CLINICAL STUDY PROTOCOL

A Phase 2, **R**andomized, Double-Blind, Pl**a**cebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of FX006 in Patie**n**ts With **G**lenohumeral Osteoarthritis or Shoulde**r** Adhesive Capsulitis **(RANGE)**

Investigational Product: FX006

Protocol Number: FX006-2018-016

Sponsor:

Flexion Therapeutics, Inc.

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SIGNATURE PAGE

STUDY TITLE: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of FX006 in Patients With Glenohumeral Osteoarthritis or Shoulder Adhesive Capsulitis

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature

Date

16 Dec 2019

Scott Kelley, MD
Chief Medical Officer
Flexion Therapeutics, Inc.

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Flexion Therapeutics, Inc. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study medication and study procedures. I will let them know that this information is confidential and proprietary to Flexion Therapeutics, Inc. and that it may not be further disclosed to third parties. I understand that the study may be terminated, or enrollment suspended at any time by Flexion Therapeutics, Inc., with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board, and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of FX006 in Patients With Glenohumeral Osteoarthritis or Shoulder Adhesive Capsulitis

PROTOCOL NUMBER: FX006-2018-016

INVESTIGATIONAL PRODUCT: FX006

PHASE: 2

INDICATIONS: Shoulder pain due to glenohumeral osteoarthritis (OA) and shoulder pain due to adhesive capsulitis (AC)

OBJECTIVES:

The primary objective of this study is to assess the efficacy of FX006 on pain following an intra-articular (IA) injection in patients with glenohumeral OA or shoulder AC.

The secondary objectives of this study are to assess the efficacy of FX006 on pain, disability, function, and global impression of change in patients with glenohumeral OA or shoulder AC, and to assess the safety of FX006 in patients with glenohumeral OA or shoulder AC.

The exploratory objectives of this study are to assess additional measures of pain, disability, function, QOL, rescue medication consumption, and proportion of responders at varying timepoints over the course of the study.

POPULATIONS:

The populations for this study are males or females, 35 to 80 years of age, inclusive, with painful symptoms associated with OA of the index glenohumeral joint for ≥3 months prior to the Screening Visit and X-ray confirmation of Grade 2 or 3 OA based on the Samilson-Prieto classification system; and male or females, 35 to 80 years of age, inclusive, with pain associated with shoulder AC of the index joint for ≥1 month but ≤6 months prior to the Screening Visit, more than 20% (25% if dominant shoulder is the index shoulder) loss of passive range of the rotation arc (external and internal rotation) of glenohumeral movement, measured with the patient in supine or sitting position and the shoulder elevated to 45 degrees, compared with the contralateral shoulder, and no X-ray evidence of OA.

STUDY DESIGN AND DURATION:

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in separate cohorts of patients with a documented history of either glenohumeral OA or shoulder AC. Glenohumeral OA and shoulder AC patients will be randomized to 1 of 2 treatment groups within their shoulder condition in a 1:1 ratio to receive a single IA injection of either 32 mg FX006 or placebo (saline) to the index shoulder with a 24-week Treatment Evaluation Period. Glenohumeral OA patients will be stratified by Baseline average daily shoulder pain with

movement score according to the following classifications: 5.0 to <7.0 or ≥7.0 to 9.0 (0 to 10 numeric rating scale [NRS]). Shoulder AC patients will be stratified by Baseline average daily shoulder pain with movement score according to the following classifications: 5.0 to <7.0 or ≥7.0 to 9.0 (0 to 10 NRS), and by pain duration since onset at Screening (1 to 3 months, inclusive, or >3 to ≤6 months). A Home Exercise Program will be implemented 3 days following injection for shoulder AC patients.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

FX006 is an extended-release formulation of triamcinolone acetonide in 75:25 poly (lactic-co-glycolic acid) microspheres. FX006 will be supplied as a sterile, white to off-white powder in a single unit dose 5 mL vial and reconstituted in 5 mL of a diluent containing an isotonic, sterile aqueous solution of sodium chloride (NaCl; 0.9% weight by weight [w/w]) carboxymethylcellulose sodium (0.5% w/w), and polysorbate-80 (0.1% w/w) to form a suspension prior to IA injection. The placebo is sterile normal saline (NaCl). FX006 or placebo will be administered as a 5 mL IA injection into the index glenohumeral joint under ultrasound guidance per the injection procedure.

EFFICACY VARIABLES AND ENDPOINTS:

The efficacy variables include the average daily shoulder pain with movement (NRS score); the Shoulder Pain and Disability Index (SPADI) pain subscale, disability subscale, and total score; the American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form (ASES) subscales for pain, function, and total; the Patient Global Impression of Change (PGIC) score; active and passive ROM; the EuroQol 5 Dimensions 5 Levels questionnaire (EQ-5D-5L); and responder status.

The primary efficacy endpoint for each of the shoulder conditions (glenohumeral OA and shoulder AC) in this study is the area under the curve (AUC) of the change from Baseline in the weekly mean of the average daily shoulder pain with movement score over 8 weeks for FX006 compared to placebo.

The secondary efficacy endpoints comparing FX006 to placebo for each of the shoulder conditions (glenohumeral OA and shoulder AC) in this study include the following:

- Change from Baseline in the weekly mean of the average daily shoulder pain with movement score at Week 12
- Change from Baseline in the SPADI pain subscale at Week 12
- Change from Baseline in the SPADI disability subscale at Week 12
- The PGIC score at Week 12
- Change from Baseline in the ROM of external rotation at Week 12

The exploratory efficacy endpoints comparing FX006 to placebo for each of the shoulder conditions (glenohumeral OA and shoulder AC) in this study include the following:

- AUC of change from Baseline in the weekly mean of the average daily shoulder pain with movement score over Weeks 4, 12, 16, 20, and 24

- AUC of change from Baseline in the SPADI pain subscale over Weeks 4, 8, 12, 16, 20, and 24
- AUC of change from Baseline in the SPADI disability subscale over Weeks 4, 8, 12, 16, 20, and 24
- Change from Baseline in the weekly mean of the average daily shoulder pain with movement score at Weeks 1, 4, 8, 16, 20, and 24
- Change from Baseline in the SPADI pain subscale at Weeks 1, 4, 8, 16, 20, and 24
- Change from Baseline in the SPADI disability subscale at Weeks 1, 4, 8, 16, 20, and 24
- Change from Baseline in the SPADI total score at Weeks 1, 4, 8, 12, 16, 20, and 24
- The PGIC score at Weeks 1, 4, 8, 16, 20, and 24
- Change from Baseline in the ROM of external and internal rotation, abduction and flexion at Weeks 4, 8, 16, 20, and 24
- Change from Baseline in the ROM of internal rotation, abduction and flexion at Week 12
- Change from Baseline in the ASES pain subscale at Weeks 1, 4, 8, 12, 16, 20, and 24
- Change from Baseline in the ASES disability subscale at Weeks 1, 4, 8, 12, 16, 20, and 24
- Change from Baseline in the ASES total score at Weeks 1, 4, 8, 12, 16, 20, and 24
- Percent of responders based on the SPADI at Weeks 1, 4, 8, 12, 16, 20, and 24
- Proportion of patients experiencing a ≥20%, ≥30%, or ≥50% decrease in the weekly mean of the average daily shoulder pain with movement score at Weeks 1, 4, 8, 12, 16, 20, and 24
- Change from Baseline in average weekly rescue medication use
- Change from Baseline in the average weekly Sleep Interference score
- Change from Baseline in the EQ-5D-5L at Weeks 1, 4, 8, 12, 16, 20, and 24

SAFETY VARIABLES:

The safety variables include adverse events, physical examinations, index shoulder examinations, vital signs, and clinical laboratory evaluations.

STATISTICAL ANALYSES:

Data collected in this study will be presented using summary tables, figures, and patient data listings. Summary tables will present data by treatment group and, if applicable, by time of collection. Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized by frequencies and percentages. Figures will be used to support the presentation of certain data. Sensitivity analyses may be performed to examine the effect of missing data, as well as the effect of Baseline imbalance, should it occur.

All confidence intervals, statistical tests, and resulting p-values will be reported as 2-sided. Multiplicity will be addressed by analyzing the key secondary endpoints sequentially in the order presented in the protocol, testing each endpoint at the nominal $\alpha = 0.05$, 2-sided level to ensure

overall type I error control at the 2-sided 0.05 level. Each shoulder condition will be analyzed completely separately. In general, the same analysis methods will be used for both shoulder conditions.

For each shoulder condition, the following populations are planned for this study:

- Full Analysis Set (FAS) Population: All patients who receive a complete dose of study medication and have Baseline and at least 1 post-dose efficacy endpoint assessment. The FAS Population will be used to examine efficacy for both the primary and secondary endpoints.
- Safety Population: All patients who receive at least 1 dose of study medication. The Safety Population will be used to assess safety and tolerability.
- Per Protocol Population: All patients in the FAS Population who complete the Week 24 visit with no major protocol deviations that may impact the evaluation of the primary efficacy endpoint based on blinded data prior to database lock.

All study analyses will be completed using analysis data sets that are derived from the Study Data Tabulation Model and follow the Clinical Data Interchange Standards Consortium Analysis Data Model architecture.

Covariates for efficacy analyses will include Baseline average daily shoulder pain with movement score, Baseline score for the endpoint, analysis site, and, for AC patients, pain duration since onset. Other covariates may also be explored.

SAMPLE SIZE DETERMINATION:

Approximately 250 patients will be randomized in a 1:1 ratio to either FX006 or placebo (approximately 136 patients with glenohumeral OA and approximately 114 patients with shoulder AC). Sample sizes were estimated to yield a statistically significant difference ($\alpha = 0.05$, 2-sided) between the FX006 and placebo groups in the average daily shoulder pain with movement score at Week 12 (the first secondary endpoint for each shoulder condition). For glenohumeral OA, the true difference between the groups was assumed to be 1, with a standard deviation of 2, based on data observed in knee OA studies of FX006 and taking into consideration the clinical significance of a 1-point difference between the treatment groups. For shoulder AC, the true difference between the groups was assumed to be 1.2, with a standard deviation of 2.1, based on a review of the existing literature. The primary endpoint analyzing the AUC for the weekly mean of the average daily shoulder pain with movement score over 8 weeks should, therefore, have >80% power to show a significant difference between the FX006 and placebo groups. As the 2 shoulder conditions (glenohumeral OA and shoulder AC) are combined into 1 protocol strictly for ease of administration, all statistical testing will be performed separately for each shoulder condition and the overall type I error rate will be controlled at the $\alpha = 0.05$ level within each shoulder condition.

For each shoulder condition, a blinded interim analysis will occur when approximately 50% of the patients have completed Week 8 to determine the need for a potential adjustment to the sample sizes. Prior data suggest the standard deviation of the primary endpoint could range from 2 to 2.5. Therefore, the interim analyses will enable a sample size increase up to 150 in each shoulder condition to ensure the desired statistical power is obtained.

SITES: Approximately 35 study sites in the United States

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
21 CFR	Title 21 of the Code of Federal Regulations
AC	Adhesive capsulitis
APR	Accurate Pain Reporting
ASES	American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form
AUC	Area under the curve
BMI	Body mass index
CDISC	Clinical Data Interchange Standards Consortium
CGIC	Clinical Global Impression of Change
CIs	Confidence intervals
CMC	Carboxymethylcellulose sodium
CRA	Clinical research associate
CSR	Clinical Study Report
CTA	Clinical trial authorization
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eDiary	Electronic diary
EOS	End of Study
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels questionnaire
ET	Early Termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
GAD-7	General Anxiety Disorder 7-item scale
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HEP	Home Exercise Program
HIV	Human immunodeficiency virus
IA	Intra-articular
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IM	Intramuscular
IRB	Institutional Review Board
ISI	Insomnia Severity Index
IV	Intravenous

Abbreviation	Definition
IxRS	Interactive voice/web response system
KOOS	Knee Injury and Osteoarthritis Outcome Score
LSM	Least square mean
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NaCl	Sodium chloride
NRS	Numeric rating scale
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
PCS	Pain Catastrophizing Scale
PD-Q	painDETECT Questionnaire
PGIC	Patient Global Impression of Change
PHQ-9	Patient Health Questionnaire-9
PK	Pharmacokinetic(s)
PLGA	Poly(lactic-co-glycol acid)
PRP	Platelet rich plasma
PRR	Placebo Response Reduction
QOL	Quality of Life
ROM	Ranges of motion
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SI	Sleep Interference
SPADI	Shoulder Pain and Disability Index
SUSAR	Suspected Unexpected Serious Adverse Reactions
TA	Triamcinolone acetonide
TAcs	Triamcinolone acetonide injectable suspension, immediate-release
TEAE	Treatment-emergent adverse event
TENS	Transcutaneous electrical nerve stimulation
USP	United States Pharmacopeia
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
w/w	Weight by weight

1 INTRODUCTION AND BACKGROUND INFORMATION

FX006 is an extended-release formulation of triamcinolone acetonide (TA) for intra-articular (IA) administration. It is approved in the United States under the trade name ZILRETTA® (TA extended-release injectable suspension) for the management of pain of osteoarthritis (OA) of the knee. FX006 is intended to deliver TA to the synovial and perisynovial tissues for a period of approximately 3 months.[1] FX006 contains TA, United States Pharmacopeia (USP), formulated in 75:25 poly(lactic-co-glycolic acid) (PLGA) microspheres with a nominal drug load of 25% (weight by weight [w/w]) and is provided as a sterile white to off-white powder for reconstitution. The drug product is reconstituted with diluent containing an isotonic, sterile aqueous solution of sodium chloride (NaCl; 0.9% w/w), carboxymethylcellulose sodium (CMC; 0.5% w/w), and polysorbate-80 (0.1% w/w) to form a suspension prior to IA injection.

