CLINICAL TRIAL PROTOCOL

Protocol Number	XT-150-1-0302
Title	A Placebo-controlled, Double-blind Evaluation of Safety, Tolerability, and Efficacy of XT-150 for the Treatment of Facet Joint Osteoarthritis Pain
Investigational Product	XT-150, plasmid DNA ([redacted]) formulated in buffered, [redacted] solution
Protocol History	Version 1.0, 12 August 2021 Version 2.0, 18 January 2022 Version 3.0, 08 June 2022
Sponsor	Xalud Therapeutics, Inc. 2120 University Avenue, Suite 205 Berkeley CA 94704 USA Telephone: +1 (925) 997-8216
Sponsor Medical Monitor	[redacted]
Sponsor Clinical Project Manager	[redacted]

Confidentiality Statement:

PROTOCOL APPROVAL PAGE

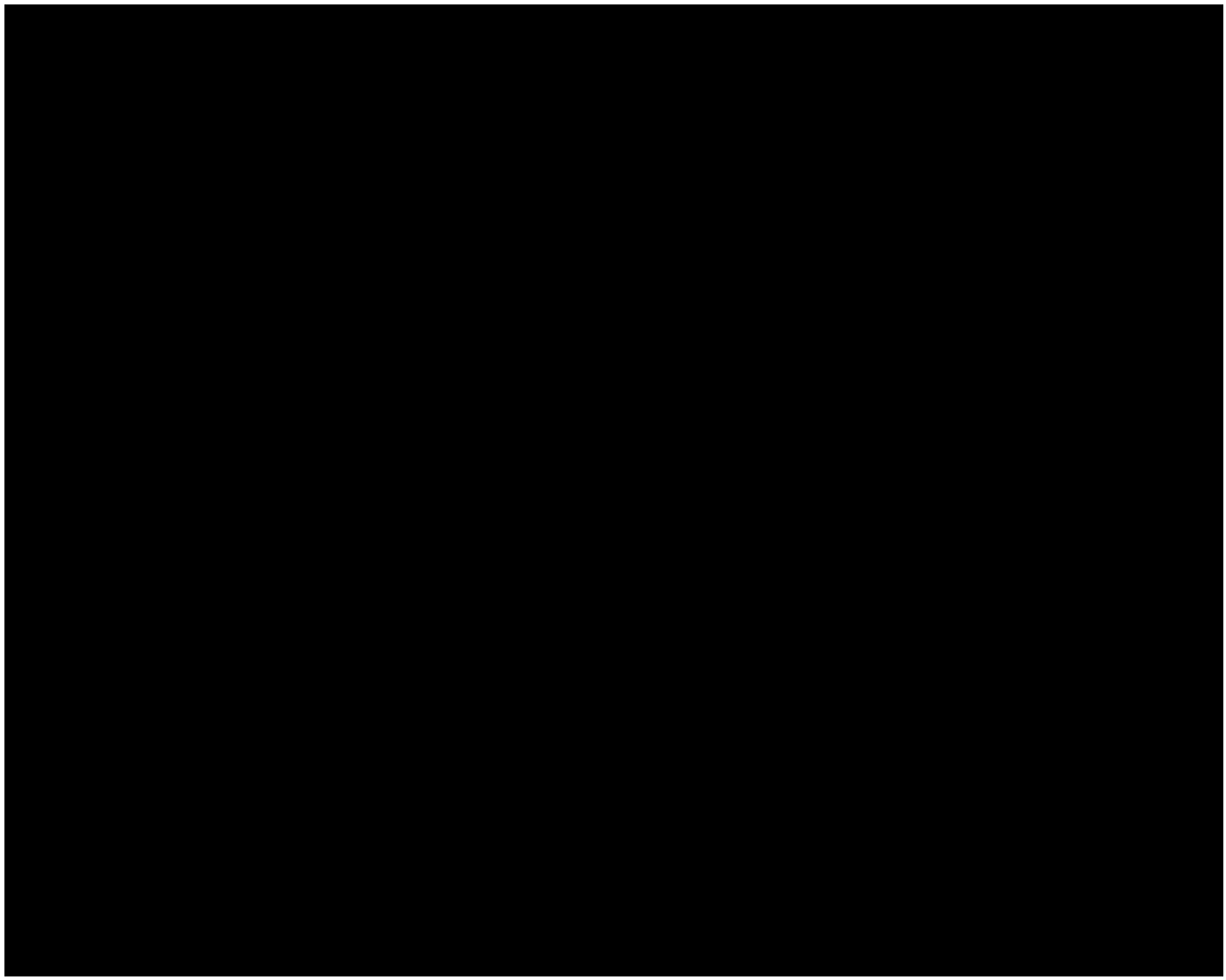
A Placebo-controlled, Double-blind Evaluation of Safety, Tolerability, and Efficacy of XT-150 for the Treatment of Facet Joint Osteoarthritis Pain

Protocol XT-150-1-0302

Version 3.0: 08 June 2022

Sponsor's Approval

The protocol has been approved by Xalud Therapeutics, Inc.



1. PROTOCOL SYNOPSIS

Sponsor: Xalud Therapeutics, Inc.	
Protocol Number: XT-150-1-0302	
Name of Investigational Product: XT-150	
Protocol Title: A Placebo-controlled, Double-blind Evaluation of Safety, Tolerability, and Efficacy of XT-150 for the Treatment of Facet Joint Osteoarthritis Pain	
Study center(s): 3	**Phase:** Phase 2a

Objectives

- Primary: To evaluate the safety and tolerability of a repeat bilateral intra-articular dose of XT-150
- Secondary: To establish the analgesic efficacy of a repeat bilateral intra-articular dose of XT-150 as a treatment for pain in participants with facet joint osteoarthritis (FJOA)

Study Design

This is a Phase 2a safety and efficacy study of XT-150 in adult participants experiencing back pain due to inflammation of the facet joint osteoarthritis (FJOA) and who are eligible for intra-articular glucocorticoid injection, or radiofrequency ablation of medial branches of the primary dorsal ramus of the exiting nerve root, which innervates the adjacent facet joints.

Participants will provide informed consent and meet all study eligibility criteria before any study procedures are initiated. Baseline assessments for study eligibility will be completed on the same day as or within 1 day before administration of study drug.

Study drug will be administered at Day 0 and Day 90 by bilateral intra-articular (IA) injection into the facet capsule, at the affected spinal level (e.g. L3-4, L4-5, or L5-S1) as determined by imaging (e.g., MRI, CT, X-Ray, etc.) and physical exam. Location responsible for facetogenic pain of the spine will be determined by clinical, radiological and diagnostic (lidocaine) intra-articular injection.

Approximately 72 participants will be randomized to placebo or one of two dose treatment groups (24 participants per treatment group).

1. 150 µg XT-150 (1.0mL total delivered by two 0.5 mL injections)
2. 450 µg XT-150 (1.0mL total delivered by two 0.5 mL injections)
3. Placebo (Sterile saline) (1.0ml total delivered by two 0.5 mL injections)

Following the first treatment with XT-150 or Placebo at Baseline (Day 0), participants will be assessed for safety and efficacy in-clinic on Days 7, 14, 30 and 60. At Day 90, all participants will receive a repeat injection with XT-150 or Placebo based on treatment arm assignment at the time of randomization. Following Day 90, participants will be assessed approximately monthly through Day 270.

Participants who have passed their Day 90 visit or who were enrolled prior to the implementation of Protocol V3.0 08Jun2022 and do not reconsent to a second dose will complete the study at Day 180. During this visit, all End of Study visit activities should be completed.

The Schedule of Assessments and Procedures is presented in Table 1. Day 0 is defined as the day of study drug administration. Subsequent study days are defined by the number of consecutive calendar days after drug administration.

Number of Participants and Treatment Groups

Approximately 72 participants will be enrolled in one of 2 XT-150 treatment groups or placebo (24 participants/group).

Inclusion Criteria

Participants are required to meet ALL of the following inclusion criteria:

1. Male or female, between 18 and 90 years of age, inclusive.
2. Sufficiently severe facet arthropathy of lumbar facets as determined by imaging (e.g., MRI, CT, X-Ray, etc.) to establish an underlying basis of disease, as determined by usual bony and ligamentous signs of osteoarthritis (OA). Use of historical images permitted if obtained within the last 12 months.
3. Complaint of nociceptive, mechanical pain of lumbar spine, in particular pain localized to paramedian axis as opposed to midline or radicular. Radicular pain as a secondary finding may be allowed if it is in addition to mechanical pain and can be clinically distinguished by subject
4. LBP (Low Back Pain) worsened by activity or motion of region
5. Have had a positive diagnostic facet pain block with lidocaine; admittance if subject gains 50% relief of pain within 30 minutes of test injection
6. Be free of local or intra-articular infection, tumor or other causes of localized LBP, for example, spondylolysis/pars defect, and adjacent vertebral body compression fracture based on imaging evaluation.
7. Symptomatic disease because of osteoarthritis, established by imaging of facet joint and defined as a worst pain of at least 50 at the Screening Visit and the Baseline (Day 0) Visit (based on scale of 0 to 100, with 100 representing "pain as bad as you can imagine") using Visual Analog Scale (VAS).
8. Stable analgesic regimen during the 4 weeks prior to enrollment. Participants who are not currently on any analgesics at the time of enrollment because they have discontinued prior analgesic therapy due to intolerance or lack of effect may be included. New analgesics or changes to the pre-established regimen during the study, with the exception of rescue medication use, are not permitted.
9. Inadequate pain relief with prior therapies lasting ≥3 months.
10. In the judgment of the Investigator, acceptable general medical condition
11. Heterosexually active participants, male and female who are not surgically sterile or post-menopausal, must agree to use effective contraception, including abstinence, for the duration of the study and for 3 months after the study is completed
12. Have suitable facet joint anatomy for intra-articular injection
13. Willing and able to return for the follow-up (FU) visits
14. Able to read and understand study instructions, and willing and able to comply with all study procedures

Exclusion Criteria

Participants must NOT meet any of the following exclusion criteria:

1. Hypersensitivity, allergy, or significant reaction to lidocaine or any ingredient of the study drug, including double-stranded DNA, [redacted]
2. Facet injection with corticosteroid in the past 6 months
3. Lumbar medial branch nerve ablation (e.g., by radiofrequency technique) within the past 12 months
4. Prior lumbar fusion surgery

