Study Number	Protocol XT-150-2-0204
Title	A Double-Blind, Placebo-Controlled Assessment of the Tolerability and Efficacy of XT-150 for the Treatment of Moderate to Severe Pain Due to Osteoarthritis of the Knee
Investigational Product	XT-150, plasmid DNA ([redacted]) formulated in buffered, [redacted] solution
Protocol History	Original Version, 1 Oct 2019 Amendment 1, 6 January 2020 Amendment 2, 25 March 2020
Sponsor	Xalud Therapeutics, Inc. Xalud Therapeutics Australia Pty Ltd 2120 University Avenue, Suite 532 Berkeley CA 94704 Telephone: +1 (925) 997-8216
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PROTOCOL APPROVAL PAGE

A DOUBLE-BLIND, PLACBO-CONTROLLED ASSESSMENT OF THE TOLERABILITY AND EFFICACY OF XT-150 FOR THE TREATMENT OF MODERATE TO SEVERE PAIN DUE TO OSTEOARTHRITIS OF THE KNEE

Protocol XT-150-2-0204
Version 1: 1 October 2019
Amendment 1: 6 January 2020
Amendment 2: 25 March 2020

1.0 PROTOCOL SYNOPSIS

Sponsor: Xalud Therapeutics, Inc./Xalud Therapeutics Australia Pty LTD
Study Number: Protocol XT-150-2-0204
Product Name: XT-150
Protocol Title: A Double-Blind, Placebo-Controlled Assessment of the Tolerability and Efficacy of XT-150 for the Treatment of Moderate to Severe Pain Due to Osteoarthritis of the Knee
Planned Study Centers: 5 (US and Australia)
Phase of Development: 2
Objectives Primary: To confirm the safety and tolerability of intra-articularly-injected XT-150 Secondary: To establish analgesic efficacy of intra-articularly-injected XT-150
Study Design This is a Phase 2 safety and efficacy study of XT-150 in adult participants experiencing moderate to severe pain due to osteoarthritis of the knee. Participants will provide informed consent and meet all study eligibility criteria before any study procedures are initiated. Baseline confirmation of study eligibility will be completed the day before or day of study drug administration. The Index Knee for study drug injection will be the OA-affected joint identified by Kellgren-Lawrence grade of 2 or 3; and WOMAC Pain Subscale ≥ 8 on a scale of 20. Study drug will be administered by intra-articular (IA) injection into the joint space of the Index Knee. About 270 participants will be randomly enrolled into 1 of 3 treatment groups (approximately 90 participants/ group). Treatment Groups: A. Placebo (1 mL) B. 150 µg XT-150 (1 mL) C. 450 µg XT-150 (1 mL) Participants will undergo the study in 2 stages, A and B: D. Placebo-controlled for 6 months E. Continued follow up for 6 months with the option of randomly receiving a single 150 µg or 450 µg injection as the second injection to the Index Knee (knee dosed in Stage A). Safety parameters and efficacy endpoints for each participant will be evaluated monthly for about 1 year from the first XT-150 dose (Stage A, Day 0) The Schedule of Assessments and Procedures is presented in Table 1 (Stage A) and Table 2 (Stage B). 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: About 270 participants will be enrolled in one of 3 treatment groups (90 participants/group) and evaluated.

Inclusion Criteria

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

1. Symptomatic disease due to osteoarthritis, defined as a WOMAC Pain score ≥ 8 (worst possible = 20)
2. Focused Analgesia Selection Test (Analgesic Solutions, Wayland, MA) will be used to determine whether patients can report pain with sufficient consistency to enter the clinical trial (See Appendix 4)
3. Males and females between 45 and 85 years of age, inclusive
4. Kellgren-Lawrence grading of 2 or 3 within the last 6 months
5. Stable analgesic regimen during the 4 weeks prior to enrollment
6. In the judgment of the Investigator, acceptable general medical condition
7. Life expectancy >6 months
8. 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
9. Have suitable knee joint anatomy for intra-articular injection
10. Willing and able to return for the follow-up (FU) visits
11. 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 any ingredient of the study drug, including double-stranded DNA, [redacted]
2. Previously received XT-150 injection(s)
3. Scheduled partial or complete knee replacement within 6 months; participant agrees not to schedule a knee replacement during Stage A of the study
4. History of knee arthroplasty on the Index Knee, i.e., selected for study injection(s)
5. History of rheumatoid arthritis or other inflammatory disease
6. History of immunosuppressive therapy; systemic steroids in the last 3 months
7. Received knee injection with hyaluronic acid or stem-cells in the last 6 months
8. Knee injection of glucocorticoid in the last 3 months
9. Current treatment with systemic immunosuppressive (systemic corticosteroid therapy or other strong immunosuppressant)
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)
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/mm^3; <LLN - 0.8 x 10^9 /L, neutrophils <LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L)
13. Positive serology for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus

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 anticoagulant or anti-platelet treatment (e.g., warfarin, heparins, factor X inhibitors, clopidogrel, prasugrel, ticagrelor, or dipyridamole). Low-dose (≤ 325 mg/day) aspirin is permitted.
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 3 months 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 Investigator, could compromise the safety of the participant, the participant's ability to communicate with the study staff, or the quality of the data

Test Product, Dose, and Mode of Administration

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

Participants will be randomly enrolled into 1 of 3 treatment arms to receive either Placebo or XT-150 (150 µg or 450 µg) as a single, 1-mL, intra-articular knee injection.