Further details of the physiochemical properties of FX006 can be found in the Investigator's Brochure (IB).[2]

1.1 Rationale

Results of the primary endpoint from the Phase 3, multicenter, adequate, and well-controlled trial on pain secondary to OA of the knee showed that patients treated with 32 mg FX006 had a rapid, durable, and meaningful analgesic response that was statistically significantly better than placebo treated patients ($p<0.0001$). This finding was supported by a second, smaller Phase 2b study, where a highly similar pattern of response to 32 mg FX006 was demonstrated.[3,4,5] Thus, one aspect of the current clinical development program focuses on evaluating the potential therapeutic effects of FX006 on pain in patients with OA of the shoulder where conventional steroid IA injection shows short-lived efficacy in shoulder OA patients,[6] consistent with the efficacy observed in knee OA.[7,8] Likewise, FX006 is anticipated to have efficacy in the relief of pain due to OA in the synovial shoulder joint as it shares similar pathogenesis to knee OA.

Shoulder adhesive capsulitis (AC) is a common painful and disabling disorder. The exact etiology is unknown, though the incidence is higher among patients with diabetes than observed in the general population. The disease pathogenesis is characterized by early synovial inflammation, hyperplasia, and hypervascularity, as well as fibroblastic proliferation and fibrosis in the late phase.[9] Patients present with severe pain, limited ranges of motion (ROM), and frozen shoulder. Some patients end up with spontaneous recovery within 2 to 3 years, but up to 40% of patients may experience persistent symptoms with 7% to 15% having some degree of permanent functional loss.[10] Intra-articular corticosteroid injection shows short-lived pain relief with a prolonged effect on passive ROM.[11] It is hypothesized that an extended-release formulation of corticosteroid would provide long-lasting pain relief and functional improvement for patients with shoulder AC.

The glenohumeral joint is a large synovial joint. The injection volume of FX006 (5 mL) is believed to be appropriate as such a volume has been routinely used in the combination of conventional corticosteroid with lidocaine.

1.2 Overview of Nonclinical Studies with FX006

Overall, toxicology studies showed that single or repeat IA administration of FX006 at the proposed clinical dose of 32 mg had no new safety liabilities compared to triamcinolone acetonide injectable suspension, immediate-release (TAcs), in healthy animals.

Information available for TA from the literature, corticosteroid product labels, and clinical experience suggests that the potential of genetic toxicity, reproductive toxicity, and carcinogenicity of TA is well understood. Similarly, the biocompatibility and local safety of PLGA microspheres and genotoxic, reproductive toxicological, and carcinogenic potential of PLGA have been described in a combination of literature and product information packages. Therefore, no new risks relative to TAcs are presented by FX006 as intended for use.

Further details of the nonclinical studies with FX006 can be found in the IB.[2]

1.3 Overview of Clinical Studies with FX006

1.3.1 Systemic and Local Pharmacokinetics in Patients with Osteoarthritis of the Knee and Shoulder

Overall, FX006 displayed a favorable plasma pharmacokinetic (PK) profile relative to that of TAcs. Pharmacokinetic observations resulted in a controlled and stable release of TA from PLGA microspheres into synovial tissues, where concentrations remained high relative to plasma concentrations for at least 12 weeks. Triamcinolone acetonide was absorbed systemically, with a plateau in plasma TA concentrations occurring in the first 24 hours post-dose, and slow elimination from the systemic circulation observed in the weeks thereafter.[1,12]

Relative to TAcs, 32 mg FX006 produced substantially lower peak plasma concentrations. FX006 performed as expected, prolonging the residence of TA in the knee joint while minimizing systemic peak exposure to TA. Similarly, the FX006 plasma PK profile in shoulder OA patients following IA administration was comparable to the plasma PK profile in knee OA patients.

1.3.2 Pharmacodynamics in Patients with Osteoarthritis of the Knee

In a Phase 2 PK/pharmacodynamics study evaluating 3 dose levels of FX006 (10 mg, 40 mg, and 60 mg) administered as a 3 mL injection, suppression of cortisol in the days following injection produced by the 10 mg and 40 mg doses of FX006 was less than that produced by injection of TAcs; the 60 mg dose of FX006 produced effects similar to 40 mg TAcs. Cortisol suppression subsequent to Days 1 to 2 associated with all doses of FX006 would not be expected to be of clinical consequence in adult patients without otherwise compromised hypothalamic-pituitary-adrenal axis function. In a Phase 2 study in diabetic patients with knee OA, treatment with 32 mg FX006 resulted in a statistically significant ($p=0.0452$) reduction in blood glucose elevation relative to TAcs over a 72-hour period following IA injection. The time in glycemic target range (70 to 180 mg/dL)[13] was greater for FX006 as compared to TAcs over the 48 hours post-IA injection, providing another indication of the improvement in glycemic control.

This observation is consistent with PK studies demonstrating low systemic maximum plasma concentration for TA associated with FX006.

1.3.3 Efficacy in Patients with Osteoarthritis of the Knee

Efficacy data from 3 studies provide substantial evidence supporting the effectiveness of 32 mg FX006 in the management of OA pain.[3,4,5] Results of the primary endpoint from the Phase 3, multicenter, adequate, and well-controlled study showed that patients treated with 32 mg FX006 had a rapid, durable, and meaningful analgesic response that was significantly better than

placebo-treated patients ($p<0.0001$). This finding was supported by a second smaller Phase 2b study where a highly similar pattern of response to 32 mg FX006 was demonstrated.

Robustness of the primary outcome in the Phase 3 study was further supported by the internal consistency demonstrated in favor of 32 mg FX006 through secondary analyses utilizing the primary outcome data (average daily pain) to evaluate durability and magnitude of response. These included least square mean (LSM) testing at each week and area under the effect curve analyses for Weeks 1 through 12 and Weeks 1 through 24. Results demonstrated that the analgesic effect of 32 mg FX006 was significant at Week 1, increased through Week 7, and was sustained through at least Week 16. Responder analyses further suggested that FX006 provided clinically relevant improvement from Weeks 1 through 16 relative to placebo.

Analyses utilizing data collected from other instruments or measures (i.e., Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC], Patient Global Impression of Change [PGIC], Clinical Global Impression of Change [CGIC], and Knee Injury and Osteoarthritis Outcome Score [KOOS] Quality of Life [QOL]) provided additional insight into the effects on pain relief, as well as physical function and global well-being. At 32 mg, FX006 provided clinically relevant improvement relative to placebo through Week 12 for WOMAC and KOOS QOL and through at least Week 16 for PGIC and CGIC. Additionally, a significant reduction in rescue medication utilization in patients treated with 32 mg FX006 was of potential important clinical consequence and added a meaningful element to the overall effectiveness profile of 32 mg FX006. Collectively, these results provide substantial evidence to support 32 mg FX006 as an effective therapy for the management of OA knee pain.

1.3.4 Systemic and Local Safety in Patients with Osteoarthritis of the Knee

The evaluation of 934 patients treated with a single or repeat IA injection(s) of FX006 at any dose in FX006 clinical studies suggested that it was well tolerated with systemic and local safety profiles similar to those of TAcs and placebo. In the Phase 3 study, qualitative assessments based on X-rays of the index knee at Baseline and 24 weeks post injection, including joint space narrowing, subchondral bone changes, osteonecrosis, and insufficiency fracture,[5] showed no differences between the FX006, TAcs, and placebo groups. In the FX006 repeat dosing study, qualitative X-ray showed no clinically meaningful joint structure differences from Baseline up to 52 weeks post injection.

1.4 Risk/Benefit

FX006, an extended-release microsphere formulation of TA, demonstrated a comparable safety profile to TAcs in animals after single or repeated IA administration. Much lower peak plasma levels and much longer duration than TAcs after IA injection in knee OA patients contributed to a better systemic safety profile, as evidenced by decreased duration and magnitude in hyperglycemia of diabetic patients. Furthermore, FX006 demonstrated comparable local joint safety as compared to TAcs in patients with knee OA. Larger magnitude and longer duration of efficacy was observed with FX006 compared to TAcs, as demonstrated by WOMAC pain and function scores. Given the insufficient symptomatic management of glenohumeral OA and similar pathogenesis between knee and glenohumeral OA, it is anticipated that FX006 will provide a favorable risk/benefit profile to glenohumeral OA patients.

Adhesive capsulitis is another painful shoulder condition that is commonly managed by IA conventional corticosteroids with short duration of pain relief but greater improvement in passive

ROM in both the short and long terms. Thus, it is hypothesized that an extended-release formulation of TA will provide meaningful benefits in both pain relief and functional improvement for patients with shoulder AC.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the efficacy of FX006 on pain following an IA injection in patients with glenohumeral OA or shoulder AC.

2.2 Secondary Objectives

The secondary objectives of this study are the following:

- To assess the efficacy of FX006 on pain, disability, function, and global impression of change in patients with glenohumeral OA or shoulder AC
- To assess the safety of FX006 in patients with glenohumeral OA or shoulder AC

2.3 Exploratory Objectives

The exploratory objectives of this study are to assess additional measures of pain, disability, function, QOL, rescue medication consumption, and proportion of responders at varying timepoints over the course of the study.

3 STUDY DESCRIPTION

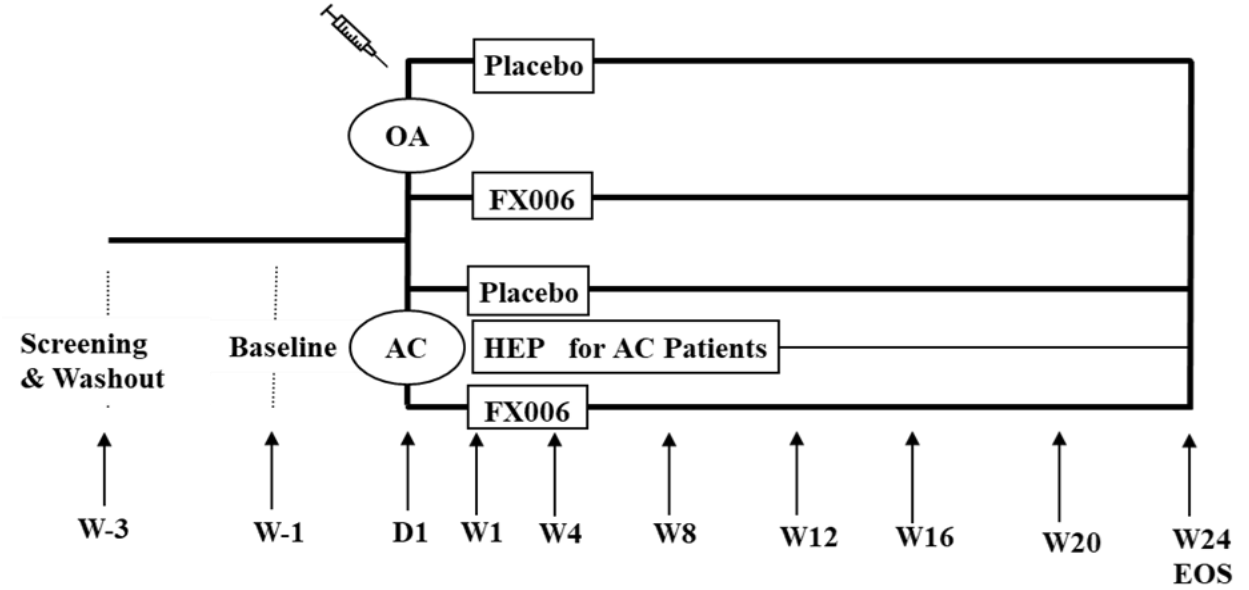
3.1 Summary of Study Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of a single IA injection of either 5 mL of the reconstituted FX006 (32 mg) or 5 mL of placebo (sterile normal saline) in separate cohorts of patients with a documented history of glenohumeral OA or shoulder AC.