5. Prior or existing medial branch nerve stimulation device (e.g., Mainstay device)
6. Scheduled surgical procedure or nerve ablation to joint within the next 6 months; participant agrees not to schedule a surgical procedure, nerve ablation, or added facet injection within 6 months of study treatment
7. High peri-operative risks which in the judgment of the investigator preclude a safe facet joint injection procedure (e.g. extreme obesity putting injection accuracy at risk, etc.)
8. Current treatment with immunosuppressive (systemic corticosteroid therapy [equivalent to >10mg/day prednisone] or other strong immunosuppressant)
9. History of immunosuppressive therapy; high-potency systemic steroids in the last 3 months.
10. Currently receiving systemic chemotherapy or radiation therapy for malignancy
11. Clinically significant hepatic disease as indicated by clinical laboratory results ≥3 times the upper limit of normal for any liver function test (e.g., aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase)
12. Severe anemia (Grade 3; hemoglobin <8.0 g/dL, <4.9 mmol/L, <80 g/L; transfusion indicated), Grade 1 white cell counts (lymphocytes <LLN - 800/mm3; <LLN - 0.8 x 109 /L, neutrophils <LLN - 1500/mm3; <LLN - 1.5 x 109 /L)
13. Positive serology with reflex for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus within 4 weeks of commencing the study
14. Significant neuropsychiatric conditions, dementia, major depression, or altered mental state that in the opinion of the Investigator will interfere with study participation
15. Current treatment with systemic antibiotics or antivirals (EXCEPTION: topical treatments)
16. Current treatment with anticoagulants, other than low-dose aspirin. Patients, if medically feasible, can interrupt anticoagulant therapy by following local medical practice protocol for intra-articular injections for patients on anticoagulant, antiplatelet therapy.
17. Known or suspected history of active alcohol or intravenous/oral drug abuse within 1 year before the screening visit
18. Use of any investigational drug or device within 1 month before enrollment or current participation in a trial that included intervention with a drug or device; or currently participating in an investigational drug or device study.
19. Any condition that, in the opinion of the Principal Investigator, could compromise the safety of the participant, the participant's ability to communicate with the study staff, or the quality of the data

Investigational Product, Dose and Mode of Administration

XT-150 is a plasmid DNA ([redacted]) formulated in buffered, [redacted] saline solution.

Participants will be randomly enrolled into 1 of 3 treatment arms to receive either Placebo or XT-150 (150 µg, 450 µg) on Day 0 and Day 90. Two 0.5 mL intra-articular (facet) injections (for a total dose of 1.0 mL) administered bilaterally will deliver placebo or study drug in a 1:1:1 ratio.

Diagnostic injection with 0.5 mL lidocaine solution at the affected levels, as determined by imaging and physical exam, L3-4, L4-5, or L5-S1 (or the three lumbar cephalad to the sacrum in the case of patients with a 6th lumbar vertebral body). The injection will be performed with fluoroscopic guidance, using the ipsilateral oblique projection. A spinal needle will be placed in an intra-articular position, after local anesthesia of the skin and subcutaneous tissues. The patient will be observed for 1 hour after this injection.

Comparator

Phosphate-buffered saline for injection (placebo) will be the comparator for this study.

Rescue Medication

Participants will be allowed to take acetaminophen (≤3,000 mg in 24 hours) as rescue medication during participation in the study. Rescue medication must not be taken within 12 hours preceding any planned post-treatment visit.

Duration of Treatment

Participation will require a commitment of approximately 270 days of primary safety, tolerability, and efficacy evaluation. Additionally, a screening visit will occur up to 30 days before enrollment.

Baseline assessments for study eligibility will be completed on the day of or within one day before study drug administration. Day 0 is defined as the day of study drug administration. Subsequent study days are defined by the number of consecutive calendar days after drug administration.

Follow-up visits will occur over approximately 9 months on Study Days 7 (±1 day), 14 (±1 day), 30 (±2 days), 60 (±7 days), 90 (±7 days) and about monthly thereafter.

If a participant fails to participate in the follow-up visits, multiple efforts will be made to determine the reason(s), including contacts by telephone and/or registered letter requesting that the participant contact the site and complete the termination assessments.

Criteria for Outcome Measures

Safety

Safety assessments will be recorded throughout the study (up to Study Day 270 [±14 days]) as described in Table 1. All participants will be assessed for adverse events (AEs) and serious adverse events (SAEs), abnormal hematology and chemistry laboratory values, physical examination findings, and vital signs following signing of the informed consent form (ICF) and throughout the study until the visit on Day 270 (±14 days) for each treatment group.

Procedures for collection, storage, and shipping of biodisposition samples are described in the Laboratory Manual.

Efficacy

Efficacy assessments will be recorded throughout the study (as described in Table 1).

The primary efficacy outcome measure is change from baseline in pain intensity at Day 270 but will be collected at each visit, as recorded on a 0-100 VAS.

[redacted]

Secondary outcomes:

- Low back disability: Change from baseline in back disability assessed using the Oswestry Disability Questionnaire, a validated scale ranging from 0 % to -100% disability.
- Patient Assessment: Change from baseline in response to the question "Considering all the ways that facet pain, the pain that brought you into this study, affects you, how are you doing today?", with 1 being very good (asymptomatic and no limitation of normal activities) to 5, very poor (very severe, intolerable symptoms and inability to carry out normal activities)
- Change from baseline in self-reported physical activity will be assessed using the International Physical Activity Questionnaire (IPAQ short form).

Additional outcomes:

- Quality of Life: change from baseline using the Short Form Health Survey (SF12) Physical Health Composite Scores (SF-12 PCS) and Mental Health Composite Scores (SF-12 MCS) components

[redacted]

Statistical Methods

Study results will provide initial estimates of dose-related measures: safety, tolerability, and efficacy.

[redacted]

Efficacy will be assessed by comparing the difference between treatment groups in the reduction in pain (as measured by the change from baseline in pain intensity as recorded on VAS) at Day 270 and at each study visit, starting at Day 7 [±1 day]. [redacted]

All participants who receive study drug will be included in the safety analysis. The incidence of treatment-emergent AEs will be presented by treatment group and system organ class and preferred term according to the Medical Dictionary of Regulatory Affairs (MedDRA®) version 24 or higher, relationship to the study drug, and severity. Adverse events will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Dose-limiting toxicity is defined as any related, Grade 2 or higher toxicity (according to CTCAE), where relationship to investigational product cannot be ruled out.

Table 1: Schedule of Assessments and Procedures

Scheduled Event	**Screen**	**Baseline[a] and Dosing**	**Follow-up**				**Dosing**	**Follow-Up**					**EOS**
Study Day	**-30 to -1**	**0**	**7 (±1)**	**14 (±1)**	**30 (±2)**	**60 (±7)**	**90 (±7)**	**120 (±7)**	**150 (±7)**	**180[l] (±7)**	**210 (±7)**	**240 (±7)**	**270 (±14)**
Informed Consent[b]	X												
Complete Medical History, Demographics and Physical Examination[c]	X												
Record Prior Medications[d]	X	X											
Confirmation of FJOA by Imaging[e]	X												
Lidocaine Facet Selection	X												
Efficacy Assessments													
VAS	X[k]	X[k]	X	X	X	X	X	X	X	X	X	X	X
Oswestry Disability Index		X	X	X	X	X	X	X	X	X	X	X	X
International Physical Activity Questionnaire (IPAQ)		X	X	X	X	X	X	X	X	X	X	X	X
SF12		X	X	X	X	X	X	X	X	X	X	X	X
Participant Global Assessment[f]		X	X	X	X	X	X	X	X	X	X	X	X
[redacted]			X	X	X	X	X	X	X	X	X	X	X
Clinical Assessments													
Record Height and Weight, Calculate BMI	X												X

Scheduled Event	**Screen**	**Baseline[a] and Dosing**	**Follow-up**				**Dosing**	**Follow-Up**					**EOS**
Study Day	**-30 to -1**	**0**	**7 (±1)**	**14 (±1)**	**30 (±2)**	**60 (±7)**	**90 (±7)**	**120 (±7)**	**150 (±7)**	**180[l] (±7)**	**210 (±7)**	**240 (±7)**	**270 (±14)**
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Exam of the Back (injection site)	X	X	X	X	X	X	X	X	X	X	X	X	X
Brief Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X
Record AEs		X	X	X	X	X	X	X	X	X	X	X	X
Record SAEs		X	X	X	X	X	X	X	X	X	X	X	X
Record Concomitant Medications[g]		X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments													
HIV, Hepatitis B and C	X												
Serum Chemistries	X												
CBC with Differential and Platelet Count	X												
Pregnancy Test (for WOCBP)[m]	X						X						X
Whole Blood for Plasmid DNA Biodisposition[h]		X	X	X	X								
Serum for IL-10 and Anti-IL-10 Antibody Assessments		X	X	X	X	X	X			X			X
Study Drug Administration													
Enroll Participant[i]		X											
Administer Study Drug[j]		X					X[l]						

Key: AE= adverse event; BMI = body mass index; CBC = complete blood count; FJOA = facet joint osteoarthritis; IL-10 = interleukin 10; SAE = serious adverse event; SF12 = short form health survey; VAS = visual analog scale of pain intensity; WOCBP = women of childbearing potential

[a] Baseline assessments are performed before injection on Day 0 OR up to one day before study drug administration. Vital signs also assessed at 1 hour after study drug administration.

[b] Informed consent must be obtained before initiating any study procedures.

[c] Obtain demographics (age, race, gender) and complete, relevant, medical, and surgical history (including currently active conditions and inactive pain conditions diagnosed) at the Screening visit. Update medical and surgical and pain treatment history at the baseline visit. The physical examination includes the injection site for infections or reactions.

[d] Record prior medications, including prescription and nonprescription medications and herbal supplements. Update prior medications at the baseline visit.

[e] For inclusion in the study, the patient must have sufficiently severe facet arthropathy of lumbar facets as determined by imaging (e.g., MRI, CT) to establish an underlying basis of disease, as determined by usual bony and ligamentous signs of OA. Use of historical images is permitted if the images were obtained within the last 12 months.

[f] Participant global assessment will be recorded by answering the question: "Considering all the ways that facet pain, the pain that brought you into this study, affects you, how are you doing today?" on a scale of 1 to 5, 1 being very good (asymptomatic and no limitation of normal activities) to 5, very poor (very severe, intolerable symptoms and inability to carry out normal activities)

[g] Pain therapy and concomitant medications are recorded [redacted].

[h] Whole blood for PCR analysis of DNA plasmid biodisposition will be drawn at Baseline, before study drug injection then approximately 4 hours after injection, then on Days 7, 14, and 30 scheduled clinic visits.

[i] Verify that the participant meets all study inclusion and exclusion criteria before enrollment as close to study drug dosing as possible.

[j] Participant will receive one intra-articular, 1-mL dose of study drug by intra-articular injection to the facet capsule at time zero. Participant to be monitored for 4 hours after administration for signs of study drug reaction.

[k] Participants must have a VAS score of at least 50 out of 100 at Screening and at Baseline in order to qualify for study inclusion and treatment.

[l] Participants who were enrolled in the study prior to implementation of Protocol Version 3.0 08Jun2022 and either are past their Day 90 visit or do not consent to the Day 90 dose will complete the study at Day180. At this visit, all EOS procedures should be completed.

[m] A serum pregnancy test will be performed for WOCBP at Screening and Day 270/EOS. A urine pregnancy test will be performed for WOCBP at Day 90 prior to study drug administration.