Comparator

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

Duration of Treatment

Participation will require a commitment of approximately 1 year of safety, tolerability, and efficacy evaluation. Additionally, a screening visit will occur up to 30 days before enrollment.

Baseline assessments to confirm study eligibility will be completed no more than 1 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 on Study Days 7, 30, and about monthly thereafter for 1 year.

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. All participants will be assessed with the measures below from signing of the informed consent form (ICF) throughout the study.

- Adverse events and concomitant medications used
- Vital signs (temperature and the collection site [i.e. oral, rectal, temporal, or tympanic], heart rate, blood pressure, and respiratory rate)
- Physical examination including all major organ systems
- Injection site examination

Safety assessments conducted after completion of the study by all participants include serum assay results for anti-IL-10 antibody.

Efficacy

Efficacy assessments will be recorded throughout the study as described in Table 1 and Table 2.

The primary efficacy outcome measure is whether the subject achieves at least a 30% improvement from baseline in WOMAC Pain Score (obtained from the KOOS questionnaire) at Day 180, as recorded on a 0 to 20 point scale with 20 being the maximum (worst) score.

Key secondary efficacy outcome measures are:

- Change from baseline in the WOMAC Function Score (from KOOS questionnaire) at Day 180
- Change from baseline in patient response at Day 180, using a scale of 1 – 5, to the OA question: "Considering all the ways the OA in your knee 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)

Additional endpoints include:

- [redacted]
- Total and individual parameter scores for the Brief Pain Inventory of Intensity and Interference (BPI)
- The Knee Outcome and Osteoarthritis Scores (KOOS)
- [redacted]

Statistical Methods

Efficacy measures will be recorded at baseline (before XT-150 injection) and at each study visit, starting at Day 7 [±1 day].

All participants 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 18 or higher, relationship to the study drug, and severity. Adverse events will be graded using the CTCAE v5.0. Descriptive statistics and the change from baseline of vital signs, and laboratory assessments will be presented, as will a summary of abnormal physical examination findings. Adverse events leading to discontinuation will be reported to the respective ethics committees or Institutional Review Boards (IRBs).

Table 1. Schedule of Assessments and Procedures – Stage A

Scheduled Event	Screen	Baseline[a]	Follow up Visit Day[l]						
	Day -30 to Baseline	Day 0	7 (±1)	30 (±2)	60 (±7)	90 (±7)	120 (±7)	150 (±7)	180 (± 7)
Informed consent [b]	X								
Complete medical history and physical examination [c]	X								
Kellgren-Lawrence grading (may require new radiograph)	X								
Quantitative Sensory Testing	X								
Patient training on pain reporting	X	X	X	X	X	X	X	X	X
Record prior medications [d]	X								
Efficacy Assessments									
KOOS/WOMAC [e]	X	X	X	X	X	X	X	X	X
BPI		X	X	X	X	X	X	X	X
Patient response to OA question[f]		X	X	X	X	X	X	X	X
[redacted]		X	X	X	X	X	X	X	X
[redacted]		X		X	X		X		X
[redacted]		X	X	X	X	X	X	X	X
Clinical Assessments									
Brief physical examination		X	X	X	X	X	X	X	X
Record height and weight, calculate BMI	X								X
Vital signs	X	X	X	X	X	X	X	X	X
Clinical exam of the treated joints	X	X	X	X	X	X	X	X	X
Record AEs		X	X	X	X	X	X	X	X
Record SAEs		X	X	X	X	X	X	X	X
Record concomitant medications		X	X	X	X	X	X	X	X
Laboratory Assessments									
HIV, Hepatitis B and C	X								
Serum pregnancy[i]	X								
PT/INR, PTT	X				X				
CBC with differential and platelets count	X				X				

Scheduled Event	Screen	Baseline[a]	Follow up Visit Day[l]						
	Day -30 to Baseline	Day 0	7 (±1)	30 (±2)	60 (±7)	90 (±7)	120 (±7)	150 (±7)	180 (± 7)
Serum chemistry	X				X				
Serum for anti-IL-10 antibody assessments		X	X	X	X				X
Study Drug Administration									
Enroll participant[j]		X							
Administer study drug[k]		X							X