This study will be conducted at approximately 35 study sites in the United States. Patients will be screened to confirm the diagnosis of OA or AC and eligibility based on the Inclusion and Exclusion Criteria. Eligible patients will be randomized to treatment on Day 1. Glenohumeral OA patients will be stratified by the Baseline average daily shoulder pain with movement score (0 to 10 numeric rating scale [NRS]) (5.0 to <7.0 or ≥7.0 to 9.0). Shoulder AC patients will be stratified by the Baseline average daily shoulder pain with movement score (0 to 10 NRS) (5.0 to <7.0 or ≥7.0 to 9.0), and pain duration since onset at Screening (1 to 3 months, inclusive, or >3 to ≤6 months).

Approximately 250 male or female patients, 35 to 80 years of age, inclusive (approximately 136 glenohumeral OA patients and approximately 114 shoulder AC patients), will be enrolled in this study. The study duration is approximately 27 weeks, including a Screening Period of up to a maximum of 3 weeks and treatment on Day 1 followed by a 24-week Treatment Evaluation Period. The study design can be seen in Figure 1.

Figure 1. Study Flow Chart



AC = adhesive capsulitis; D = Day; EOS = End of Study; HEP = Home Exercise Program; OA = osteoarthritis; W = Week.

For each shoulder condition, a blinded interim analysis will occur when approximately 50% of the patients have completed Week 8 to determine the need for potential adjustment to sample sizes. All final analyses will be completed following database lock once all patients complete Week 24.

The study will involve a Screening Period (up to a maximum of 21 days), dosing on Day 1, and 7 additional study site visits: during Week 1, and then every 4 weeks (Weeks 4, 8, 12, 16, 20, and 24) through Week 24.

At the times specified in Table 1, patients will undergo physical examinations, index shoulder assessments, and index shoulder X-rays; blood will be collected for clinical laboratory tests; and vital signs will be collected. A Home Exercise Program (HEP) will be implemented 3 days following injection for shoulder AC patients (see Appendix C).

Information regarding adverse events and concomitant medications will be collected. Information regarding rescue medication usage, average daily shoulder pain with movement score, Sleep Interference (SI), and HEP compliance will be completed daily via an electronic diary (eDiary) and at each study site visit. At the Screening Visit, patients will be registered in the eDiary and receive instructions on its use. Questionnaires to be completed daily by the patient in the eDiary must follow the order defined in Table 2.

Patients will complete the Accurate Pain Reporting (APR) and Placebo Response Reduction (PRR) trainings prior to completing the PainDETECT Questionnaire (PD-Q), Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder 7-item scale (GAD-7), Pain Catastrophizing Scale (PCS), Insomnia Severity Index (ISI), EuroQol 5 Dimensions 5 Levels questionnaire (EQ-5D-5L), Shoulder Pain and Disability Index (SPADI) questionnaire, American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form (ASES), and PGIC questionnaire per the visit schedule in Table 3. Questionnaires competed at study site visits must follow the order defined in Table 3.

3.2 Study Indications

There are 2 shoulder conditions included in the study: shoulder pain due to glenohumeral OA and shoulder pain due to AC.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

A patient who meets all of the following criteria will be eligible to participate in the study:

1. Has 1 of the following diagnoses (can be diagnosed at the Screening Visit) and meets the following criteria:
   a. Glenohumeral OA:
      - Male or female, 35 to 80 years of age, inclusive, on the day of consent.
      - Painful symptoms associated with OA of the index glenohumeral joint for ≥3 months prior to the Screening Visit.
      - Grade 2 or 3 OA in the index glenohumeral joint based on the Samilson-Prieto classification system as confirmed by X-ray (axillary view and true anterior-posterior view) taken at the Screening Visit or within 6 weeks of the Screening Visit.

   b. Shoulder AC:
      - Male or female, 35 to 80 years of age, inclusive, on the day of consent.
      - Pain associated with AC of the index joint for ≥1 month but ≤6 months prior to the Screening Visit.
      - More than 20% (25% if dominant shoulder is the index shoulder) loss of passive range of the rotation arc (external and internal rotation) of glenohumeral movement, measured with the patient in supine or sitting position and the shoulder elevated to 45 degrees, compared with the contralateral shoulder.
      - No X-ray evidence of OA of the index shoulder (axillary view and true anterior-posterior view) at the Screening Visit or within 6 weeks of the Screening Visit.
2. Is willing and able to sign the informed consent form (ICF), indicating that the patient understands the purpose of the study and procedures required for the study before the initiation of any study-specific procedures. Patients who are unable to provide informed consent will not be included in the study.
3. Is willing and able to comply with the study procedures and visit schedules and able to follow verbal and written instructions.
4. Has a body mass index (BMI) ≤40 kg/m^2.
5. Has an average daily mean shoulder pain with movement score ≥5.0 and ≤9.0 in the index shoulder (0 to 10 NRS) using the average daily ratings for at least 5 out of the 7 days prior to Day 1.

   Note: The required mean average daily shoulder pain with movement score will not be disclosed to the patient.
6. Has shoulder pain present >15 days in the month prior to the Screening Visit.
7. Is willing to complete a washout of protocol-specified excluded medications 7 days prior to Day 1 and abstain from use of protocol-specified excluded medications throughout the study (see Section 5.6.1).

8. Is willing to abstain from nonpharmacological therapies (e.g., physical therapy, acupuncture, transcutaneous electrical nerve stimulation (TENS), or bracing) for the index joint for 2 weeks prior to Day 1 and throughout the study.
9. Shoulder AC patients only: Agrees to complete a standardized, protocol-specified shoulder HEP starting 3 days after injection until the End of Study (EOS) Visit.
10. Sexually active males or females of childbearing potential (defined as not surgically sterile or postmenopausal [defined as 12 consecutive months with no menses without an alternative medical cause] for at least 1 year as documented in medical history) must agree to use 1 of the following highly effective methods of contraception: abstinence; oral, injected, or implanted hormonal methods of contraception; intrauterine device or intrauterine system; condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; or monogamous intercourse with a partner who is surgically sterile (post-vasectomy, post-hysterectomy, or tubal ligation). Such contraceptive measures should be used throughout the duration of the study.

4.2 Exclusion Criteria

A patient who meets any of the following criteria will be excluded from participation in the study:

1. Is unable to washout from excluded (see Section 5.6.1) or restricted medications (see Section 5.6.2).
2. Has both glenohumeral OA and shoulder AC.
3. Has bilateral AC.
4. Has bilateral glenohumeral OA with glenohumeral OA pain of the shoulder contralateral to the index shoulder >3.0 (0 to 10 NRS) within 1 month prior to the Screening Visit (patient self-report acceptable).
5. Has a history of symptomatic arthritis in other joints of the index shoulder (e.g., acromioclavicular joint or scapulothoracic joint), as confirmed by medical history and physical examination.
6. Has a history or suspicion of full thickness rotator cuff tear in the index shoulder as assessed by the Investigator per medical history and physical examination, ultrasound, or magnetic resonance imaging (MRI) obtained within 6 months of the Screening Visit.
7. Has symptomatic partial rotator cuff tear, tendinopathy, tendonitis, or bursitis in the index shoulder as assessed by Investigator per medical history and physical examination, ultrasound, or MRI obtained within 6 months of the Screening Visit.
8. Has a subchondral bone insufficiency fracture or humeral head necrosis/collapse in the index shoulder based on X-ray used for study qualification.
9. Shoulder AC patients only: Has a history of shoulder surgery in the index shoulder or radiotherapy (e.g., for breast, neck, or upper limb tumors).
10. Glenohumeral OA patients only: Has a previous shoulder injury in the index shoulder with functional limitation ≥1 month (e.g., dislocation or fracture) or surgery in the index shoulder (including clavicle or scapula) within 52 weeks prior to the Screening Visit.

11. Has an index shoulder with major dysplasia or congenital abnormality, osteochondritis dissecans, acromegaly, ochronosis, hemochromatosis, Wilson's disease, primary osteochondromatosis, or a history of avascular necrosis with secondary OA.
12. Has current or history of infection (e.g., osteomyelitis) in the index shoulder or current skin infection at injection site.
13. Has any concurrent chronic pain condition with a pain score >3.0 (0 to 10 NRS) within 1 month prior to the Screening Visit (patient self-report acceptable), including but not limited to, cervical spine conditions causing radicular pain or peripheral nerve injury/entrapment (e.g., brachial plexus injury or suprascapular nerve entrapment) that may affect sensation of the index shoulder; diabetic neuropathy; post-herpetic neuralgia; post-stroke pain; or fibromyalgia.
14. Has a PD-Q score >18 during the Screening Visit.
15. Has a history or current evidence of reactive arthritis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or arthritis associated with inflammatory bowel disease, systemic lupus erythematosus, calcium pyrophosphate dihydrate crystal deposition disease (CPPD) or other autoimmune diseases.
16. Has any planned surgeries in the upper limbs during the study or any other surgery during the study that would require use of a restricted medication.
17. Has surgical hardware or other foreign body present in the index shoulder.
18. Has received an IA corticosteroid of any joint within 3 months of the Screening Visit (investigational or marketed, including FX006).
19. Has received an IA treatment of the index shoulder with any of the following agents within 6 months of the Screening Visit: any biologic agent (e.g., platelet rich plasma [PRP] injection, stem cells, prolotherapy, or amniotic fluid injection; investigational or marketed) or hyaluronic acid.
20. Has received intravenous (IV), intrabursal, intratendinous, intramuscular (IM), or epidural corticosteroids (investigational or marketed) within 3 months of the Screening Visit.
21. Has received oral corticosteroids (investigational or marketed) within 1 month of the Screening Visit.
22. Has received inhaled, intranasal, or topical corticosteroids (investigational or marketed) within 2 weeks of the Screening Visit.
23. Has significant changes with regard to physical activity and lifestyle, within 1 month of the Screening Visit or any planned changes throughout the duration of the study.
24. Has a total score ≥15 or score >0 on question #9 on the PHQ-9 at the Screening Visit.
25. Has a score ≥15 on the GAD-7 at the Screening Visit.
26. Has a clinically relevant level of pain catastrophizing, defined as a PCS score ≥30 at the Screening Visit.
27. Has an ISI questionnaire score ≥15 (moderate severity) at the Screening Visit.
28. Has known hypersensitivity to TA orPLGA.

29. Has laboratory evidence of infection with human immunodeficiency virus (HIV), a positive test for hepatitis B surface antigen (HBsAg), or positive serology for hepatitis C virus (HCV) with positive test for HCV ribonucleic acid.
30. Has an electrocardiogram (ECG) abnormality judged clinically significant by the Investigator.
31. Has a medical history suggesting the patient will or is likely to require a course of systemic corticosteroids during the study.
32. Has uncontrolled diabetes as indicated by a hemoglobin A1c of >8% (>59 mmol/mol).
33. Has a history or evidence of active or latent systemic fungal or mycobacterial infection (including tuberculosis), or of ocular herpes simplex.
34. Has a history of sarcoidosis or amyloidosis.
35. Has a history of or active Cushing's syndrome.
36. Has used chemotherapeutic agents, immunomodulators, or immunosuppressants other than corticosteroids within 5 years of the Screening Visit.