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3. LIST OF ACRONYMS, ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 2: Abbreviations

Abbreviation	Explanation
AE	Adverse event
BMI	Body mass index
CBC	Complete blood count
COVID-19	Coronavirus Disease of 2019
CTCAE	Common Terminology Criteria for Adverse Events (V5.0)
CRF	Case report form
CRO	Contract Research Organization
CT	Computed Tomography
DNA	Deoxyribonucleic acid
ePRO	Electronic Patient Reported Outcome
FDA	Food and Drug Administration
FJOA	Facet Joint Osteoarthritis
FU	Follow-up
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIV	Human Immunodeficiency Virus
IA	Intra-articular
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IL-10	Interleukin-10
IPAQ	International Physical Activity Questionnaire
IRB	Institutional Review Board
IT	Intrathecal
ITT	Intent-to-treat
LBP	Lower back pain
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated-Measures

Abbreviation	Explanation
MRI	Magnetic Resonance Imaging
OA	Osteoarthritis
ODI	Oswestry Disability Index
OTC	Over the counter
PBS	Phosphate Buffered Saline (placebo)
PI	Principal Investigator
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical analysis plan
SF12	Short Form Health Survey
SOC	System Organ Class
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
VAS	Visual Analog Scale of Pain Intensity
WOCBP	Women of childbearing potential
XT-150	Plasmid DNA, [redacted], expressing a proprietary variant of human IL-10 protein, formulated in a [redacted] solution for injection.

4. BACKGROUND AND RATIONALE

4.1. XT-150

Complete and current information on XT-150 can be found in the Investigator's Brochure (IB).

XT-150 is a new treatment for chronic pain from pathogenic inflammation. It is a plasmid designed to transiently express a variant of the anti-inflammatory cytokine interleukin-10 (IL 10).

The mechanism of action of XT-150 is through a reduction in inflammation. XT-150 returns target tissues to normal function by induction and release of a single-amino acid variant human IL-10 (IL-10v), that acts to modulate inflammation through multiple pathways: suppressing pro-inflammatory cytokine production and release, down-regulating cytokine receptors and up-regulating antagonists; and inhibiting hydrogen peroxide and nitric oxide production (Moore, 2001; Sawada, 1999).

[redacted]

When XT-150 is administered by injection at the site of chronic inflammation, low levels of human IL-10v protein are produced over the following weeks, which reduces the pain associated with joint inflammation. [redacted] Additionally, the targeted delivery of XT-150 inside the joint capsules restricts the potential for systemic adverse events (AEs).

XT-150 presents a treatment opportunity for patients suffering significant pain from osteoarthritis, such as those in need of knee replacement or interventions in other joints; or the many patients who are not good surgical candidates. This study will help select doses to establish safety, tolerability, and effectiveness in subsequent clinical trials.

4.2. Nonclinical Pharmacology and Toxicology

The IB provides detailed summaries of Good Laboratory Practice (GLP) and non-GLP preclinical pharmacology and toxicology studies.

[redacted]

[redacted]

4.3. Clinical Experience

In osteoarthritis, three clinical trials with XT-150 are complete and one is in progress. XT-150 has been safe and well tolerated after a single injection of up to 600 µg (the highest dose yet delivered) in 1 mL or 2 mL (600 µg) intra-articular knee injections. Study subjects have been followed for up to 6 months following the XT-150 injection. No Serious Adverse Events (SAEs) related to XT-150 have been reported to date. The IB contains detailed summaries.

XT-150 is not marketed in any country.

Table 3: Human Clinical Trials in Osteoarthritis with XT-150

Study	Design	Sites	Results Summary
XT-150-1-0201 NCT03282149 (Completed March 30, 2019)	Sequential dose escalation (15, 150, and 450 µg) Placebo controlled (1:3) 8 subjects per cohort (6 active:2 placebo) Safety and Efficacy follow-up assessments for 6 months [redacted]	University of Adelaide	No Serious Adverse Events Mild injection site reactions No changes in acute phase biomarkers or lab chemistries No induction of anti-drug antibodies [redacted]
XT-150-1-0202 NCT03477487 (Completed July 12, 2019)	Sequential dose escalations (15, 150, 450 and 600 µg) Open label, non-comparator 8 subjects per group Safety and efficacy follow-up assessments for 6 months	Napa Pain Institute (Neurovations)	No Serious Adverse Events Mild injection site reactions No changes in acute phase biomarkers or lab chemistries [redacted]

Study	Design	Sites	Results Summary
XT-150-1-0203 NCT03769662 (Completed Oct 30, 2019)	Single dose – 450 µg Open-label, non-comparator Up to 24 participants who completed the 0201 study • Placebo – first injection; or • Injection into 0201-untreated knee; or • Second injection of the 0201-treated knee Safety and efficacy follow-up assessments for 6 months [redacted] Test for anti-IL-10 antibody following a second injection	University of Adelaide	16 of 24 participants from 0201 study received 450 µg XT-150 as of 1 May 2019. One unrelated SAE of a fall leading to hospitalization for a broken hip No XT-150-related AEs [redacted]
XT-150-2-0204 NCT04124042 (Started 14 Feb 2020, enrollment completed 26 April 2021)	Double-blind, placebo-controlled comparison to 150 µg or 450 µg XT-150 Approximately 90 participants per arm. Total 270 participants Stage A (6 months) – single injection, placebo controlled. Stage B (6 months) – Option for second injection to the Index Knee, randomly assigned to 150 µg or 450 µg XT-150. Efficacy Measures: • 30% Responder Rate for WOMAC Pain • WOMAC, KOOS, and BPI measures of pain and activities of daily living	Neurovations, USA University of Adelaide/CMAX Alfred Health Melbourne, AU Carolinas Pain Research Institute, USA eStudySite, USA Source Healthcare, USA	Study is ongoing.

4.4. Summary of Known Benefits and Potential Risks

4.4.1. Potential Benefits

Participants will receive active investigational product or phosphate-buffered saline injection (placebo). The effects of XT-150 for FJOA have not been previously explored, however potential therapeutic benefits of XT-150 for the treatment of FJOA pain are:

- Increased mobility for many weeks following a single dose of XT-150
- Reduction in requirement for pain medications and therapies
- Reduction in pain symptoms for many weeks following a single dose of XT-150.

4.4.2. Known Risks

Intra-articular injection in the knee with XT-150 has been well tolerated in clinical trials of OA pain. Based on multiple animal studies and 4 clinical trials in osteoarthritis, XT-150-related adverse events are most commonly minor injection site reactions.

4.4.3. Potential Risks

Nonclinical studies and clinical studies with XT-150 are described in the IB. XT-150 posed minimal risk in these studies. General risks associated with IA injection are injection site reactions and infection, which will be explicitly captured in follow-up safety assessments.

4.4.3.1. Safety of DNA as a Therapeutic Agent

DNA as a therapeutic agent has been well tolerated. The main theoretical safety concerns regarding the clinical use of DNA are that they might integrate with the host/patient DNA, or that injection of foreign DNA might stimulate anti-DNA antibodies or an autoimmune reaction (Prazeres 2014).

With both DNA vaccines and DNA plasmids, the risk of integration was repeatedly found to be low with years of research into the possibility (FDA 2007; Prazeres 2014). With plasmids, the potential for integration has been removed by excluding any sequences that might drive homologous recombination and integration into the genome. In fact, excluding these elements lowers the risk of plasmid integration to less than the rate of naturally occurring mutations (Prazeres 2014). XT-150 has been designed to transiently express a variant of human IL-10 without integrating into the genome.

Immunogenicity of DNA appears to be low (Ferraro 2011), and correlates to the lack of success of DNA agents (even pathogenic bacterial sequences) as vaccines. No link has been found between plasmid DNA injections and any clinical markers of autoimmunity (Prazeres 2014). In addition, DNA plasmids have been used in research and development for 25 years. Synthetic vectors share the non-infectious properties of viral vectors and elicit low immunogenicity and lower toxicity compared to viral vectors (Xu 2011; Gôrecki 2006).

4.4.4. Safety of Interleukin-10

Published studies in the literature have reported IL-10 protein therapy to be safe in humans. The safety of IL-10 protein injections was studied in healthy volunteers at doses up to 100 µg/kg. Details of these studies can be found in the IB.

After injection in healthy volunteers at doses up to 100 µg/kg, wild-type human IL-10 protein was found to be rapidly degraded with a half-life of 2.0 to 4.5 hours (Chernoff 1995; Huhn 1996; Huhn 1997; Milligan, 2005). In the Huhn, 1997 study, after intravenous administration of high doses of IL-10 protein (100 µg/kg), 42% (15/36) of the volunteers experienced flu-like adverse effects, the most common of which were headache (11/36 participants, 31%), fever (5/36, 14%), and back pain (3/36, 8%). Pharmacodynamic effects from intravenous IL-10 treatment included transient increases in neutrophils and monocytes, and decreases in lymphocytes, which peaked around 6 hours after injection (Chernoff, 1995). When given intravenously, IL-10 was also found to inhibit production of the cytokines IL-1β and tumor necrosis factor-alpha (TNF-α), and reduce T-lymphocyte stimulation.

Recombinant human IL-10 has been clinically tested as a therapy in humans in a number of indications without serious or irreversible side effects. In these trials, IL-10 injections of up to 25 µg/kg were reported to be well tolerated. With chronic intravenous and high doses, statistically significant hematological changes were observed, as well as fever. Adverse events of neutrophilia, headache, injection site pain, anemia, and nausea were observed with daily dosages in patients with Crohn's Disease.

As an anti-inflammatory agent, the biological activity of IL-10 is different than that of other interleukins. Exogenous IL-10 is the only interleukin shown to be well tolerated. However, the anti-inflammatory activity of IL-10 treatment could mask latent infections (Moore, 2001). Since IL-10 has been theorized to mask latent infections, any participant who has a current autoimmune condition or documented immunodeficiency, has a history of immunosuppression, or is currently receiving treatment with immunosuppressive agents is excluded from this study.

Note that XT-150 is a sterile aqueous formulation of a plasmid designed to transiently express a proprietary variant of IL-10. XT-150 expression of the variant IL-10 is expected to be safer than systemic injection of active IL-10 protein as therapy for the following reasons:

- Rather than injections of IL-10 protein, XT-150 treatment will result in IL-10v levels that exist transiently and at a much lower concentration.
- The IL-10v levels from XT-150 expression will be localized in the intra-articular joint space. Low systemic levels of IL-10 from XT-150 treatment may be present for short periods of time and if present are unlikely to lead to adverse effects, [redacted].

4.4.5. Possible Anticipated Adverse Events and Clinical Monitoring

Anticipated AEs for which there will be specific safety monitoring in humans will be based on the preclinical studies [redacted] as well as the published reports of studies of IL-10 protein injections to healthy volunteers. In a publication of the incidence and characteristics of intra-articular facet joint injection by Kim, 2020, the incidence of major procedure-related complications, such as local injections site infection, was demonstrated to be

very low (< 1%). Aseptic technique will be used, and the investigators are highly trained and experienced in the administration of intra-articular injections.

