167.
3. Williams MF, London DA, Husni EM, Navaneethan S, Kashyap SR. Type 2 diabetes and osteoarthritis: a systematic review and meta-analysis. *J Diabetes Complications.* 2016;30(5):944-950.26.
4. Puenpatom RA, Victor TW. Increased prevalence of metabolic syndrome in individuals with osteoarthritis: an analysis of NHANES III data. *Postgrad Med*. 2009;121(6):9-20.
5. Kuusalo L, Felson DT, Wang N, Lewis CE, Torner J, Nevitt MC, Neogi T; Multicenter Osteoarthritis Study Group. Metabolic osteoarthritis - relation of diabetes and cardiovascular disease with knee osteoarthritis. *Osteoarthritis Cartilage*. 2021 Feb;29(2):230-234.
6. Katz JN, Arant KR, Loeser RF. Diagnosis and Treatment of Hip and Knee Osteoarthritis: A Review. *JAMA*. 2021;325(6):568–578.
7. Habib G, Safia A. The effect of intra-articular injection of betamethasone acetate/betamethasone sodium phosphate on blood glucose levels in controlled diabetic patients with symptomatic osteoarthritis of the knee. *Clin Rheumatol*. 2009;28(1):85-87.
8. Kraus VB, Conaghan PG, Aazami HA, et al.. Synovial and systemic pharmacokinetics (PK) of triamcinolone acetonide (TA) following intra-articular (IA) injection of an extended-release microsphere-based formulation (FX006) or standard crystalline suspension in patients with knee osteoarthritis (OA). *Osteoarthritis and Cartilage*. 2018;26(1):34-42
9. Russell SJ, Sala R, Conaghan PG, Habib G, Vo Q, Manning R, Kivitz A, Davis Y, Lufkin J, Johnson JR, Kelley S, Bodick N. Triamcinolone acetonide extended-release in patients with osteoarthritis and type 2 diabetes: a randomized, phase 2 study. *Rheumatol*. 2018;57:2235-2241.