    Note: Restrictions pertinent to corticosteroid use specified in Exclusion Criteria 18, 20, 21, and 22.
37. Has current or history of malignancy within 5 years prior to the Screening Visit, except for basal or squamous cell carcinoma of the skin or cervical carcinoma in situ that has been treated successfully.
38. Has active substance use disorder (drugs or alcohol) or history of substance use disorder within 12 months prior to the Screening Visit as per The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.
39. Has received a live (e.g., measles, mumps, and rubella vaccine; chicken pox vaccine; or rotavirus vaccine) or live-attenuated vaccine (e.g., FluMist® or Zostavax®) within 3 months of the Screening Visit.
40. Has used any other investigational drug, biologic, or device within 3 months of the Screening Visit.
41. Has any infection requiring IV antibiotics 4 weeks prior to Day 1 or oral antibiotics 2 weeks prior to Day 1.
42. Has any other clinically significant acute or chronic medical condition(s) that, in the judgment of the Investigator, would preclude the use of an IA corticosteroid or that could compromise patient safety, limit the patient's ability to complete the study, and/or compromise the objectives of the study.
43. Has a contraindication to the use of acetaminophen (allowed rescue pain medicine) per National Product Labeling and the Investigator's judgment.
44. Is the Investigator or any sub-Investigator, research assistant, pharmacist, study coordinator, other staff, or relative thereof directly involved in the conduct of the study.
45. Is a female that is pregnant or nursing or plans to become pregnant during the study; or is a male who plans to inseminate a partner or donate sperm during the study.

4.3 Withdrawal Criteria

If a patient withdraws, he/she should continue to be followed for safety assessments up to 24 weeks after treatment. A patient may withdraw from the study at any time for any reason, without any consequences. In addition, a patient may be withdrawn from the study for the following reasons:

- Adverse event (typically a serious adverse event [SAE])
- Patient choice (withdrawal of consent, Investigator will attempt to ascertain reason)
- Protocol violation/noncompliance
- Lack of efficacy (lack of expected or desired effect related to a therapy)
- Physician decision (a position, opinion, or judgment reached after consideration by a physician with reference to the patient)
- Progressive disease (a disease process that is increasing in extent or severity)
- Study terminated by Sponsor
- Technical problem (a problem with some technical aspect of a clinical study, usually related to an injection)
- Other

If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study site records.

If a patient withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the EOS Visit (Week 24) (see Section 6.6). The reason for patient withdrawal must be documented in the electronic case report form (eCRF). Those patients who withdraw from the study will be referred to a physician for follow-up care.

Withdrawn patients will not be replaced.

4.3.1 Lost to Follow-Up

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the study site for a required study visit:

- The study site must attempt to contact the patient and reschedule the missed visit as soon as possible, counsel the patient on the importance of maintaining the assigned visit schedule, and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.

Should the patient continue to be unreachable, he/she will be considered to be lost to follow-up.

4.3.2 Termination of Study

Although the Sponsor has every intention of completing the study, the Sponsor may terminate the study at any time for clinical or administrative reasons.

4.3.3 Screening Failures

Screening failures are defined as patients who consent to participate in the clinical study but are not subsequently randomized into the study. A minimal set of screening failure information is required to ensure transparent reporting of screening failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screening failure details, eligibility criteria, and any SAE(s).

Patients who do not meet criteria for participation in the study (screen failure) may be rescreened at the discretion of the Medical Monitor. The Medical Monitor will clearly document the rationale for any rescreening decision. Rescreened patients will be assigned a new screening number, be reconsented, and may have screening assessments repeated if necessary.

5 STUDY TREATMENTS

5.1 Treatment Groups

Eligible patients with glenohumeral OA or shoulder AC will be randomized in a 1:1 ratio within their shoulder condition (OA or AC) and treated in the following arms:

- Nominal 32 mg FX006 as a 5 mL IA injection to the index shoulder
- Placebo (sterile normal saline) as a 5 mL IA injection to the index shoulder

5.2 Rationale for Dosing

FX006 at IA doses up to 60 mg has been tested in knee OA patients with an acceptable safety profile. FX006 has been approved to treat knee OA pain at a dose of 32 mg. The glenohumeral joint is also a large synovial joint. Similar doses of conventional corticosteroids have been used for the glenohumeral joint as in the knee joint. Likewise, the same dose of FX006 for the glenohumeral joint as for the knee joint is reasonable, particularly as the FX006 formulation results in much lower drug exposure to joint tissues. Therefore, a 32 mg IA dose has been selected for glenohumeral OA or shoulder AC.

5.3 Randomization and Blinding

Patients from each shoulder condition will be randomized on Day 1 to 1 of 2 treatment arms (FX006 or placebo) using centralized randomization accessed through an interactive voice/web response system randomization (IxRS) module.

Glenohumeral OA patients will be stratified by the Baseline average daily shoulder pain with movement score (0 to 10 NRS) (5.0 to <7.0 or ≥7.0 to 9.0). Shoulder AC patients will be stratified by the Baseline average daily shoulder pain with movement score (0 to 10 NRS) (5.0 to <7.0 or ≥7.0 to 9.0) and pain duration since onset at Screening (1 to 3 months, inclusive, or >3 to ≤6 months).

The blinded-assessor technique will be used in this study to maintain double-blind conditions. Key study site staff roles are defined below and a site-specific blinding plan will be developed to ensure the blind is maintained throughout the duration of the study. Treatments will be prepared by an unblinded pharmacist/coordinator who has experience with the preparation of study medication and who has been properly trained by the Sponsor or designee. Intra-articular injections will be performed by an unblinded injector.

Overall unblinded team responsibilities may include the following:

- Will have no other contact with the patient and will not have any blinded roles in the study (the only exception is that the unblinded injector may be delegated the role of obtaining informed consent at the Screening Visit).
- Will not share treatment assignments with the blinded assessor, the patient, other blinded study personnel, or Sponsor personnel/representatives.

- Will make every effort to maintain the blind (e.g., reconstitute the study medication in an isolated room to prevent others from seeing and hearing tapping process).
    - If an adverse event occurs during the injection procedure, the unblinded injector will record the details of the adverse event in the patient's chart and provide a full report of the event to the blinded assessor in a blinded manner.

Detailed responsibilities for the unblinded study site staff may include the following:

- **Unblinded pharmacist/coordinator**
    - Will receive the randomization notification of the patient's study medication
    - Will dispense the appropriate prepared study medication and necessary materials for the injection
    - Will perform study medication reconstitution
    - Will transport the assigned treatment to the location where injection will take place
    - Will ensure that the FX006 investigational product is resuspended prior to injection
    - Will ensure the blind is maintained by following the site-specific blinding plan to ensure the patient is unaware of the treatment assignment prepared for injection
    - Will remain with the patient and unblinded injector until the injection is completed
    - Will record details of study medication preparation, transport (if applicable), and administration
    - Will store the used vials in the study medication storage location to be held until study medication accountability is performed by the unblinded monitor
    - Will complete the study medication accountability logs

    Note: Depending on site-specific requirements, the unblinded pharmacist/coordinator may be split into 2 roles. Details will be specified in the site-specific blinding plan.

- **Unblinded injector**
    - Will perform study medication reconstitution (if not completed by the unblinded pharmacist/coordinator)
    - Will ensure that the FX006 investigational product is resuspended prior to injection
    - Will perform the aspiration and injection of the index shoulder using ultrasound in accordance with both his/her experience and the protocol-specified procedure

The unblinded pharmacist/coordinator will report any product-related issues relating to reconstitution or administration of FX006 according to Sponsor instructions located in the Unblinded Pharmacy Manual.

All other study site and Sponsor personnel/representatives involved in the study at the study site will be blinded with regards to the study medication being administered with the following Sponsor/representative exceptions:

- **Unblinded monitor(s)**
  - Will be responsible for unblinded study site monitoring
  - Will perform study medication accountability (used and unused vials)
- **Unblinded clinical trial manager**
  - Will be responsible for oversight of unblinded study site monitoring
  - Will review unblinded monitoring visit reports and escalate unblinded study site issues to unblinded Sponsor representative
- **Unblinded Sponsor representative**
  - Will be the point of escalation for the unblinded team
  - Will address any product-related issues
  - Will escalate, in a blinded manner, to the blinded study team, if necessary
- **Sponsor regulatory and pharmacovigilance personnel for safety assessment and reporting, if necessary**

Information regarding treatment assignments will be kept secure by the Sponsor or designee, per standard operating procedures.

5.4 Breaking the Blind

Investigators are not to break the study treatment blind except when information concerning the study medication is necessary for the medical treatment of the patient. If a medical emergency requiring unblinding occurs, the Investigator (or designated physician) is strongly encouraged to contact the medical or safety monitor to assess the necessity of breaking the study medication blind.

If unblinding is warranted, the Investigator will obtain the treatment assignment information from the IxRS. Every effort is to be made to limit study site personnel unblinding only to those individuals providing direct care to that patient.

Any intentional or unintentional breaking of the blind is to be reported immediately to the Sponsor that unblinding has occurred, without revealing the treatment. The other circumstances in which unblinding may be necessary are at the request of a patient who becomes pregnant during the study, or for regulatory reporting purposes.

If the blind is broken, the date, time, and reason must be recorded in the patient's eCRF, and any associated SAE report, if applicable.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

FX006 is an extended-release formulation of TA in 75:25 PLGA microspheres. FX006 will be supplied as a sterile, white to off-white powder in a single unit dose 5 mL vial with a butyl rubber stopper, aluminum seal, and plastic cap. FX006 will be reconstituted in diluent that will be supplied as a sterile aqueous solution in a 5 mL vial with a butyl rubber stopper, aluminum seal, and plastic cap.

Placebo (NaCl injection, USP) is a sterile, nonpyrogenic, isotonic solution of NaCl and water for injection.

Instructions for shipment, storage, accountability, reconciliation, and destruction of study medication are provided in the Unblinded Pharmacy Manual.

5.5.2 Study Medication Preparation and Dispensing

Dispensing, preparation, and administration of investigational products will occur under the supervision of the Principal Investigator. The Principal Investigator may only delegate these activities in accordance with state licensing board requirements, local institutional policies, and applicable law. Before delegating this activity, the Principal Investigator should also ensure that the delegate is trained on and understands the requirements of the protocol.

Immediately prior to IA injection, FX006 will be reconstituted in 5 mL of a diluent containing an isotonic, sterile aqueous solution of NaCl (0.9% w/w), CMC (0.5% w/w), and polysorbate-80 (0.1% w/w) to form a suspension prior to IA injection.

The reconstitution process should not be witnessed by any blinded study staff or by the patients.

Refer to the Unblinded Pharmacy Manual for detailed instructions on study medication preparation and IA administration.

5.5.3 Study Medication Administration

Only patients enrolled in the study may receive study medication and only authorized site staff may supply or administer study medication.

Any difficulties with the study medication administration should not be reported to the blinded assessor unless it is a direct cause of an adverse event. In the event of difficulties during the procedure with administering the study medication, please proceed as follows:

- Stop the procedure.
- Do not attempt to reinject.
- Report the event to the unblinded coordinators at the site and to the unblinded team at Flexion Therapeutics, Inc. via the Product Complaint Form.
- The patient and blinded study personnel (coordinators and Investigators) should not be informed the procedure was stopped.

5.5.3.1 Index shoulder aspiration

Aspiration must be attempted prior to injection of study medication on Day 1. If effusion is detected by ultrasound guidance, the injector must withdraw to near dryness prior to the injection.

Refer to the Unblinded Pharmacy Manual for detailed instructions on study medication preparation and IA administration.

5.5.4 Treatment Compliance

Study medication will be administered by the unblinded injector in the clinic. Details regarding study medication administration will be documented in the eCRF. The receipt, dispensation, and return/destruction of any study medication will be properly documented.

If for any reason the administration of study medication is stopped before the entire volume is injected, the injector should document the reason for stopping administration.

5.5.5 Storage and Accountability

The packaged kits of FX006 must be stored under refrigeration at 2°C to 8°C in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to authorized, unblinded site staff.

Placebo will be stored according to the commercial label and USP guidelines in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the authorized, unblinded site staff.

The Investigator, or designee, must confirm appropriate temperature conditions have been maintained during transit for all study medications received and any discrepancies must be reported and resolved before the use of study medication. Any temperature excursions should be documented according to the Unblinded Pharmacy Manual instructions for Sponsor assessment and authorization for continued use.

All study medication required for completion of this study will be provided by the Sponsor or designee.

The Investigator, site, or the head of the site (where applicable) is responsible for study medication accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition of records).

In the event of a product complaint, complete the Product Complaint Form located in the Unblinded Pharmacy Manual.