Based on published reports of IL-10 protein injections in humans, the following AEs could be attributed to XT-150-produced IL-10v. IL-10 protein doses were more than 1000-fold higher than can be expected with XT-150.

- Minor decreases in neutrophils and T-lymphocytes.
- Changes in hemoglobin, platelet counts, and leukopenia
- Flu-like adverse effects related to IL-10, including symptoms of headache, and fever, chills, nausea, and myalgias, as reported by Chernoff, 1995, Huhn, 1996, Huhn, 1997, and van Deventer, 1997.

None of these AEs have been recorded for [redacted] participants across all clinical studies following knee injections with XT-150 doses up to 600 µg, including 0201 study participants who received a second injection in the 0203 study.

4.4.6. Risk-Benefit Summary

The IL-10v expressed by XT-150 is nearly identical to IL-10 that occurs naturally in the body. The targeted delivery of XT 150 directly to the osteoarthritic joint capsules reduces potential systemic adverse effects since it primarily localizes in the synovial tissues with very low, transient expression levels of IL-10v in the circulation. Potential for local injection site infection is low since aseptic technique will be used and the investigators are highly trained and experienced in the administration of intra-articular injections.

Benefit has been demonstrated in multiple animal models of [redacted]. The doses used to provide pain relief have been consistent across animal models [redacted]. Those doses will be tested in this study.

In two clinical trials, XT-150-1-0201 and 0202, [redacted] There have been no SAEs. AEs possibly related to XT-150 were mild, transient injection site reactions and knee pain.

Overall, based on risk/benefit analysis, the current study appears to be suitable for the planned population in this clinical trial.

4.5. Justification for Dosing Regimen

XT-150 is administered by targeted delivery (i.e., directly at the site of intervention). For OA, the delivery is via intra-articular injection. [redacted]

A standard 1 mL volume of administration will be used for all treatment groups.

4.6. Population to be Studied

About 72 adult participants with a diagnosis of moderate to severe pain due to facet osteoarthritis will be enrolled in this study.

4.7. Statement of Compliance

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), the ethical principles of the Declaration of Helsinki, and applicable regulatory and Institutional Review Board (IRB) requirements.

5. STUDY PURPOSE, OBJECTIVES AND ENDPOINTS

The purpose of this study is to gather evidence for the safety, tolerability, and efficacy of XT-150 as a treatment for pain associated with FJOA.

5.1. Study Objectives

5.1.1. Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of a repeat bilateral intra-articular dose of XT-150.

5.1.2. Secondary Objectives

The secondary objective is to establish the analgesic efficacy of a repeat bilateral intra-articular dose of XT-150 as a treatment for pain in participants with facet joint osteoarthritis (FJOA).

5.2. Study Endpoints

5.2.1. Safety Endpoints

Safety assessments will be recorded throughout the study (up to Study Day 270 [±14 days]) as described in Table 1. All participants will be assessed for:

- Adverse events (AEs) and serious adverse events (SAEs),
- Abnormal hematology and chemistry laboratory values,
- Physical examination findings, and
- Vital signs

following signing of the informed consent form (ICF) and throughout the study until the visit on Day 270 (±14 days) for each treatment group.

5.2.2. Efficacy Endpoints

5.2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is change from baseline in pain intensity at Day 270 as recorded on a 0-100 VAS.

5.2.2.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- [redacted]
- Change from baseline in Oswestry Disability Index (ODI) scores
- Change from baseline in Patient Global Assessment scores
- Change from baseline in International Physical Activity Questionnaire (IPAQ) scores

5.2.2.3. Exploratory Efficacy Endpoints

Exploratory efficacy endpoints include:

- Change from baseline Short Form Health Survey (SF12) Physical Health Composite Scores (SF-12 PCS) and Mental Health Composite Scores (SF-12 MCS)

[redacted]

6. STUDY DESIGN

6.1. Description of the Study

This is a Phase 2a, safety and efficacy study of XT-150 in adult participants experiencing back pain due to inflammation of the facet joint (Facet Joint Osteoarthritis [FJOA]) and who are eligible for intra-articular glucocorticoid injection, or radiofrequency ablation of medial branches of the primary dorsal ramus of the exiting nerve root, which innervates the adjacent facet joints.

Participants will provide informed consent and meet all study eligibility criteria before any study procedures are initiated. Baseline assessments for study eligibility will be completed on the same day as or within 1 day before administration of study drug.

Study drug will be administered at Day 0 and Day 90 by intra-articular (IA) injection into the facet capsules, bilaterally at the affected spinal level (e.g. L4-5 and L5-S1). Location responsible for facetogenic pain of the spine will be determined by clinical, radiological and diagnostic (lidocaine) intra-articular injection.

Up to 72 participants will be randomized to one of two dose treatment groups or to placebo (24 participants per treatment group).

1. 150 µg XT-150 (1.0 mL total delivered by two 0.5 mL injections)
2. 450 µg XT-150 (1.0 mL total delivered by two 0.5 mL injections)
3. Placebo (Sterile phosphate-buffered saline for injection, PBS) (1.0 mL total delivered by two 0.5 mL injections).

Following the first treatment with XT-150 or Placebo at Baseline (Day 0), participants will be assessed for safety and efficacy in-clinic on Days 7, 14, 30 and 60. At Day 90, all participants will receive a repeat injection with XT-150 or Placebo based on treatment arm assignment at the time of randomization. Following Day 90, participants will be assessed approximately monthly through Day 270.

Participants who have passed their Day 90 visit or who were enrolled prior to the implementation of Protocol V3.0 08Jun2022 and do not reconsent to a second dose will complete the study at Day 180. During this visit, all End of Study visit activities should be completed.

The Schedule of Assessments and Procedures is presented in Table 1. Day 0 is defined as the day of study drug administration. Subsequent study days are defined by the number of consecutive calendar days after drug administration.

6.2. Follow Up Assessments

All participants will be assessed for physical examination findings and vital signs following signing of the informed consent form (ICF) and for AEs and SAEs, throughout the study for each treatment group.

Serum samples will be collected from all participants to test for the presence of anti-IL-10 antibodies and IL-10 protein. Samples will be analyzed using a validated assay by an independent, central bioanalytical laboratory. Procedures for collection, storage, and shipping of immunogenicity samples are described in the study Lab Manual.

Whole blood samples will be collected from all participants to test for the presence of XT-150 plasmid. Samples will be analyzed using a validated assay by an independent, central bioanalytical laboratory. Procedures for collection, storage, and shipping of immunogenicity samples are described in the study Lab Manual.

Efficacy assessments will be performed at Baseline, on Day 7, Day 14, Day 30, and approximately monthly thereafter for up to 9 months. Efficacy endpoints will be evaluated at each study visit and overall.

A telephone call documenting safety and efficacy assessments may be used for participants unable to physically attend follow up visits due to COVID-19 infection or SARS-CoV-2 exposure concerns. Home services may be employed for blood collections.

6.3. Number of Participants

Up to 72 participants will receive study drug administration and evaluated.

6.4. Expected Duration of Subject Participation

Subject participation will require a commitment of approximately 9 months of safety, tolerability, and efficacy evaluation. In addition, a screening visit will occur up to 30 days before enrollment.

Baseline assessments for study eligibility will be completed within one day before study drug administration. Day 0 is defined as the day of study drug administration. Subsequent study days are defined by the number of consecutive calendar days thereafter.

Follow-up visits will occur on Study Day 7, Study Day 14, Study Day 30, and approximately monthly thereafter.

6.5. Method of Treatment Assignment and Blinding

After informed consent has been obtained, participants will be screened for study eligibility before enrollment.

Participants will be randomly enrolled into one of 3 groups, two XT-150 treatment groups (150 μg or 450 μg) or placebo.

Instructions for study drug preparation and dosing are given in Section 8.

7. SELECTION, DISCONTINUATION, AND WITHDRAWAL OF SUBJECTS

To be enrolled in this study, all participants must meet all of the following inclusion criteria and none of the exclusion criteria.

7.1. Participant Inclusion Criteria

Participants are required to meet ALL of the following inclusion criteria:

1. Male or female, between 18 and 90 years of age, inclusive.
2. Sufficiently severe facet arthropathy of lumbar facets as determined by imaging (e.g., MRI, CT, X-Ray, etc.) to establish an underlying basis of disease, as determined by usual bony and ligamentous signs of osteoarthritis (OA). Use of historical images permitted if obtained within the last 12 months.
3. Complaint of nociceptive, mechanical pain of lumbar spine, in particular pain localized to paramedian axis as opposed to midline or radicular. Radicular pain as a secondary finding may be allowed if it is in addition to mechanical pain and can be clinically distinguished by subject
4. LBP (Low Back Pain) worsened by activity or motion of region
5. Have had a positive diagnostic facet pain block with lidocaine; admittance if subject gains 50% relief of pain within 30 minutes of test injection
6. Be free of local or intra-articular infection, tumor or other causes of localized LBP, for example, spondylolysis/pars defect, and adjacent vertebral body compression fracture based on imaging evaluation.
7. Symptomatic disease because of osteoarthritis, established by imaging of facet joint and defined as a worst pain of at least 50 at the Screening Visit and the Baseline (Day 0) Visit (based on scale of 0 to 100, with 100 representing “pain as bad as you can imagine”) using Visual Analog Scale (VAS).
8. Stable analgesic regimen during the 4 weeks prior to enrollment. Participants who are not currently on any analgesics at the time of enrollment because they have discontinued prior analgesic therapy due to intolerance or lack of effect may be included. New analgesics or changes to the pre-established regimen during the study, with the exception of rescue medication use, are not permitted.
9. Inadequate pain relief with prior therapies lasting ≥3 months.
10. In the judgment of the Investigator, acceptable general medical condition
11. Heterosexually active participants, male and female who are not surgically sterile or post-menopausal, must agree to use effective contraception, including abstinence, for the duration of the study and for 3 months after the study is completed
12. Have suitable facet joint anatomy for intra-articular injection
13. Willing and able to return for the follow-up (FU) visits

14. Able to read and understand study instructions, and willing and able to comply with all study procedures

7.2. Subject Exclusion Criteria

Participants must NOT meet any of the following exclusion criteria:

1. Hypersensitivity, allergy, or significant reaction to lidocaine or any ingredient of the study drug, including double-stranded DNA, [redacted]
2. Facet injection with glucocorticoid/corticosteroid in the past 6 months
3. Lumbar medial branch nerve ablation (e.g., by radiofrequency technique) within the past 12 months
4. Prior lumbar fusion surgery
5. Prior or existing medial branch nerve stimulation device (e.g. Mainstay device)
6. Scheduled surgical procedure or nerve ablation to joint within the next 6 months; participant agrees not to schedule a surgical procedure, nerve ablation, or added facet injection within 6 months of study treatment
7. High peri-operative risks which in the judgment of the investigator preclude a safe facet joint injection procedure (e.g. extreme obesity putting injection accuracy at risk, etc.)
8. Current treatment with immunosuppressive (systemic corticosteroid therapy [equivalent to >10mg/day prednisone] or other strong immunosuppressant)
9. History of immunosuppressive therapy; high-potency systemic steroids in the last 3 months.
10. Currently receiving systemic chemotherapy or radiation therapy for malignancy
11. Clinically significant hepatic disease as indicated by clinical laboratory results ≥3 times the upper limit of normal for any liver function test (e.g., aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase)
12. Severe anemia (Grade 3; hemoglobin <8.0 g/dL, <4.9 mmol/L, <80 g/L; transfusion indicated), Grade 1 white cell counts (lymphocytes <LLN - 800/mm3; <LLN - 0.8 x 109 /L, neutrophils <LLN - 1500/mm3; <LLN - 1.5 x 109 /L)
13. Positive serology with reflex for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus within 4 weeks of commencing the study
14. Significant neuropsychiatric conditions, dementia, major depression, or altered mental state that in the opinion of the Investigator will interfere with study participation
15. Current treatment with systemic antibiotics or antivirals (EXCEPTION: topical treatments)
16. Current treatment with anticoagulants, other than low-dose aspirin. Patients, if medically feasible, can interrupt anticoagulant therapy by following local medical practice protocol for intra-articular injections for patients on anticoagulant, antiplatelet therapy.

17. Known or suspected history of active alcohol or intravenous/oral drug abuse within 1 year before the screening visit
18. Use of any investigational drug or device within 1 month before enrollment or current participation in a trial that included intervention with a drug or device; or currently participating in an investigational drug or device study.
19. Any condition that, in the opinion of the Principal Investigator (PI), could compromise the safety of the participant, the participant's ability to communicate with the study staff, or the quality of the data

7.3. Requalification for Entry

Participants not fulfilling the entry criteria and not treated may be rescreened for participation if their eligibility characteristics have changed. The screening lidocaine facet injection procedure may be repeated one time to identify the joint that is causing pain.

7.4. Participant Withdrawal Criteria

7.4.1. Withdrawal from Study Protocol

Participants who wish to withdraw completely from this clinical study should be encouraged to complete the assessments for Day 270/Termination. However, participants may withdraw consent to participate in this study at any time without penalty or loss of benefits to which the participant is otherwise entitled. Every reasonable effort should be made to determine the reason a participant withdraws prematurely, and this information should be recorded on the appropriate page(s) of the case report form (CRF). Participants may be withdrawn from the study for any of the following reasons:

- Participant unable or unwilling to continue
- Participant's perceived lack of benefit
- Participant elects to withdraw informed consent
- Due to an adverse event
- Protocol non-compliance
- Participant is lost to follow up
- The PI considers that it is in the participant's best interest not to continue participation in the study

7.4.2. Early Discontinuation from Study Drug Administration

If a participant needs to discontinue study drug, the reason (i.e. due to an SAE, need for an excluded medication, etc.) should be documented in the eCRF.

NOTE: The Medical Monitor should be contacted to discuss whether to continue with planned XT-150 dosing in the event that the participant situation changes significantly in the 24 hours prior to XT-150 injection such that participant safety is at risk.

7.5. Replacement of Participants

After randomization, withdrawn participants will not be replaced.

7.6. Study Termination by Sponsor and Termination Criteria

The Sponsor reserves the right to terminate an investigational site or this clinical study at any time. Reasons for termination may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies of XT-150 indicate a potential health hazard to participants
- Serious or persistent noncompliance by the Investigator with the protocol, clinical research agreement, or applicable regulatory guidelines in conducting the study
- IRB decision to terminate or suspend approval for the investigation or the Investigator
- Investigator request to withdraw from participation
- Participant enrollment is unsatisfactory

8. STUDY DRUGS

Participants will be randomly enrolled into XT-150 (150 µg, or 450 µg) or placebo groups and will receive two 0.5 mL intra-articular injections bilaterally (total dose of 1.0 mL) into the facet joint on Day 0 and Day 90.

8.1. Formulation and Preparation of Study Drug

XT-150 is a plasmid DNA formulated as a sterile, aqueous phosphate-buffered saline solution. [redacted] Table 4 lists the quantitative composition of the final drug product per vial.

Table 4: Final Drug Product Quantitative Composition Per Vial

Ingredient	Function	Target Amount per Vial
[redacted] plasmid DNA	Active ingredient	150 µg/mL or 450 µg/mL
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Phosphate-buffered isotonic solution	Solution	

[redacted]

8.1.3. Placebo Formulation

Sterile phosphate-buffered saline (PBS) for injection (two 0.5 mL injections for total of 1 mL) will be the placebo comparator for this study.

Data from pilot studies in animals showed that saline solutions produce no efficacious benefit in a wide variety of pain models. PBS has not demonstrated clinical benefit for pain and is therefore suitable for use as a placebo.

8.2. Investigational Product Administration

Investigational product (XT-150 or placebo) will be administered as two bolus, bilateral intra-articular injections into the facet joint. The injection will be performed with fluoroscopic guidance.

8.3. XT-150 Blinding

The Investigator, study staff, and participants will be blinded to the treatment administration. The unblinded pharmacy will provide ready-to-use syringes, coded by participant number to the clinical staff. The Pharmacy will maintain a log in a secure location with the participant number and the assigned lot number of the investigational product. Lot numbers are unique to dosage strengths.

8.4. Compliance

Treatment compliance for intra-articular study drugs will be documented in the CRF by recording the date, injection time, and whether the dose of study drug was completely injected.

8.5. Previous and Concomitant Medications and Substances

All pain therapy (both medications and treatments) and all prescription and over-the-counter medications and supplements administered within the last month prior to enrollment will be documented in the CRF.

8.5.1. Prohibited Medications

See exclusion criteria (Section 7.2).

The following treatments are prohibited prior to study drug administration at Day 0 and Day 90:

- Current treatment with antibiotics or antiviral agents (exception: topical treatments)
- Current treatment with immunosuppressive agents
- Current use of systemic steroids (equivalent to >10 mg/day prednisone)
- Current treatment with anticoagulants, other than low-dose aspirin. Patients, if medically feasible, can interrupt anticoagulant therapy by following local medical practice protocol for intra-articular injections for patients on anticoagulant, antiplatelet therapy.

Concomitant medications for pain will be allowed at doses and frequencies prescribed prior to the study treatment. In the event a participant requires additional analgesic treatment during study participation, he/she should take the protocol-specified rescue medication. Introduction of new medications to treat FJOA pain during the study period is prohibited and considered a protocol deviation.

8.5.2. Rescue Medication

Acetaminophen (≤ 3,000 mg in 24 hours) will be allowed as rescue medication during participation in the study. Rescue medication must not be taken within 12 hours preceding any planned post-treatment visit.

[redacted]

8.6. Accountability Procedures

The pharmacy or study personnel are responsible for ensuring that all XT-150 study drug shipments, inventory, and use are recorded and accountability is maintained.

The Sponsor's site monitors will be responsible for checking drug accountability at the site. Inventory records must be readily available for inspection by regulatory authorities at any time. Each shipment of study drug will contain an acknowledgment of receipt section for site signature. Upon receipt of study drug, the pharmacy or study personnel will visually inspect the shipment and verify the number and condition of vials or capsules received. Refer to the Pharmacy Manual for additional information.

8.7. Study Drug Handling and Disposal

Upon completion of the study, termination of the study, or upon written authorization from the Sponsor, all unused and partially used study drug will be centrally destroyed. All records of disposal by a centralized destruction site will be maintained by the Sponsor.

9. STUDY PROCEDURES

Study procedures should be completed within the windows provided in the Schedule of Assessments and Procedures located in Table 1.

A telephone call documenting safety and efficacy assessments may be used for participants unable to physically attend follow up visits due to COVID-19 infection or coronavirus exposure concerns. Home services may be employed for blood collections.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

9.1. Screening

Unless otherwise indicated, screening assessments should be performed within 30 days of enrollment.

- Obtain signed informed consent prior to initiating any study-related assessments or procedures
- Obtain a complete medical history and risk factors (e.g., active malignancy, diabetes mellitus, immunosuppression, transplant recipient, trauma, dialysis) and Intensive Care Unit admission and discharge (if applicable)
- Obtain demographics (age, race, gender)
- Obtain history of all pain medications (prescription and non-prescription) and therapies (e.g., physical therapy, acupuncture) and all other medications and supplements (prescription and over-the-counter [OTC]) administered within the last month prior to enrollment
- Confirm severe facet arthropathy of lumbar facets as determined by imaging (e.g., MRI, CT, X-Ray, etc.) to establish an underlying basis of disease, as determined by usual bony and ligamentous signs of osteoarthritis (OA). Use of historical images permitted if obtained within the last 12 months.
- Clinical assessments
  - Conduct complete physical examination, including height and weight (calculate body mass index [BMI]) and examination of the injection site
  - Measure vital signs (temperature and the site collected [oral, rectal, temporal, or tympanic], heart rate, blood pressure, and respiratory rate)
  - Verify VAS ≥50 prior to lidocaine injection to verify eligibility (see Inclusion Criterion #7). A second VAS should be completed post-lidocaine injection to verify participant's reduction in pain is ≥50% (see Inclusion Criterion #5).
- Laboratory Assessments
  - Obtain blood samples for:
  - Hematology tests (complete blood count [CBC] with differential and platelets count),

  - HIV, Hepatitis B and C serology with reflex
  - Serum pregnancy test for women of child-bearing potential
  - Serum chemistry tests (21)
- Lidocaine testing for target facet joint for study drug injection:
  - Diagnostic unilateral injection with approximately 0.5 mL lidocaine solution at the affected level, as determined by imaging (e.g., MRI, CT, X-Ray, etc.) and physical exam, L3-4, L4-5, or L5-S1 (or the three lumbar cephalad to the sacrum in the case of patients with a 6th lumbar vertebral body). The injection will be performed with fluoroscopic guidance, using the ipsilateral oblique projection. A spinal needle will be placed in an intra-articular position, after local anesthesia of the skin and subcutaneous tissues. The patient will be observed for 1 hour after this injection.
  - Retesting may be performed once at the same level or a different level. If retesting is performed on the same day as the initial test, the retest should be separated from the initial test by at least 1 hour.
- Confirm participant qualification by inclusion/exclusion

9.2. Baseline (Day-1 or Day 0)

Baseline assessments may be completed the day before or day of study drug administration, before the XT-150 injection.