5.5.6 Rescue Medication

The study site will supply rescue pain medication (acetaminophen) that will be provided by the Sponsor. At the site, the rescue medication should be stored according to the commercial label. To standardize pain relief rescue medication across all patients, starting at the Screening Visit, patients will discontinue all excluded or restricted medications and observe the following procedures:

- The designated rescue medication is acetaminophen 500 mg. The recommended dosing is 2 tablets every 6 hours as needed, up to a maximum of 6 tablets (3000 mg) per 24-hour period.

- Starting at the Screening Visit, each patient will be provided with a sufficient quantity of rescue medication for the interval to the next scheduled study site visit.
- Patients will record their dosage regimen of the rescue medication over the past 24 hours daily in their eDiary.

At each visit, patients will return any unused rescue medication provided at the previous visit for rescue medication accountability and be issued a new supply.

As with FX006/placebo, the Investigator, site, or the head of the site (where applicable) is responsible for rescue medication accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition of records).

5.6 Prior and Concomitant Medications and/or Procedures

Prior therapy is defined as all medications taken by or administered to the patient prior to providing informed consent. Concomitant therapy is defined as all medications taken by or administered to the patient from providing informed consent to the EOS Visit. Review of any concomitant medications should be performed and documented in the source documentation.

5.6.1 Excluded Medications and/or Procedures

The following medications are excluded for the duration of the study. If a patient is taking any of these excluded medications, they must, after signing the ICF, complete a washout consisting of a period of 5 half-lives of the excluded drug 7 days prior to Day 1.

- Oral nonsteroidal anti-inflammatory drugs (NSAIDs).
- Aspirin (>325 mg/day).
- Centrally-acting pain medications (e.g., pregabalin, gabapentin, duloxetine, and/or milnacipran) unless specifically allowed, or allowed with restriction, in the protocol.
- Opioids.
- Topical therapies (e.g., NSAIDs, capsaicin, lidocaine patches, CBD products, or other local treatments) applied to the index shoulder.
- Anesthetic medications injected locally in the index shoulder (other than the selected anesthetic if used for the IA injection procedure).
- Muscle relaxants (e.g., cyclobenzaprine, tetrazepam, and/or diazepam).

The following medications and/or procedures should not be taken and/or performed throughout the study:

- IV or IM corticosteroids within 3 months of the Screening Visit.
- Oral corticosteroids within 1 month of the Screening Visit.
- Inhaled, intranasal, or topical corticosteroids within 2 weeks of the Screening Visit.
- IA corticosteroids in any joint within 3 months of the Screening Visit.
- IA viscosupplementation (hyaluronic acid) or any IA intervention (e.g., IA injection) in the index shoulder within 6 months of the Screening Visit.

- Any investigational drug, biologic, or device within 3 months of the Screening Visit.
- Chemotherapeutic agents, immunomodulators, or immunosuppressants other than corticosteroids within 5 years of the Screening Visit.
- Live or live-attenuated vaccines within 3 months of the Screening Visit.
- Significant changes with regard to physical activity and lifestyle, within 1 month prior to the Screening Visit and changes throughout the duration of the study.

5.6.2 Restricted Medications and/or Procedures

The following medications/nonpharmacologic therapies may be taken or used throughout the study with the following restrictions:

- Aspirin for cardioprotection at a maximum dose of 325 mg/day provided the dose has been stable over the 3 months prior to study entry.
- Medical therapy for depression, including selective serotonin reuptake inhibitors, non-selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and tricyclic antidepressants provided the dose has been stable over the 3-month period prior to the Screening Visit (see Appendix E).

5.6.3 Allowed Medications and/or Procedures

The following medications/nonpharmacologic therapies may be taken or used throughout the study:

- Any treatment for a pre-existing condition or for an adverse event, outside of the study indication, that is not listed as excluded or restricted.
- Study-allocated rescue medication.
- Patients should be advised to maintain a stable lifestyle with regard to physical activity throughout the duration of the study. Patients treated for shoulder AC will begin the HEP (see Appendix C) beginning 3 days post injection.

5.6.4 Documentation of Prior and Concomitant Medication Use

During the study, prior medications, changes to concomitant medications, and/or the addition of new medications and the associated reasons for use and/or changes will be documented and recorded on the applicable eCRF.

6 STUDY PROCEDURES

6.1 Informed Consent

Prior to initiation of any study related procedures, patients will review and sign the study's ICF to participate in the study after having been informed about the nature and purpose of the study, participation and termination conditions, and risks and benefits. Patients who are unable to provide informed consent will not be included in the study.

6.2 Order of Questionnaires and Electronic Diary Entries

Entries to be completed daily in the eDiary must follow the order defined in Table 2. Questionnaires to be completed during study site visits must follow the order defined in Table 3.

6.3 Screening Visit (Days -21 to -1)

The study will include a Screening Period of a maximum of 21 days. The following procedures will be performed at the Screening Visit:

- Obtain informed consent.
- Confirm eligibility based on Inclusion and Exclusion Criteria (see Sections 4.1 and 4.2, respectively).
- Complete APR and PRR trainings prior to patient questionnaires.
- Administer the PD-Q, PHQ-9, GAD-7, PCS, and ISI.
- Record medical history, including OA medical history and AC medical history.
    - For glenohumeral OA patients, OA medical history will include American College of Rheumatology diagnosis details; OA diagnosis date (if available); number of days with index shoulder pain in the last month; previous IA corticosteroid, PRP, or hyaluronic injections; presence of OA in other joints; and prior procedures or surgeries for index shoulder OA.
    - For AC patients, AC diagnosis date (if available); pain duration since onset at Screening; previous IA corticosteroid, PRP, or hyaluronic injections; presence of OA in other joints; and prior procedures or surgeries for index shoulder AC.
- Record patient demographics.
- Record prior treatments and medications.
- Record the average daily shoulder pain with movement score (0 to 10 NRS), SI question, and rescue medication usage in the eDiary.
- Record the pain with duration since onset (AC patients only).
- Perform physical examination.
- Perform shoulder assessment, including active and passive ROM, on the index and contralateral shoulder.

- Perform index shoulder X-ray.
  - X-ray of the index shoulder will include axillary view and true anterior-posterior view.
  - For glenohumeral OA patients, the Screening Visit X-ray will be read centrally to confirm Grade 2 or 3 OA in the index glenohumeral joint based on the Samilson-Prieto classification system.
  - For shoulder AC patients, the Screening Visit X-ray will be read centrally to confirm there is no evidence of OA in the index shoulder.
  - An x-ray acquired within 6 weeks of the Screening Visit may be used for study qualification if the specified imaging protocol was followed. The x-ray will be read centrally to confirm there is no evidence of OA in the index shoulder.
- Obtain vital signs.
- Perform ECG.
- Record height and weight and calculate BMI.
- Collect blood samples for hematology and chemistry, including hemoglobin A1c.
- Perform HIV, HBsAg, and HCV screens.
- Perform serum pregnancy test (for women of childbearing potential only). Follicle-stimulating hormone in perimenopausal women who have not had a menstrual period for 1 year will be measured at the Screening Visit.
- Begin washout of excluded medications.
- Register patients in eDiary and provide instructions on its use.
- Dispense rescue medication.
- Assess adverse events and concomitant medications.
- Review HEP video with AC patients to ensure agreement to be compliant.

6.4 Treatment Visit (Day 1)

The following procedures will be performed at the Treatment Visit (Day 1):

- Confirm eligibility based on Inclusion and Exclusion Criteria (see Sections 4.1 and 4.2, respectively) prior to administration of study medication.
  - Review the average daily shoulder pain with movement (0 to 10 NRS) to ensure at least 5 out of the 7 days prior to Day 1 have been recorded.
- Complete APR and PRR trainings prior to patient questionnaires and administration of study medication.
- Administer the EQ-5D-5L, SPADI, and ASES after completion of APR and PRR training, but prior to any other assessments.
- Review and update medical history prior to administration of study medication.

- Review and update prior treatments and medications prior to administration of study medication.
- Review SI question and rescue medication usage in the eDiary.
- Perform index shoulder assessment including active and passive ROM prior to administration of study medication.
- Obtain vital signs prior to administration of study medication.
- Perform urine pregnancy test prior to administration of study medication (for women of childbearing potential).
- Perform randomization prior to administration of study medication.
- Perform index shoulder aspiration prior to administration of study medication.
- Administer study medication following standard of care procedure.
- Dispense/return rescue medication as needed.
- Assess adverse events and concomitant medications (post injection).
- For shoulder AC patients only, a Home Exercise Program (HEP) will be implemented 3 days following injection and performed twice daily (see Appendix C).

6.5 Treatment Evaluation Period (Weeks 1 to 24)

Following the Treatment Visit, patients will return to the study site for visits that will occur within ±3 days of the scheduled time.

6.5.1 Weeks 1 to 20

The following procedures will be performed on Weeks 1, 4, 8, 12, 16, and 20:

- Complete APR and PRR trainings prior to patient questionnaires.
- Administer the EQ-5D-5L, SPADI, and ASES after completion of APR and PRR training, but prior to any other assessments.
- Review the average daily shoulder pain with movement score (0 to 10 NRS), SI question, and rescue medication usage in the eDiary.
- Perform index shoulder assessment including active and passive ROM.
- Obtain vital signs.
- Dispense/return rescue medication as needed.
- Record HEP compliance in the eDiary (AC patients only).
- Administer the PGIC.
- Assess adverse events and concomitant medications.
- For shoulder AC patients only, a Home Exercise Program (HEP) will be implemented 3 days following injection and performed twice daily (see Appendix C).

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6.5.2 Week 24 (End of Study Visit)

The following procedures will be performed at the EOS Visit (Week 24):

- Complete APR and PRR trainings prior to patient questionnaires.
- Administer the EQ-5D-5L, SPADI, and ASES after completion of APR and PRR training, but prior to any other assessments.
- Review the average daily shoulder pain with movement score (0 to 10 NRS), SI question, and rescue medication usage in eDiary.
- Perform physical examination.
- Perform index shoulder assessment including active and passive ROM.
- Obtain vital signs.
- Perform ECG.
- Record weight and calculate BMI.
- Collect blood samples for hematology and chemistry.
- Perform urine pregnancy test (for women of childbearing potential).
- Return rescue medication as needed.
- Record HEP compliance in eDiary (AC patients only).
- Administer the PGIC.
- Assess adverse events and concomitant medications.

6.6 Early Termination Visit and Withdrawal Procedures

The end of treatment for patients completing the study is the EOS Visit (Week 24). For patients who withdraw from the study prior to completion (Early Termination [ET]), all EOS Visit procedures will be performed at the corresponding visit. See Section 6.5.2 for the procedures that will be performed.

7 EFFICACY ASSESSMENTS

7.1 Efficacy Endpoints

7.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint for each of the shoulder conditions (glenohumeral OA and shoulder AC) in this study is the area under the curve (AUC) of the change from Baseline in the weekly mean of the average daily shoulder pain with movement score over 8 weeks for FX006 compared to placebo.

7.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints comparing FX006 to placebo for each of the shoulder conditions (glenohumeral OA and shoulder AC) in this study include the following:

- Change from Baseline in the weekly mean of the average daily shoulder pain with movement score at Week 12
- Change from Baseline in the SPADI pain subscale at Week 12
- Change from Baseline in the SPADI disability subscale at Week 12
- The PGIC score at Week 12
- Change from Baseline in the ROM of external rotation at Week 12

7.1.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints comparing FX006 to placebo for each of the shoulder conditions (glenohumeral OA and shoulder AC) in this study include the following:

- AUC of change from Baseline in the weekly mean of the average daily shoulder pain with movement score over Weeks 4, 12, 16, 20, and 24
- AUC of change from Baseline in the SPADI pain subscale over Weeks 4, 8, 12, 16, 20, and 24
- AUC of change from Baseline in the SPADI disability subscale over Weeks 4, 8, 12, 16, 20, and 24
- Change from Baseline in the weekly mean of the average daily shoulder pain with movement score at Weeks 1, 4, 8, 16, 20, and 24
- Change from Baseline in the SPADI pain subscale at Weeks 1, 4, 8, 16, 20, and 24
- Change from Baseline in the SPADI disability subscale at Weeks 1, 4, 8, 16, 20, and 24
- Change from Baseline in the SPADI total score at Weeks 1, 4, 8, 12, 16, 20, and 24
- The PGIC score at Weeks 1, 4, 8, 16, 20, and 24
- Change from Baseline in the ROM of external and internal rotation, abduction and flexion at Weeks 4, 8, 16, 20, and 24
- Change from Baseline in the ROM of internal rotation, abduction and flexion at Week 12
- Change from Baseline in the ASES pain subscale at Weeks 1, 4, 8, 12, 16, 20, and 24

- Change from Baseline in the ASES disability subscale at Weeks 1, 4, 8, 12, 16, 20, and 24
- Change from Baseline in the ASES total score at Weeks 1, 4, 8, 12, 16, 20, and 24
- Percent of responders based on the SPADI at Weeks 1, 4, 8, 12, 16, 20, and 24
- Proportion of patients experiencing a ≥20%, ≥30%, or ≥50% decrease in the weekly mean of the average daily shoulder pain with movement score at Weeks 1, 4, 8, 12, 16, 20, and 24
- Change from Baseline in average weekly rescue medication use
- Change from Baseline in the average weekly SI score
- Change from Baseline in the EQ-5D-5L at Weeks 1, 4, 8, 12, 16, 20, and 24

7.2 Efficacy Assessments

Efficacy variables include the following:

7.2.1 Shoulder Pain with Movement Score

The average shoulder pain with movement (NRS score) experienced in the previous 24 hours will be recorded daily in the eDiary.

7.2.2 Shoulder Pain and Disability Index

The SPADI will be administered at the study visits indicated in Appendix A.

The SPADI will include the pain subscale, disability subscale, and total score.[14,15]

7.2.3 American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form

The ASES will be administered at the study visits indicated in Appendix A.

The ASES will include subscales for pain, function, and total.[14]

7.2.4 Patient Global Impression of Change

The PGIC will be administered at the study visits indicated in Appendix A.

The PGIC will be scored on a 7-point scale.[16,17,18]

7.2.5 Active and Passive Ranges of Motion

Active and passive ROM will be assessed with a goniometer per standardized measurement protocol, as outlined in Appendix D at the study visits indicated in Appendix A.

7.2.6 EuroQol 5 Dimensions 5 Levels Questionnaire

The EQ-5D-5L will be administered at the study visits indicated in Appendix A.

The EQ-5D-5L consists of 2 pages (the EuroQol 5 Dimensions descriptive system and the EuroQol visual analogue scale[19]).

7.2.7 Responder Status

Responder status will be defined by:

- Proportion of patients experiencing either a ≥20%, ≥30%, or ≥50% decrease (improvement) in pain (minimum, at least moderate, and substantial clinically important differences, respectively, as defined by Dworkin et al[20])

7.2.8 Daily Sleep Interference Score

The degree to which index shoulder pain has interfered with sleep during the previous 24 hours will be recorded daily in the eDiary.

8 SAFETY ASSESSMENTS

8.1 Adverse Events

Patients will be monitored for adverse events from the time of informed consent through the end of their participation in the study.

An adverse event is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

Patients should be instructed to report any adverse event that they experience to the Investigator, whether or not they think the event is due to study medication. Beginning at the time of informed consent, Investigators should make an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. For example, a diagnosis of 'influenza' should be reported as an adverse event instead of the symptoms of fever, fatigue, malaise, and positive flu test. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure itself.

Any medical condition already present at the time of informed consent should be recorded as medical history and not be reported as an adverse event unless the medical condition or signs or symptoms present at Baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Clinically significant abnormal laboratory or other examination findings that are detected or significantly worsen during the study should be reported as adverse events, as described below. The Investigator will exercise his/her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Abnormal test results that are determined to be an error should not be reported as an adverse event.

8.1.1 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each adverse event and its potential relationship to study medication.

Assessment of Severity

Each adverse event should be evaluated for severity or intensity. This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose

a threat to a patient's life or functioning. The severity of adverse events will be assessed according to the following definitions:

- Mild – The adverse event is noticeable to the patient and/or the Investigator but does not interfere with routine activity.
- Moderate – The adverse event interferes with routine activity but responds to symptomatic therapy or rest.
- Severe – The adverse event significantly limits the patient's ability to perform routine activities despite symptomatic therapy.

Causality Assessment

A medically qualified Investigator must assess the relationship of any adverse events (including SAEs) to the use of the investigational product, as **related** or **not related**, based on clinical judgment and using all available information according to the following definitions:

- Not related – Temporal relationship is lacking (e.g., the event did not occur within a reasonable time frame following administration of the study medication), **or** other causative factors more likely explain the event (e.g., a pre-existing condition or other concomitant treatments).
- Related – There is a positive temporal relationship (e.g., the event occurred within a reasonable time frame following administration of study medication), **and** the adverse event is more likely explained by the investigational product than by another cause (e.g., the adverse event shows a pattern consistent with previous knowledge of the investigational product or the class of the investigational product).

The definition implies a reasonable possibility of a causal relationship between the event and the study medication. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study medication administration-

  The event should occur after the study medication is given. The length of time from study medication exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases-

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.

- Concomitant drug-

  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study medication-

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses-

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and PK of the study medication-

  The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study medication should be considered.

8.2 Serious Adverse Events

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening adverse event.

  Note: An adverse event or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalizations.

  Note: Any hospitalization over 24 hours will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from Baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits, or respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- An important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

All SAEs occurring from the time of informed consent until the EOS/ET Visit must be entered into the electronic data capture (EDC) system within 24 hours of the knowledge of the occurrence.

To report the SAE, complete the SAE form electronically in the EDC system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. Flexion Pharmacovigilance will also receive notification. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at medpace-safetynotification@medpace.com or call the Medpace SAE Reporting Line (phone number listed below), and fax/email the completed paper SAE form to Medpace (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information: Medpace Clinical Safety
Medpace SAE reporting line – USA:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-579-0444
E-mail: medpace-safetynotification@medpace.com

Follow-Up Reports

The Investigator is required to follow SAEs until resolution or withdrawal of consent. Resolution is defined as:

- A return to Baseline for a pre-existing condition.
- Resolved with or without residual effects.
- The Investigator does not expect any further improvement or worsening of the event.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any requested documentation (e.g., patient discharge summary or autopsy reports) to the Sponsor via e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

Fatal Outcomes

If an autopsy is performed on a deceased patient, the autopsy report should be provided to the Medical Monitor and Flexion Pharmacovigilance as soon as it is available.

8.4 Clinical Management of Index Shoulder-Related Events

In the event the patient has an immediate reaction following administration of study medication or returns to the clinic with an acute exacerbation (e.g., tenderness, increased pain, swelling, effusion, or decreased mobility of the index shoulder), the patient should be treated according to local clinical guidelines and physician experience.

If the index shoulder is aspirated at any time other than administration of study medication for any reason, the volume of synovial fluid aspirated must be documented, synovial fluid should be (1) cultured, (2) evaluated for the presence of crystals, and (3) assessed for white cell count at a local laboratory, and the results should be documented.

Any event that is a change from the patient's Baseline status (new or worsening case) should be reported as an adverse event and those meeting the definition of an SAE must be reported in accordance with Section 8.3.

8.5 Pregnancy Reporting

A pregnancy is not considered to be an adverse event or SAE; however, it must be reported to Medpace Clinical Safety within 24 hours of knowledge of the event. Medpace Clinical Safety will then provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax or e-mail it back to Medpace Clinical Safety.

If the female partner of a male patient becomes pregnant during the study, the Investigator should notify Medpace Clinical Safety as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the Exposure In Utero form should be completed and emailed to Medpace Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE. Additional subsequent follow-up is not needed when a newborn baby is healthy.

8.6 Expedited Reporting

The Sponsor/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSAR) that are fatal or life-threatening as soon as possible to the Food and Drug Administration (FDA), and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated according to the required regulatory timelines.

All other SUSAR will be reported to the FDA as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined by the FDA.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to an investigational medicinal product.

8.7 Reporting Arthralgia in the Index Shoulder

Since all enrolled patients are required to have a certain level of arthralgia in the index shoulder before they receive study medication, the Investigator must take care to fully assess any patient reports of index shoulder arthralgia that occur during the study. Incremental return of pre-existing index shoulder arthralgia following postinjection pain relief does not meet the criteria for an adverse event unless the arthralgia is clinically significantly worse from Baseline (before study medication administration).

Changes in the patient's typical average daily shoulder pain with movement, which serves as the primary efficacy outcome measure, will be assessed utilizing the NRS scale via the daily eDiary and would not meet the criteria for an adverse event of arthralgia unless the pain has clearly worsened relative to Baseline. However, any new arthralgia, including any new type of arthralgia in the index shoulder joint, should be recorded as an adverse event.

8.8 Clinical Laboratory Evaluations

See Appendix B for the list of clinical laboratory tests to be performed and to the Schedule of Procedures in Appendix A for the timing and frequency. See the Central Laboratory Manual for detailed sample collection, handling, storage, and shipping instructions.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If such values do not return to normal/Baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
- All protocol required laboratory assessments, as defined in Appendix B, must be conducted in accordance with the Central Laboratory Manual and the Schedule of Procedures.
- If laboratory values from non-protocol specified laboratory assessments performed at the site's local laboratory require a change in patient management or are considered clinically significant by the Investigator (e.g., SAE or adverse event), then the results must be recorded in the eCRF.

8.9 Vital Signs

Vital signs will be measured as indicated in Appendix A. The following measurements will be obtained: sitting blood pressure, heart rate, respiratory rate, and oral temperature.

- Temperature, blood pressure, respiratory rate, and heart rate measurements will be assessed in a seated position. Blood pressure will be measured with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure, heart rate, and respiratory rate measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (e.g., television or cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 heart rate and 1 blood pressure measurement and recorded on the eCRF.

8.10 Height, Weight, and Body Mass Index Determination

Height and weight will be assessed as indicated in Appendix A.

- Height will be recorded in centimeters. Weight will be recorded in kilograms. Body mass index will be calculated using the following formula:[21]
    - Kilograms and centimeters.
        - With the metric system, the formula for BMI is weight in kilograms divided by height in meters squared. Since height is commonly measured in centimeters, divide height in centimeters by 100 to obtain height in meters.

8.11 Physical Examinations

A complete physical examination will be performed as indicated in Appendix A. A physical examination will be performed at the Screening Visit and Week 24.

The physical exam will assess the following body systems:

- General appearance
- Skin
- Lymphatics
- Head, ears, eyes, nose, and throat
- Cardiovascular
- Respiratory
- Abdominal
- Musculoskeletal
- Neurological

Any clinically significant findings must be documented in the source and added to the medical history if found at the Screening Visit or recorded as an adverse event if new or worsened from Baseline at one of the post-Baseline visits.

8.12 Electrocardiograms

A single 12-lead ECG will be obtained as indicated in Appendix A using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Results will be recorded in the eCRF.

8.13 Index Shoulder Assessment

The index shoulder assessment will be performed by the blinded assessor at the days indicated in Appendix A. The index shoulder will be assessed for tenderness, heat/redness, swelling, and effusion. The index shoulder assessment will also include a measurement of active and passive ROM. Ranges of motion will be measured with a goniometer and include glenohumeral joint flexion, glenohumeral joint abduction, glenohumeral external rotation, and glenohumeral internal rotation in 45° or comfort abduction as defined in Appendix D. Ranges of motion assessments will be performed bilaterally (on the index and contralateral shoulder) at the Screening Visit.

8.14 Placebo Response Reduction and Accurate Pain Reporting Trainings

8.14.1 Placebo Response Reduction Training

The PRR training[22] consists of a set of patient and staff educational materials for training on appropriate expectations of personal benefit while participating in a clinical trial. The purpose is to provide patients truthful information that will neutralize the typically excessive expectations that drive high placebo responses in clinical studies. Patients will receive training as indicated in Appendix A. The training video is approximately 10 minutes and must be completed prior to any patient questionnaires.

8.14.2 Accurate Pain Reporting Training

The APR training[23] consists of a set of patient and staff educational materials and instructions on how to accurately and reliably report pain scores and on the proper use of pain intensity scales, with the aim of increasing patients' pain reporting accuracy. Patients will receive training as indicated in Appendix A. The training video is approximately 10 minutes and must be completed prior to any patient questionnaires.

9 STATISTICS

A comprehensive Statistical Analysis Plan (SAP) will be written and approved prior to database lock for this study. Each shoulder condition will be analyzed completely separately. In general, the same analysis methods will be used for both shoulder conditions, and any differences in analyses between the shoulder conditions will be detailed in the SAP.