[redacted]

- Brief physical exam, including examination of the injection site.
- Obtain any changes from the complete medical history.
- Record any changes or updates in medications, including pain medications (prescription and non-prescription) and therapies (e.g., physical therapy, acupuncture) administered since Screening visit.
- Efficacy assessments
  - VAS score. Verify VAS ≥50.
  - Oswestry Disability Index
  - International Physical Activity Questionnaire (IPAQ) short form
  - SF12
  - Record participant's response to the OA question: "Considering all the ways that facet pain, the pain that brought you into this study, affects you, how are you doing today?" on a scale of 1 to 5, 1 being very good (asymptomatic and no limitation of normal activities) to 5, very poor (very severe, intolerable symptoms and inability to carry out normal activities)
- Clinical assessments

  - Measure vital signs (temperature and the site collected [oral, rectal, temporal, or tympanic], heart rate, blood pressure, and respiratory rate)
- Laboratory assessments
  - Obtain serum for analysis of IL-10 protein and anti-IL-10 antibodies
  - Obtain whole blood for plasmid DNA analysis
- Confirm participant qualification by inclusion/exclusion criteria. Enroll participant prior to dosing

9.3. Day 0

- Before administration of study drug:
  - Confirm that all study criteria are met (inclusion and exclusion)
  - Brief physical exam
  - Injection site examination
  - Record any ongoing medical observations that occurred since Screening visit
  - Record any new AEs since Screening
  - Record any concomitant medications since Screening including prescription, OTC and herbal medications. Ensure no excluded medications.
- Administer study drug (see Section 8 for details on preparation)
  - Aseptic techniques will be used in the preparation and administration of XT-150
  - Injections will be guided by ultrasound, fluoroscopy or equivalent visualization
  - All injections of study drug must be performed by a specialist who is qualified, trained, and experienced to perform intra-articular injections to the Facet joint.
  - Examine injection site for infections or reactions
- Clinical assessments
  - Monitor Participant for approximately for 4 hours for signs of study drug reaction.
  - Measure vital signs (temperature, heart rate, blood pressure, and respiratory rate) at least once about 1 hour after injection
- Laboratory assessments
  - Approximately **4 hours** after administration, obtain whole blood for XT-150 plasmid analysis

[redacted]

9.4. Day 90 (±7 days)

- Clinical Assessments:
  - Brief physical exam, including the injection site for infections or inflammation
  - Measure vital signs (temperature, heart rate, blood pressure, and respiratory rate)
- Efficacy assessments
  - VAS score
  - Oswestry Disability Index
  - IPAQ short form
  - SF12
  - Record participant's response to the question: "Considering all the ways that Facet pain, the pain that brought you into this study, affects you, how are you doing today?" on a scale of 1 to 5, 1 being very good (asymptomatic and no limitation of normal activities) to 5, very poor (very severe, intolerable symptoms and inability to carry out normal activities)
  - Record changes in drug regimens or pain therapy
- Assess, identify, and record any AEs since last visit
- Record any changes in concomitant medications since including prescription, OTC, and herbal medications.
- Laboratory assessments
  - Obtain urine pregnancy test and evaluate results. Participant must have negative urine pregnancy test prior to dosing.
  - Obtain serum for analysis of IL-10 protein and anti-IL-10 antibodies
- Administer study drug (see Section 8 for details on preparation)
  - Aseptic techniques will be used in the preparation and administration of XT-150
  - Injections will be guided by ultrasound, fluoroscopy or equivalent visualization
  - All injections of study drug must be performed by a specialist who is qualified, trained, and experienced to perform intra-articular injections to the Facet joint.
  - Examine injection site for infections or reactions
- Clinical assessments post-study drug administration
  - Monitor Participant for approximately for 1 hour for signs of study drug reaction
  - Measure vital signs (temperature, heart rate, blood pressure, and respiratory rate) at least once about 1 hour after injection

9.5. Between Clinic Visits

[redacted]

9.6. Follow Up Visits – Day 7 (±1 day), Day 14 (±1 day), Day 30 (±2 Days), Day 60 (±7 days), Day 120 (±7 days), Day 150 (±7 days), Day 180 (±7 days), Day 210 (±7 days) and Day 240 (±7 days)

Participants who were enrolled in the study prior to implementation of Protocol Version 3.0 08Jun2022 and either are past their Day 90 visit or do not consent to the Day 90 repeat dose will have their End of Study Visit at Day 180. In this situation, participants should complete all of the End of Study / Day 270 Assessments. Refer to Section 9.7.

- Clinical assessments
  - Brief physical exam, including the injection site for infections or inflammation
  - Measure vital signs (temperature, heart rate, blood pressure, and respiratory rate)
- Efficacy assessments
  - VAS score
  - Oswestry Disability Index
  - IPAQ short form
  - SF12
  - Record participant's response to the question: "Considering all the ways that Facet pain, the pain that brought you into this study, affects you, how are you doing today?" on a scale of 1 to 5, 1 being very good (asymptomatic and no limitation of normal activities) to 5, very poor (very severe, intolerable symptoms and inability to carry out normal activities)
  - Record changes in drug regimens or pain therapy
- Laboratory assessments
  - Days 7 (±1 day), 14 (±1 day), and 30 (±2 days): Obtain whole blood for analysis of XT-150 plasmid DNA analysis
  - Days 7 (±1 day), 14 (±1 day), 30 (±2 days), 60 (±7 days), and 180 (±7 days): Obtain serum for analysis of IL-10 protein and anti-IL-10 antibodies
- Assess, identify, and record any AEs since last visit
- Record any changes in concomitant medications since screening visit including prescription, OTC, and herbal medications.

[redacted]

9.7. End of Study Visit – Day 270 (±14 days)

- Clinical assessments
  - Brief physical exam, including height and weight (calculate body mass index [BMI]) and examination of the injection site for infections or inflammation
  - Measure vital signs (temperature, heart rate, blood pressure, and respiratory rate)
- Efficacy assessments
  - VAS score
  - Oswestry Disability Index
  - IPAQ short form
  - SF12
  - Record participant's response to the question: "Considering all the ways that Facet pain, the pain that brought you into this study, affects you, how are you doing today?" on a scale of 1 to 5, 1 being very good (asymptomatic and no limitation of normal activities) to 5, very poor (very severe, intolerable symptoms and inability to carry out normal activities)
  - Record changes in drug regimens or pain therapy
- Laboratory assessments
  - Obtain blood sample for serum pregnancy test for women of child-bearing potential
  - Obtain serum for analysis of anti-IL-10 antibodies
- Assess, identify, and record any AEs since last visit
- Record any changes in concomitant medications since screening visit including prescription, OTC, and herbal medications.
- [redacted]

10. ASSESSMENT OF SAFETY

10.1. Safety Parameters

Safety will be assessed through the evaluation of AEs, vital signs, and serum laboratory data according to the Schedules of Assessments and Procedures presented in Table 1 and assessment of anti-IL-10 antibodies as described in Section 12.

10.2. Adverse Events

Medical history will be collected for all participants at the time of informed consent. After consent, all adverse events (AEs)/serious adverse events (SAEs) will be collected through the last study visit on Day 270. All AEs/SAEs that occur during or after the time of study drug treatment will be considered treatment-emergent AEs (TEAEs). The Investigator will assess all AEs and SAEs and will record the following information on the appropriate CRF page and SAE Report Form (as applicable):

- Event term
- Date of onset
- Date of resolution or stabilization
- Severity
- Relationship to study drug
- Action taken with study medication

Medically indicated laboratory tests (emergency or unscheduled tests) should be conducted at the local laboratory. The Investigator should employ best medical judgment in determining how to manage AEs and SAEs. Any questions regarding AE or SAE management should be directed to the Medical Monitor.

10.3. Adverse Event Reporting

The Sponsor has obligations for expedited reporting of SAEs meeting specific criteria to worldwide regulatory authorities. Therefore, the Sponsor must be notified immediately regarding any SAE that occurs after informed consent.

All SAEs must be reported to the Medical Monitor or Contract Research Organization (CRO) Drug Safety Team within 24 hours of the investigational site's knowledge of the event.

All SAEs and discontinuations due to AEs will be reported to the IRB based on the IRB's reporting requirements.

The study site will transmit a SAE report to the CRO Drug Safety Team by email or facsimile (email is preferred method) within 24 hours. Contact details will be provided to all sites. An initial report can be made via telephone, but a completed SAE report must still be emailed or faxed within 24 hours of the site's knowledge of the event. The study sites will be provided with SAE report forms wherein the following information is requested.

- Participant identification, Investigator name, and site number

- SAE information: event term, onset date, severity, and causal relationship
- The outcome(s) attributable to the event (i.e., death, a life-threatening AE, inpatient hospitalization, prolongation of existing hospitalization, a persistent or significant disability or incapacity, or other important medical event[s])
- A summary of relevant test results, pertinent laboratory data, and any other relevant medical history
- The first and last dates of study drug administration. NOTE: as this is a double-blind study, SAE reports should not indicate specific study drug assignments
- Indicate if the study drug was discontinued or the study drug administration schedule was modified
- Supplemental information may include the following hospital records: laboratory results, radiology reports, progress notes, admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates

In addition, relevant CRF pages should be appended to communicate relevant study drug and participant outcome information. The SAE report should be emailed or faxed within 24 hours with as much of the above information as available at the time. The following minimum information is required for reporting an SAE: participant identification, reporting source, the event, and the causality assessed by the Investigator (or medically qualified designee). Supplemental information may be transmitted using a follow-up SAE report and should not delay the initial report. The Sponsor or designee may contact the investigational site to solicit additional information or follow up on the event.

The Investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the appropriate pages of the participant's CRF.

10.4. Definitions

10.4.1. Adverse Event

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An AE can arise with any use of the drug and with any route of administration, formulation, or dose, including an overdose.

Facet Joint Osteoarthritis-related events should not be considered or recorded as AEs or SAEs.

Laboratory abnormalities should not be recorded as AEs or SAEs unless they are associated with clinical signs or symptoms, or require medical intervention. However, each laboratory abnormality (e.g., clinically significant changes detected on hematology, or lab chemistries) independent from any underlying medical condition that requires medical or surgical intervention, or that leads to interruption of study drug infusion or discontinuation, must be

recorded as an AE, or SAE if applicable. If the laboratory abnormality is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than as the individual laboratory abnormality. In addition, laboratory abnormalities or other abnormal test assessments that are associated with signs or symptoms must be recorded as AEs or SAEs if they meet the definition of an AE (or SAE) as described above or in Section 10.4.4.

10.4.2. Suspected Adverse Drug Reaction

A suspected adverse drug reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of Investigational New Drug safety reporting, ‘‘reasonable possibility’’ means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse drug reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

10.4.3. Life-Threatening AE or Life-Threatening Suspected Adverse Drug Reaction

An AE or suspected adverse drug reaction is considered ‘‘life threatening’’ if, in the view of either the Investigator or Sponsor, its occurrence places the patient or participant at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

10.4.4. Serious AE or Serious Suspected Adverse Reaction

An AE or suspected 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 AE – see definition above
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect in the offspring of a participant who received study drug

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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 hospitalization, or the development of drug dependency or drug abuse.