9.1 General Considerations and Methods

Data collected in this study will be presented using summary tables, figures, and patient data listings. Summary tables will present data by treatment group and, if applicable, by time of collection. Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized by frequencies and percentages. Figures will be used to support the presentation of certain data. Sensitivity analyses may be performed to examine the effect of missing data, as well as the effect of Baseline imbalance, should it occur.

All confidence intervals (CIs), statistical tests, and resulting p-values will be reported as 2-sided. Multiplicity will be addressed by analyzing the key secondary endpoints sequentially in the order presented in the protocol, testing each endpoint at the nominal $\alpha = 0.05$, 2-sided level to ensure overall type I error control at the 2-sided 0.05 level.

9.1.1 Demographics and Baseline Characteristics

Demographic and Baseline characteristics will be listed by study site and patient and will be summarized by treatment.

9.1.2 Exposure

Treatment exposure will be listed by study site and patient and will be summarized by treatment.

9.2 Study Data

Study data identified in this protocol will be collected and source verified at the study sites completing the study visits. All study data will be formulated into data sets to provide transparency, traceability, and integrity of study analysis results from collection sources. Observed study data will be mapped to the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) and serve as the source data from the study. All study analyses will be completed using analysis data sets that are derived from the SDTM and follow the CDISC Analysis Data Model (ADaM) architecture.

9.2.1 Clinical Data – Clinical Data Interchange Standards Consortium Study Data Tabulation Model

Clinical data will be mapped to CDISC SDTM using implementation guide version 3.2. No derived data required for analyses will be included in the SDTM domains. All SDTM domains will be fully documented with define documents (DEFINE.XML) and a Study Data Reviewer's Guide after database lock and final analyses are completed.

9.2.2 Analysis Data – Clinical Data Interchange Standards Consortium Analysis Data Model

All planned and exploratory analyses will be completed using CDISC compliant ADaM data sets derived from the SDTM domains for this study. Analysis data sets will contain all derived study endpoints required for analysis. All ADaM analysis data sets will be fully documented with define documents (DEFINE.XML) and an Analysis Data Reviewer's Guide after database lock and final analyses are completed.

9.3 Analysis Populations

For each shoulder condition, the following populations are planned for this study:

- Full Analysis Set (FAS) Population: All patients who receive a complete dose of study medication and have Baseline and at least 1 post-dose efficacy endpoint assessment. The FAS Population will be used to examine efficacy for both the primary and secondary endpoints.
- Safety Population: All patients who receive at least 1 dose of study medication. The Safety Population will be used to assess safety and tolerability.
- Per Protocol Population: All patients in the FAS Population who complete the Week 24 visit with no major protocol deviations that may impact the evaluation of the primary efficacy endpoint based on blinded data prior to database lock.

9.4 Statistical Methods

9.4.1 Analysis of Efficacy

9.4.1.1 Primary efficacy analyses

For each shoulder condition, the primary AUC endpoint will be calculated and comparisons will be estimated from an Analysis of Covariance model with parameters for treatment group, Baseline average daily shoulder pain with movement score, and analysis site. In addition, the model for shoulder AC will also include a covariate for pain duration since onset. Full details of the AUC analyses will be detailed in the SAP.

9.4.1.2 Secondary efficacy analyses

The key secondary change from Baseline endpoints will be analyzed with longitudinal mixed models for repeated measures with fixed effects for treatment group, study week, treatment-by-week interaction, analysis site, and Baseline score. Patient will be the random effect. Treatment differences from control will be estimated via LSMs from the analysis model along with 95% CIs and associated 2-sided p-values. This model assumes data are missing at random and includes only observed data. In addition, the model for shoulder AC will also include a covariate for pain duration since onset.

Multiplicity will be addressed by analyzing the key secondary endpoints sequentially in the order presented in the protocol, testing each endpoint at the nominal $\alpha = 0.05$, 2-sided level to ensure overall type I error control at the 2-sided 0.05 level.

9.4.1.3 Exploratory efficacy analyses

Area under the curve and continuous exploratory efficacy endpoints will be analyzed similarly to the primary and key secondary endpoints for each shoulder condition. Categorical endpoints will be compared via chi-square or exact tests depending on incidence rates. No adjustments will be made for multiplicity for exploratory efficacy endpoints.

9.4.2 Analysis of Safety

9.4.2.1 Analysis of adverse events

Safety analyses will be performed on the Safety Population. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Incidences (number and percent) of treatment-emergent adverse events (TEAEs), those events that start after dosing or worsened in severity after dosing, will be presented by treatment. Incidences of TEAEs will also be presented by maximum severity and relationship to study medication.

Similar presentations will be provided for SAEs, adverse events leading to withdrawal from the study, or adverse events leading to death. Analysis of adverse event data will include examination of the incidence rates of index shoulder-related TEAEs.

9.4.2.2 Other safety analyses

Laboratory data and vital sign information will be summarized by treatment and will be presented as descriptive summary statistics for value and change from Baseline at each individual time point.

9.4.3 Interim Analyses

For each shoulder condition, a blinded interim analysis will occur when approximately 50% of the patients have completed Week 8 to determine the need for a potential adjustment to the sample sizes. Prior data suggest the standard deviation of the primary endpoint could range from 2 to 2.5. Therefore, the interim analyses will enable a sample size increase up to 150 in each shoulder condition to ensure the desired statistical power is obtained.

9.4.4 Final Analyses

All final analyses will be completed following database lock for each shoulder condition. Final analyses specified in the protocol and SAP will be completed and reported in the Clinical Study Report (CSR). Post-hoc, exploratory analyses may be completed to further understand and elucidate study results. Any post-hoc, exploratory analyses completed will be clearly identified as such in the final CSR.

9.4.5 Subgroups and Covariates

Preplanned subgroup analyses including aspiration status, OA grade based on the Samilson-Prieto classification system, gender, and Baseline average daily shoulder pain with movement score will be detailed in the SAP. In addition, subgroups of pain duration since onset are preplanned for shoulder AC patients. Further subgroups may be defined and explored after all preplanned analyses have been completed to further elucidate study results.

Covariates for efficacy analyses will include Baseline average daily shoulder pain with movement score, Baseline score for the endpoint, analysis site, and, for AC patients, pain duration since onset. Other covariates may be explored and will be fully defined in the SAP.

9.4.6 Sample Size Determination

Approximately 250 patients will be randomized in a 1:1 ratio to either FX006 or placebo (approximately 136 patients with glenohumeral OA and approximately 114 patients with shoulder AC). Sample sizes were estimated to yield a statistically significant difference ($\alpha = 0.05$, 2-sided) between the FX006 and placebo groups in the average daily shoulder pain with movement score at Week 12 (the first secondary endpoint for each shoulder condition). For glenohumeral OA, the true difference between the groups was assumed to be 1, with a standard deviation of 2, based on data observed in knee OA studies of FX006 and taking into consideration the clinical significance of a 1-point difference between the treatment groups. For shoulder AC, the true difference between the groups was assumed to be 1.2, with a standard deviation of 2.1, based on a review of the existing literature. The primary endpoint analyzing the AUC for the weekly mean of the average daily shoulder pain with movement score over 8 weeks should, therefore, have >80% power to show a significant difference between the FX006 and placebo groups. As the 2 shoulder conditions (glenohumeral OA and shoulder AC) are combined into 1 protocol strictly for ease of administration, all statistical testing will be performed separately for each shoulder condition and the overall type I error rate will be controlled at the $\alpha = 0.05$ level within each shoulder condition.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the study site on eCRFs and reviewed by the clinical research associate (CRA) during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All study site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR) Part 11 and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- MedDRA (latest) for adverse events
- World Health Organization Drug Dictionary for prior and concomitant medications

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the study site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study medication, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the study site. Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records. Current medical records must be available. These records will be retained in a

secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10.3 End of Study Definition

A patient is considered to have completed the study if he/she has completed all phases of the study through Week 24.

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment for the last patient in the study.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board

The Institutional Review Board (IRB) will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

Federal regulations and International Council for Harmonisation (ICH) Guidelines require that approval be obtained from an IRB prior to participation of patients in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB.

No study medication will be released to the study site for dosing until written IRB authorization has been received by the Sponsor.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. Patients must be reconsented to the most current version of the ICF(s) during their participation in the study. The original signed copy of the ICF and any updates to the ICF must be maintained by the Investigator and are subject to inspection by the Sponsor, their representatives, auditors, the IRB, and/or regulatory agencies. A copy of all signed ICFs will be given to the patient.

Patients who are rescreened will be required to sign a new ICF.

11.4 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review with the Investigator and study site personnel the following documents: protocol, IB, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data are entered by the study site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the study site by signature and date on the study-specific monitoring log.

11.5 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.6 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, e.g., eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.7 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of patients.

The first act of recruitment is the first site opening (site activation) and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study

completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further study medication development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patients and should assure appropriate patient therapy and/or follow-up.

11.8 Publication Policy

The results of this study may be published or presented at scientific meetings. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

11.9 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to the IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually, or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
- Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, and all other applicable local regulations.

11.10 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

11.11 Data Protection

Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

Patients must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law(s). The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the ICF.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

11.12 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor has taken out patient liability insurance for all patients who have given their consent to the clinical study. This cover is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

11.13 Legal Aspects

The clinical study is submitted to the relevant national competent authorities in all participating countries to achieve a clinical trial authorization (CTA).

The study will commence (i.e., initiation of study sites) when the CTA and favorable Ethics opinion have been received.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

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APPENDIX A: SCHEDULE OF PROCEDURES

Table 1. Schedule of Procedures

Visit/Period	Screening Visit	Treatment Visit	Treatment Evaluation Period	
Time Point	Days -21 to -1	Day 1	Weeks 1, 4, 8, 12, 16, & 20	Week 24 (EOS/ET)[1]
Window			±3 Days	
Assessment				
Informed consent	X[2]			
Inclusion/exclusion review	X	X[3]		
APR and PRR trainings[4]	X	X[3]	X	X
PD-Q, PHQ-9, GAD-7, PCS, and ISI	X			
SPADI, ASES, and EQ-5D-5L[5]		X[3]	X	X
PGIC			X	X
Medical history	X	X[3]		
OA medical history	X			
Patient demographics	X			
Prior treatment and medications	X	X[3]		
Shoulder pain with movement, SI, and rescue medication (eDiary)[6]	X	X	X	X
Pain duration since onset (shoulder AC patients only)	X			
Physical examination	X			X
Index shoulder assessment[7]	X	X[3]	X	X
Contralateral shoulder assessment[7]	X			
Index shoulder X-ray[8]	X			
Vital signs	X	X[3]	X	X
12-lead ECG	X			X
Height	X			
Weight and BMI	X			X
Hematology and chemistry[9]	X			X
Hemoglobin A1c	X			
HIV, HBsAg, and HCV	X			
Serum pregnancy test and FSH[10]	X			
Urine pregnancy test[10]		X[3]		X
Washout of excluded medications[11]	X			
Randomization		X[3]		

Index shoulder aspiration[12]		X[3]		

Table 1. Schedule of Procedures (Continued)

Visit/Period	Screening Visit	Treatment Visit	Treatment Evaluation Period	
Time Point	Days -21 to -1	Day 1	Weeks 1, 4, 8, 12, 16, & 20	Week 24 (EOS/ET)[1]
Window			±3 Days	
Assessment				
Study medication administration		X		
eDiary registration[13]	X			
Rescue medication (dispense/return)[14]	X	X	X	X[15]
HEP compliance (shoulder AC patients only)[16]			X	X
Adverse event assessment[17]	X	X	X	X
Concomitant medications[18]	X	X	X	X

1. For patients who are withdrawn from the study prior to completion, all EOS Visit procedures will be performed at the corresponding visit.
2. Written informed consent must be obtained prior to performing any study-specific procedures.
3. Must be collected or assessed prior to administration of study medication.
4. To be completed prior to questionnaires completed at study site visits.
5. To be completed after APR and PRR training, but prior to any other assessments.
6. These assessments will be collected daily each evening in the eDiary and reviewed (not completed) at site visits.
7. To include assessment of active and passive ranges of motion per standardized measurement protocol. Performed bilaterally (index and contralateral) at the Screening Visit.
8. X-ray of shoulder will include axillary view and true anterior-posterior view to be taken at the Screening Visit (or within 6 weeks of the Screening Visit) and read centrally to confirm eligibility criteria are met.
9. To be analyzed by the Central Laboratory.
10. Pregnancy tests will be performed in women of childbearing potential only. Follicle-stimulating hormone in perimenopausal women who have not had a menstrual period for 1 year will be measured at the Screening Visit.
11. After signing the ICF, patients must stop taking excluded medications (see Section 5.6.1). Excluded medication washout should be for 5 half-lives of the medication and be completed 7 days prior to Day 1.
12. Aspiration must be attempted prior to the injection. If effusion is detected by ultrasound guidance, injector must withdraw to near dryness prior to the injection.
13. Patients will be registered in the eDiary and provided instructions on its use.
14. Rescue medication will be dispensed to patients at the Screening Visit. At each subsequent visit, rescue medication accountability will be performed and additional rescue medication will be returned/dispensed as needed.
15. Rescue medication will be returned but not dispensed at the EOS/ET Visit.
16. Shoulder AC patients will follow a HEP beginning 3 days postinjection through the EOS/ET Visit and record their compliance daily via eDiary.
17. Adverse events will be assessed from the time of informed consent until the end of patient participation in the study.
18. Concomitant medication(s) will be captured from the time of informed consent until the end of patient participation in the study.