10.4.4.1. Serious Adverse Event Definition Clarifications

- Death is an outcome of an AE, and not an AE in itself
- All deaths during study drug administration or up to the follow-up (FU) visit on Day 180, regardless of cause or relationship, must be reported

- "Occurring at any dose" does not imply that the participant is actively receiving study drug at the time of the event
- "Life-threatening" means that the participant was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, had it occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If an AE prolongs hospitalization, it is a SAE.
- "Inpatient hospitalization" means the participant has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department (although an emergency department visit may define a medically important event, which is also considered a SAE).
- The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and other clinical information. In such cases, the diagnosis should be documented as the AE or SAE, rather than as the individual signs or symptoms.

10.4.5. Unexpected AE or Unexpected Suspected Adverse Drug Reaction

An AE or suspected adverse drug reaction is considered "unexpected" if:

- It is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if an Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if an Investigator's Brochure listed only cerebral vascular accidents.

''Unexpected,'' as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

10.5. Adverse Event Classification

10.5.1. Relationship to Investigational Drug

The Investigator's assessment of causality must be provided for all AEs (serious and non-serious) (Table 5). An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study drug caused or contributed to an AE.

Table 5: Guidelines for Assessing Relationship of Event to Study Drug

Unrelated	There is little or no chance that the Investigational Product caused the AE; other conditions, including concurrent illnesses, progression or expression of the disease state, or a reaction to a concomitant medication best explain the event
Related	The association of the AE with the Investigational Product is unknown, however, the AE is not clearly due to another condition, or a reasonable temporal association exists between the AE and treatment administration and, based on the Investigator's clinical experience, the association of the AE with the Investigational Product seems likely

10.5.2. Severity

All AEs will be graded for severity to describe the maximum intensity of the AE based on Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0) (National Cancer Institute, 2017). For purposes of consistency, these intensity grades are defined in Table 6 .

Table 6: Guidelines for Severity Assessments

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money)
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to adverse event

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment. If the event is believed to be unrelated to study drug administration, then an alternative explanation should be provided.

10.6. Adverse Event Follow-up

All unresolved SAEs (“ongoing” at discharge) will be followed by the study staff until resolution or deemed stable.

10.7. Adverse Events of Special Interest

10.7.1. Adverse Events of Noted Interest in IL-10 Protein Trials

Safety will include the following reported IL-10 protein-associated toxicities as defined by CTCAE (v5.0). Systemic levels of XT 150 produced IL-10 protein are expected to be more than 1000-fold lower than when given as a protein solution (Huhn, 1997); and XT-150 will be predominately localized to the facet joint space.

- Grade 1 (unexplained) fever – 38.6°C to 39°C

- Grade 2 allergic, cytokine release, or infusion-related reactions - Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours
- Grade 2 injection site reaction - Pain; lipodystrophy; edema; phlebitis
- Grade 2 neutropenia - <1500 to 1000/mm3; <1.5 to 1.0 x109/L

10.7.2. Localized Signs of Infection or Inflammation at the Injection Site

Events that, in the opinion of the Investigator, may represent localized signs of infection or inflammation at the XT-150 injection site (e.g., pain, erythema, swelling, pruritus, warmth, hematoma, induration) must be recorded as AEs on the CRF. In general, these events will be temporally related to the injection.

10.8. Toxicity Management

The Investigator should employ best medical judgment in determining how to manage AEs. Any questions regarding AE management should be directed to the Medical Monitor.

10.9. Risks for Women of Childbearing Potential or During Pregnancy

The risks of XT-150 administration during pregnancy have not been evaluated. Male and female participants who are heterosexually active and not surgically sterile must agree to use effective contraception, including abstinence, for the duration of the study.

During the study, participants should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual cycle). The Investigator must immediately notify the Medical Monitor or CRO Drug Safety Team of any female participant or female partner of any male participant that becomes pregnant at any time during study participation. All pregnancies must be reported to the Medical Monitor or CRO Drug Safety Team using the Pregnancy Report Form within 24 hours of the investigational site's knowledge of the event. The Medical Monitor/CRO will ask the site to obtain a separate consent from the female participant (or female partner of a male participant) using an IRB-approved template in order to follow-up periodically during the pregnancy for ongoing health and safety information through the end of the pregnancy, as applicable.

Any anomalies, complications, abnormal outcomes, or birth defect(s) observed in the child must be reported as a SAE using the SAE Report Form within 24 hours of the investigator or study personnel's first knowledge. While elective and uncomplicated induced abortion not required for medical reasons does not constitute an AE or SAE (even if the patient or patient's partner is hospitalized to undergo abortion), spontaneous abortion is considered a fatal event and must be reported as an AE and SAE, as appropriate.

All pregnancies will be reported to the IRB based on the IRB's reporting requirements.

11. ASSESSMENT OF EFFICACY PARAMETERS

11.1. Efficacy Parameters

Efficacy will be assessed through the evaluation of Visual Analog Scale (VAS) scores, Oswestry Disability Index (ODI) scores, International Physical Activity Questionnaire (IPAQ) scores, SF-12, Participant Global Assessment scores [redacted] according to the Schedule of Assessments and Procedures in Table 1.

11.1.1. VAS

The VAS will be administered via ePRO at each study visit. The participant will record his/her facet pain level on a scale from 0 (no pain) to 100 (worst pain). Paper questionnaires will be available for completion by the participant as a back-up to the ePRO if needed.

11.1.2. ODI

The ODI captures how a participant's back pain is affecting his/her ability to manage in everyday life. The ODI will be administered via ePRO at each study visit from Baseline through Day 270. Paper questionnaires will be available for completion by the participant as a back-up to the ePRO if needed.

11.1.3. IPAQ

The IPAQ measures physical activity. The IPAQ will be administered via ePRO at each study visit from Baseline through Day 270. Paper questionnaires will be available for completion by the participant as a back-up to the ePRO if needed.

11.1.4. SF-12

The SF12 measures quality of life and functional health and well-being. The SF-12 will be administered via ePRO at each study visit from Baseline through Day 270. Paper questionnaires will be available for completion by the participant as a back-up to the ePRO if needed.

11.1.5. Participant Global Assessment

The Participant Global Assessment asks the participant "Considering all the ways that facet pain, the pain that brought you into this study, affects you, how are you doing today?". The participant answers the question on a scale of 1 to 5, 1 being very good (asymptomatic and no limitation of normal activities) to 5, very poor (very severe, intolerable symptoms and inability to carry out normal activities. The Participant Global Assessment will be administered via ePRO at each study visit from Baseline through Day 270. Paper questionnaires will be available for completion by the participant as a back-up to the ePRO if needed.

[redacted]

12. ASSESSMENT OF ANTI-IL-10 ANTIBODIES

Presence of anti-IL-10 antibodies in serum will be assessed. Whole blood for detection of anti-IL-10 antibodies will be drawn at Baseline, then on Days 7, 14, 30, 60, 90, 180, and 270 then processed to serum. Testing will be conducted following completion of the study.

Procedures for collection, storage, and shipping of immunogenicity samples are described in the study Laboratory Manual.

13. ASSESSMENT OF XT-150 PLASMID DNA BIODISTRIBUTION

Presence of plasmid DNA in whole blood will be assessed. Whole blood for detection of plasmid DNA will be drawn at Baseline, Day 0 + 4 hours, then on Days 7, 14, and 30. Testing will be conducted following completion of the study.

Procedures for collection, storage, and shipping of plasmid DNA samples are described in the study Laboratory Manual.

14. STATISTICAL METHODS

A comprehensive Statistical Analysis Plan (SAP) will be prepared and finalized before database lock. Any changes to the methods described in the final SAP will be described and justified as needed in the clinical study report.

Descriptive statistics (mean, standard deviation, median, minimum, and maximum for continuous variables and count and percentages for categorical variables) for demographics and other baseline characteristics will be provided by treatment group for all participants in the Intent-to-Treat (ITT) and Safety Populations.

14.1. Determination of Sample Size

A total of 72 subjects will be randomized to the 3 treatment groups in a 1:1:1 ratio. As this study occurs early in the clinical development process, the sample size is not based on considerations of statistical power. As an illustration of sensitivity, if a treatment arm shows a responder rate of 50%, the 95% confidence interval around that rate would range approximately from 29% to 71%.

14.2. Analysis Populations

The Intent-to-Treat (ITT) Population will comprise all enrolled participants who received the treatment injection, analyzed according to randomized treatment. [redacted]

The Safety Population will comprise all participants who receive any amount of study drug, analyzed according to treatment actually received.

14.3. Analysis of Study Population and Participant Characteristics

Demographics (including age, race, and gender), medical history including history of pain medication use, Baseline assessments (including height, weight, BMI, [redacted], clinical signs and symptoms, and administration of study drug) will be summarized in the ITT and Safety Populations.

14.4. Safety Analysis

All participants who receive any amount of study drug (Safety Population) will be included in the safety analyses.

Safety will be evaluated by presenting summaries of AEs, clinical laboratory tests, and vital signs. Safety variables will be tabulated by treatment group.

Adverse events will be graded using the CTCAE v5.0 and will be coded using the Medical Dictionary of Regulatory Affairs (MedDRA®), Version 24 or higher. AEs will be collected for each participant from the signing of the informed consent through the last study visit on Day 180.

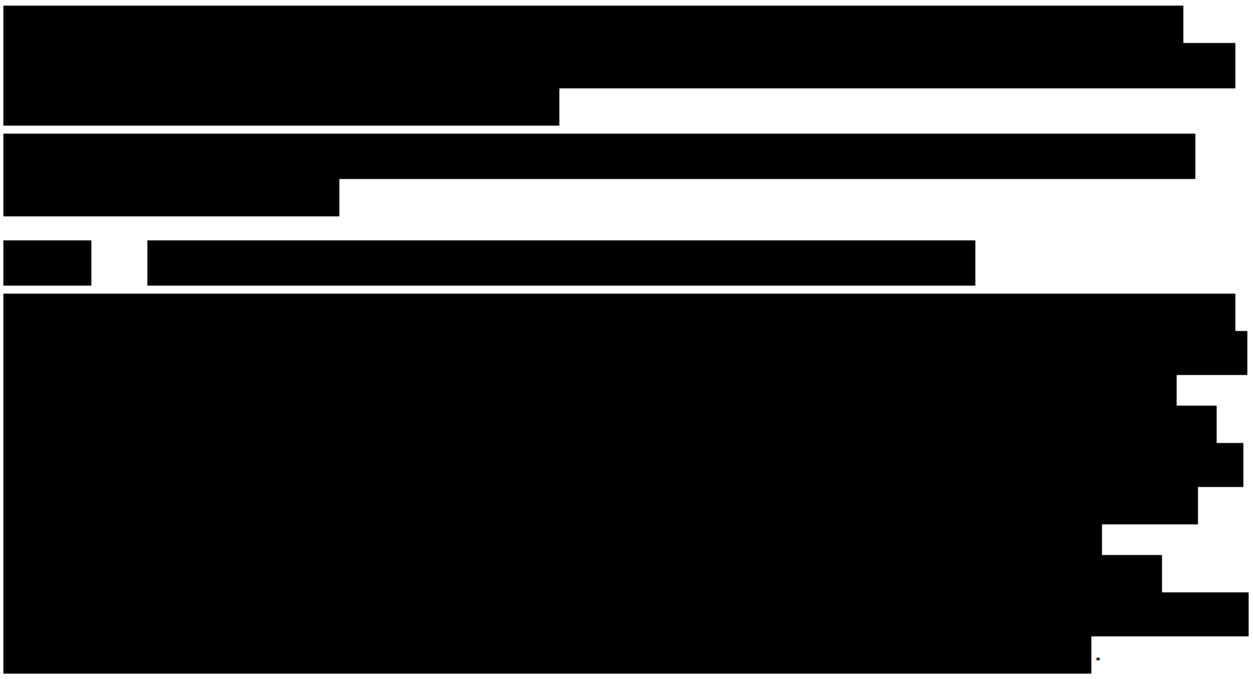
A treatment-emergent adverse event (TEAE) is defined as an AE that occurs during or after study drug administration. The incidence of TEAEs will be presented by system organ class

(SOC) and preferred term (PT), by SOC, PT, and relationship to the study drug administration, and by SOC, PT, and severity. In addition, the incidence of serious TEAEs and TEAEs leading to discontinuation of study drug will be presented by SOC and PT.