AC = adhesive capsulitis; APR = Accurate Pain Reporting; ASES = American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form; BMI = body mass index; ECG = electrocardiogram; eDiary = electronic diary; EOS = End of Study; EQ-5D-5L = EuroQol 5 Dimensions 5 Levels; ET = Early Termination; FSH = follicle-stimulating hormone; GAD-7 = General Anxiety Disorder 7-item scale; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HEP = Home Exercise Program; HIV = human immunodeficiency virus; ICF = informed consent form; ISI = Insomnia Severity Index; OA = osteoarthritis; PCS = Pain Catastrophizing Scale; PD-Q = painDETECT Questionnaire; PGIC = Patient Global Impression of Change; PHQ-9 = Patient Health Questionnaire-9; PRR = Placebo Response Reduction; SI = Sleep Interference; SPADI = Shoulder Pain and Disability Index.

Table 2. Entries to be Completed Daily by the Patient on the Electronic Diary

Sequence of Completion	Daily
1	Shoulder pain with movement
2	SI question
3	HEP compliance[1]
4	Rescue medication usage

1. Only shoulder AC patients.
AC = adhesive capsulitis; HEP = Home Exercise Program; SI = Sleep Interference.

Table 3. Questionnaires to be Completed by the Patient at Study Site Visits

Visit	Screening Visit	Day 1	Weeks 1, 4, 8, 12, 16, & 20	Week 24 (EOS)
Sequence at Visit				
1	PD-Q	SPADI	SPADI	SPADI
2	PHQ-9	ASES	ASES	ASES
3	GAD-7	EQ-5D-5L	EQ-5D-5L	EQ-5D-5L
4	PCS		PGIC	PGIC
5	ISI			

ASES = American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form; EOS = End of Study; EQ-5D-5L = EuroQol 5 Dimensions 5 Levels; GAD-7 = General Anxiety Disorder 7-item scale; ISI = Insomnia Severity Index; PCS = Pain Catastrophizing Scale; PD-Q = painDETECT Questionnaire; PGIC = Patient Global Impression of Change; PHQ-9 = Patient Health Questionnaire-9; SPADI = Shoulder Pain and Disability Index.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Aspartate aminotransferase
Bicarbonate	Blood urea nitrogen
Calcium	Chloride
Creatinine	Glucose
Potassium	Sodium
Total bilirubin	Total protein
Uric acid	

Endocrinology

Follicle-stimulating hormone [1]	Serum pregnancy test
Urine pregnancy test	

1. Follicle-stimulating hormone in perimenopausal women who have not had a menstrual period for 1 year will be measured at the Screening Visit.

Hematology

Hematocrit	Hemoglobin
Hemoglobin A1c	Mean cell volume
Platelet cell count	Red blood cell count
White blood cell count and differential [2]	

2. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Virology

Hepatitis B surface antigen	Hepatitis C antibody [3]
Human immunodeficiency virus [4]	

3. Patients positive for hepatitis C virus (HCV) antibody will have reflex testing for circulating HCV ribonucleic acid.
4. Human immunodeficiency virus screening will use a current fourth generation test for both antibody and viral antigen.

APPENDIX C: HOME EXERCISE PROGRAM FOR PATIENTS WITH SHOULDER ADHESIVE CAPSULITIS

Stretching exercises are a standard component of treatment for shoulder adhesive capsulitis and are required as part of this clinical trial. Please perform the following exercises in the order they are presented below. In performing the exercises, stretch to the point of tension but not pain. Perform each exercise twice daily.

1. Pendulum stretch

Image courtesy of HealthyAndNaturalWorld.Com

Do this exercise first.

Relax your shoulders.

Stand and lean over slightly, allowing the affected arm to hang down.

Swing the arm in a small circle — about a foot in diameter.

Perform 10 revolutions in each direction per session, do 2 sessions a day.

As your symptoms improve, increase the diameter of your swing, but **never force it.**

2. Forward finger walk

Image courtesy of HealthyAndNaturalWorld.Com

Face a wall three-quarters of an arm's length away.

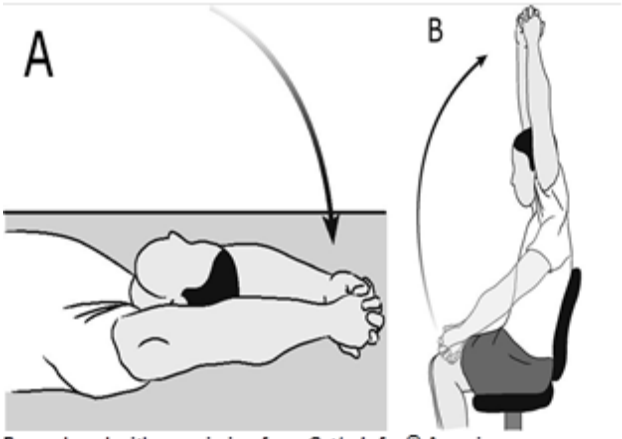
Reach out and touch the wall at waist level with the fingertips of the affected arm.

With your elbow slightly bent, slowly walk your fingers up the wall, spider-like, until you've raised your arm as far as you comfortably can. Your fingers should be doing the work, not your shoulder muscles.

Slowly lower the arm (with the help of the good arm, if necessary) and repeat.

Perform this exercise 10 times per session, do 2 sessions a day.

3. Assisted shoulder forward elevation



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This exercise can be done either lying down (A) or sitting down (B).

Clasp hands together and lift arms above head.

Keep your elbows as straight as possible.

Maintain the elevation for 10-20 seconds, then slowly lower your arms.

Slowly increase the elevation of your arms as the days progress, using pain as your guide.

Repeat 10 times per session, do 2 sessions a day.

4. Lateral finger walk

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Stand with your side toward a wall three-quarters of an arm's length away from the affected arm.

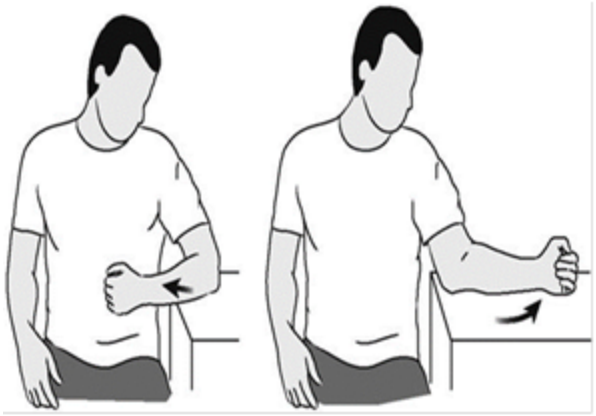
Reach out and touch the wall at waist level with the fingertips of the affected arm.

With your elbow slightly bent, slowly walk your fingers up the wall, spider-like, until you've raised your arm as far as you comfortably can. Your fingers should be doing the work, not your shoulder muscles.

Slowly lower the arm (with the help of the good arm, if necessary) and repeat.

Perform this exercise 10 times per session, do 2 sessions a day.

5. Outward rotation and inward rotation



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Keep your elbow at side of your body or place your elbow on top of a table with proper height.

Slide forearm back and forth, as shown to the maximum degree without pain.

Repeat 10 times per session, do 2 sessions a day.

6. Towel stretch

Image courtesy of HealthyAndNaturalWorld.Com

Hold one end of a towel behind your back and grab the opposite end with your other hand.

Hold the towel in a horizontal position. Use your good arm to pull the affected arm upward to stretch it.

Do this 10 times per session, do 2 sessions a day.

APPENDIX D: INSTRUCTIONS FOR MEASURING RANGE OF MOTION OF THE GLENOHUMERAL JOINT WITH A GONIOMETER[1]

Instrument: Goniometer (Medigauge® electronic digital goniometer for orthopedics, chiropractic, sports medicine, animal science, occupational therapy, physical therapy, and research)

Patient position: Sitting or supine position

Scapular position: Stabilize the scapula by grasping the coracoid process and the spine of the scapula posteriorly (2 people may be needed to fully inhibit scapular motion).

Glenohumeral joint flexion

To measure flexion range of motion (ROM), the patient must be in sitting or supine position with the arm comfortably by the side.

- The patient will be asked to actively flex the shoulder with his/her palm facing medially to end range in the sagittal plane (with no compensatory movements from the thorax or the lumbar spine). Range of motion will be measured by placing the axis of the goniometer over the humeral head. The stationary arm will be aligned with the midline of the trunk. The movable arm will be aligned with the lateral epicondyle.
- For passive ROM, the examiner will passively flex the shoulder with the patient's palm facing medially until end range is reached and measures as above.

1. Magee D. Orthopedic Physical Assessment. 6th edition. Saunders. 2013

Glenohumeral joint abduction

To measure abduction ROM, the patient must be in a sitting or supine position with the arm comfortably by his/her side.

- The patient will be asked to actively abduct the shoulder in external rotation position (palm facing up) to end range (shoulder must remain in the frontal plane). Range of motion will be measured by placing the axis of the goniometer over the anterior aspect of the acromion process.. The stationary arm will be aligned parallel with the midline of the sternum. The movable arm will be aligned with the midshaft of the humerus.
- For passive ROM, the examiner will passively abduct the shoulder with the patient's palm facing up until end range is reached and measures as above.

Glenohumeral external rotation

To measure external rotation ROM with the shoulder in the adduction position, the patient must be in a sitting or supine position. Place a folded towel under the humerus to keep the shoulder and elbow level with the elbow flexed to 90° (palm facing medially) and the forearm perpendicular to the floor.

- The patient will be asked to actively externally rotate the shoulder to end range. Range of motion will be measured by placing the axis of the goniometer on the olecranon process. The stationary arm will be perpendicular to the floor. The movable arm will be aligned with the ulnar styloid process.
- For passive ROM, the examiner will passively externally rotate the glenohumeral joint until end range is reached and measures as above.

Glenohumeral internal rotation in 45°or comfortable abduction

Internal rotation ROM must be measured with the patient in a sitting or supine position, the shoulder abducted to 45° or comfortable position, and the elbow flexed to 90°. Place a folded towel under the humerus to keep the shoulder and elbow level.

- The patient will be asked to actively internally rotate the shoulder with his/her palm facing medially to end range without scapular compensation. Range of motion will be measured by placing the axis of the goniometer on the olecranon process. The stationary arm will be perpendicular to the floor. The movable arm will be aligned with the ulnar styloid process.
- For passive ROM, the examiner will passively internally rotate the glenohumeral joint until end range is reached, ensuring that there is no scapular compensation.

APPENDIX E: COMMONLY PRESCRIBED ANTIDEPRESSANTS BY DRUG CLASS

Class	Generic Name	Brand Name(s)
Selective serotonin reuptake inhibitors	Citalopram	Celexa®
	Escitalopram	Lexapro®, Cipralex®
	Fluoxetine	Prozac®, Sarafem®
	Fluvoxamine	Luvox®
	Paroxetine	Paxil®, Seroxat®
	Sertraline	Zoloft®
Serotonin-norepinephrine reuptake inhibitors		
	Venlafaxine	Effexor®
Tricyclic antidepressants	Amitriptyline	Elavil®
	Doxepin	Sinequan®
	Imipramine	Tofranil®
	Nortriptyline	Aventyl®, Noritren®, Pamelor®
Norepinephrine-dopamine reuptake inhibitors	Bupropion	Wellbutrin®, Zyban®