Descriptive statistics for clinical laboratory test results, and vital signs, and for changes from Baseline, will be presented by time point. Baseline is defined as the measurement closest to, but prior to, the administration of study drug. Incidences of potentially clinically significant clinical laboratory results, and vital signs, as defined in the SAP, will also be summarized by time point. A summary of abnormal physical examination findings will also be presented.

14.5. Efficacy Analysis

All inferential analyses of efficacy will be based on 180 days after dose administration (Day 270). Efficacy assessments at other study visit time point will also be performed. All efficacy analyses will be specified in the SAP.



14.6. Bioanalytical Analyses

Whole blood samples from participants who received the XT-150 will be analyzed for anti-IL10 antibodies and plasmid DNA using validated assays. Any detection of anti-IL-10 antibodies or plasmid will be described by treatment and timepoint.

14.7. Handling of Dropouts and Missing, Unused, and Spurious Data

Every effort will be made to collect all data at specified times. All participants who received any dose of XT-150 study drug but with missing outcome data will nonetheless be included in the Safety Population. Treatment of missing or spurious data will be specified in the SAP.

14.8. Termination Criteria

Withdrawals from the study and from study drug will be summarized in a listing.

14.9. Deviation Reporting

Protocol deviations will be summarized by treatment group. Protocol deviations are defined as any variation from the protocol, including enrollment of a participant who did not meet all inclusion and exclusion criteria and failure to perform the assessments and procedures within the required time frame.

15. INVESTIGATOR REQUIREMENTS

15.1. Protocol Adherence

The Investigator must adhere to the protocol as detailed in this document and agree that the Sponsor must approve any change to the protocol before seeking approval from the IRB. The Investigator will be responsible for enrolling only those participants who have met the protocol inclusion and exclusion criteria.

15.1.1. Investigator or Designee Experience

The Investigator or Investigator's designee is required to be qualified, trained, and experienced in the administration of study drug by intra-articular injection.

15.2. Case Report Forms

The CRF will be supplied by the Sponsor or designee for the recording of all information and study data as specified by this protocol. All CRFs must be completed by trained study personnel. The Investigator is responsible for ensuring that the CRF data are entered and completed in a timely manner.

Once all data queries and issues have been resolved for each participant, the Investigator will electronically sign each participant's CRF to attest to the accuracy of the data.

15.3. Source Document Maintenance

Source documents are defined as documentation related to original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, study- or participant-specific e-mail correspondence, computer printouts, laboratory data, and recorded data from automated instruments. All source documents produced in this study will be maintained by the Investigator and made available for inspections by the Sponsor and by regulatory authorities. The original signed ICF (and any updates, if appropriate) for each participating participant shall be filed with records kept by the Investigator, and a copy shall be given to the participant.

A telephone call documenting safety and efficacy assessments may be used for participants unable to physically attend follow up visits due to COVID-19 infection or corona virus exposure concerns. Participant responses will be captured in source documents, including circumstances for use of telephone follow up.

15.4. Study Monitoring Requirements

An authorized Sponsor representative will conduct site visits to inspect study data, participants' medical records, and CRFs in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, GCPs, and the foreign regulations and guidelines, as applicable. A study monitor will be utilized for monitoring ongoing drug accountability and adherence to protocol procedures.

The Investigator will allow representatives of the Sponsor and regulatory authorities to inspect facilities and records relevant to this study.

15.5. Study Completion

The Sponsor requires the following data and materials before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and study test results from Screening throughout the study through Day 270
- CRFs (including data queries) properly completed by appropriate study personnel and signed and dated by the Investigator
- Copies of complete drug accountability records (drug inventory log and an inventory of returned or destroyed clinical material)
- Copies of protocol amendments and IRB/ approval and notification, if appropriate
- A summary of the study prepared by the Investigator (an IRB summary letter is acceptable)

16. QUALITY CONTROL AND QUALITY ASSURANCE

Written standard operating procedures (SOPs) will be followed to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Quality control will be applied to each stage of data handling. Regular monitoring, as defined in ICH GCP, Section 1.8, "The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirement(s)", will be conducted throughout the conduct of the study.

The purpose of monitoring is to verify that:

- Rights and well-being of the human participants are protected
- The reported study data are accurate, complete, and verifiable from source documents
- The conduct of the study is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirements
- Monitoring is an integral role in the quality control of a clinical trial and is designed to ensure and verify the quality of the study

To fulfill the Quality Assurance requirements of GCP, audits will be conducted to assess and assure the reliability and integrity of a study's quality control systems and recognized standards.

The purpose of an audit is to:

- Ensure participant safety
- Assure compliance to study protocol procedures, regulatory requirements, and SOPs
- Assure data quality

17. PROTECTION OF HUMAN PARTICIPANTS

This study will be conducted in compliance with the ICH Technical Requirements for Registration of Pharmaceuticals for Human Use E6 GCP: Consolidated Guidelines, the ethical principles of the Declaration of Helsinki, Food and Drug Administration (FDA) GCP guidelines, and any additional national or IRB-required procedures, particularly those related to the Corona Virus Disease 2019 (COVID-19) pandemic.

17.1. Informed Consent

This study will be conducted in compliance with ICH E6 GCP: Consolidated Guidelines pertaining to informed consent. Participants will give written consent to participate in the study at the first visit, prior to initiation of any study-related procedures, after having been informed about the nature and purpose of the study, participation and termination conditions, risks, and benefits. If a participant is unable to provide written informed consent, the participant's legally acceptable representative may provide written consent, as approved according to institution-specific guidelines. The ICF must be signed and dated by the participant, or the participant's legally authorized representative, prior to study participation. A copy of the ICF must be provided to the participant or the participant's legally authorized representative. If applicable, it will be provided in certified translation for non-English-speaking participants. Signed consent forms must remain in the participant's study file and be available for verification by Sponsor at any time.

17.2. IRB Approval

This protocol, the ICF, and all relevant supporting data must be submitted to the IRB for approval. The protocol, ICF, and any advertisement used to recruit study participants must be approved by the IRB. Approval by the IRB of the protocol and ICF must be obtained before the study may be initiated.

The Investigator is responsible for informing the IRB of any changes made to the protocol, and to advise them, at least once a year, about the progress of the study. The Investigator is also responsible for notifying the IRB of any significant AEs or other important events that occur during the study based on the IRB's reporting requirements.

18. DATA HANDLING AND RECORD KEEPING

Training sessions, regular monitoring of Investigators by Sponsor-designated personnel, instruction manuals, data verification, crosschecking, and data audits will be performed to ensure the quality of all study data. Investigator meetings will be performed to train Investigators and other study personnel in the appropriate collection of study data. The Sponsor or designee will review and validate study data according to standard procedures.

It will be the responsibility of the Investigator to ensure that the essential documents are available at the Investigator or institutional site. Any or all of these documents may be participant to, and should be available for, monitoring by the Sponsor or inspection by the regulatory authorities as defined in the monitoring plan.

18.1. Direct Access to Source Data/Documentation

The Investigator agrees by his/her participation that the results of this study may be used for submission to national or international registration. If required, these authorities will be provided with the name of the Investigator and his or her address, qualifications, and extent of involvement. It is understood that the Investigator is required to provide Sponsor with all study data, complete reports, and access to all study records.

Data generated by this study must be available for inspection by any regulatory authorities, by Sponsor, and by the IRB as appropriate. At a participant's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Medical information obtained from participants during the course of this study is confidential and disclosure to third parties other than those noted above is prohibited.

18.2. Study Drug Accountability

All supplies of XT-150 study drug required for completion of this study will be provided by the Sponsor. It is the responsibility of the Investigator and study staff to ensure that a current record of drug inventory and drug accountability is maintained. Inventory and accountability records must be readily available for inspection and are open to inspection at any time by applicable regulatory authorities.

18.3. Retention of Records

Essential clinical documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product and shipment and delivery of the drug for investigational use is discontinued. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements of specific ICH- and non-ICH countries, or by an agreement with the Sponsor. The Sponsor will inform the Investigator/institution as to when these documents no longer need to be retained.

19. FINANCING AND INSURANCE

The financing and insurance for this study are outlined in the Clinical Trial Agreement.

20. PUBLICATION POLICY

The data generated in this clinical study are the exclusive property of the Sponsor and are confidential. Authorship on any publication of the results from this study will be based on

21. REFERENCES

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APPENDIX 1. CLINICAL LABORATORY TESTS

Hematology

- Hemoglobin
- hematocrit
- total and differential leukocyte count
- red blood cell count
- platelet count

Serum Chemistry

- bilirubin (total and direct)
- alkaline phosphatase (ALP)
- aspartate aminotransferase (AST)
- alanine aminotransferase (ALT)

APPENDIX 2. PROTOCOL SIGNATURE PAGE

I have read and understand the current version of protocol XT-150-1-0302 and the current Investigator's Brochure. I agree to the following:

1. To conduct the trial in compliance with GCP, with applicable regulatory requirement(s), with the protocol agreed to by the Sponsor and given approval/favorable opinion by the IRB.
2. To comply with procedures for data recording and reporting
3. To permit monitoring, auditing, and inspection by the Sponsor, its designated representatives, and regulatory authorities
4. To retain the essential documents in the Investigator/institution files until the Sponsor informs the Investigator or institution that these documents are no longer needed

INVESTIGATOR SIGNATURE:

_____/_____

Investigator Signature Date

_____

Investigator Name

_____

Site Name

_____

Site Address