AE = adverse event; BMI = body mass index; BPI = Brief Pain Inventory of Intensity and Interference; CBC = complete blood count; INR = international normalized ratio; ; IL-10 = interleukin 10; KOOS=Knee injury and Osteoarthritis Outcome Score (includes WOMAC measures); PT = prothrombin time; PTT = partial thromboplastin time; SAE = serious adverse event

Footnotes to Table 1

a. Baseline assessments are performed within 1 day before drug injection.
b. Informed consent must be obtained before initiating any study procedures.
c. Obtain 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. WOMAC Total Score at Screening ≥ 8
f. Participant assessment will be recorded in response to the question: "Considering all the ways the OA in your knee affects you, how are you doing today?" on a scale of 1 to 5, 5 being worst
[redacted]
i. Women of child-bearing potential
j. Verify that the participant meets all study inclusion and exclusion criteria before enrollment as close to study drug dosing as possible.
k. Participant will receive a single, 1-mL dose of study drug into the intra-articular space of the knee on Day 0. Participant may elect a second injection on Day 180 (enters Stage B) after efficacy assessments have been recorded.
l. 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

Table 2. Schedule of Assessments and Procedures – Stage B

Scheduled Event	Follow up Visit Day[d]					
	210 (±7)	240 (±7)	270 (±7)	300 (±7)	330 (±7)	360 (±7)
KOOS/WOMAC	X	X	X	X	X	X
BPI	X	X	X	X	X	X
Patient response to OA question	X	X	X	X	X	X
[redacted]	X	X	X	X	X	X
[redacted]						X
Brief physical examination	X	X	X	X	X	X
Record height and weight, calculate BMI						X
Vital signs	X	X	X	X	X	X
Clinical exam of the treated joints	X	X	X	X	X	X
Record AEs	X	X	X	X	X	X
Record SAEs	X	X	X	X	X	X
[redacted]	X	X	X	X	X	X
Record concomitant medications	X	X	X	X	X	X
Serum for anti-IL-10 antibody assessments						X
Serum pregnancy test[b]						X
Administer study drug[c]	x	x	x	x	x	

Footnotes to Table 2

[redacted]

b. Women of child-bearing potential

c. Participants may elect for one (1) XT-150 IA injection into the Index Knee at any point during Stage B up to Day 330, inclusive. The XT-150 dose (150 µg or 450 µg) will be randomly assigned.

d. A telephone call documenting safety and efficacy assessments may be used for participants unable to physically attend follow up visits due to COVID19 infection or corona virus exposure concerns

2.0 TABLE OF CONTENTS

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3.0 LIST OF ACRONYMS, ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
ANCOVA	Analysis of covariance
Anti-interleukin-10 antibody	Antibody that binds IL-10
aPTT	Activated partial thromboplastin time
BPI	Brief Pain Inventory of Intensity and Interference
BMI	Body mass index
CBC	Complete blood count
CTCAE	Common Terminology Criteria for Adverse Events (V5.0)
CCI	Chronic Constriction Injury-induced pain model
CNS	Central nervous system
CRF	Case report form
ds DNA	Double stranded DNA
[redacted]	[redacted]
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HREC	Human Research Ethics Committee
IA	Intra-articular
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IL	Interleukin
IL-10	Interleukin-10
Index Knee	The knee receiving injection of study drug
INR	International normalized ratio

Abbreviation	Definition
IRB	Institutional Review Board
IT	Intrathecal
ITT	Intent-to-Treat
IV	Intravenous
KOOS	Knee injury and Osteoarthritis Outcome Score
MedDRA	Medical Dictionary for Regulatory Activities
NP	Neuropathic
OA	Osteoarthritis
OTC	Over the counter
pDNA	Plasmid DNA
PI	Principal Investigator
PT	Prothrombin time
PTT	Partial thromboplastin time
QST	Quantitative Sensory Testing
SAE	Serious adverse event
SAER	Serious adverse event report
SAP	Statistical Analysis Plan
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
TGA	Therapeutics Goods Administration
VASPI or VAS	Visual Analog Scale of Pain Intensity
VNRS	Verbal Numerical Rating Scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
XT-150	Plasmid DNA, [redacted], expressing a proprietary variant of human IL-10 protein, formulated in a [redacted] solution for injection.

4.0 BACKGROUND AND RATIONALE

4.1 XT-150

Complete and current information on XT-150 can be found in the Investigator's Brochure (IB) version 7, 24 May 2019.

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 (a human anti-inflammatory cytokine, IL-10var), 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 2001).

[redacted]

[redacted]

When XT-150 is administered by injection at the site of chronic inflammation, low levels of human IL-10var protein are produced over the following weeks, which reduces the pain associated with joint inflammation. [redacted] Additionally, the targeted delivery of XT-150 directly to the joint knee space restricts the potential for systemic AEs.

XT-150 presents a treatment opportunity for patients suffering significant damage from osteoarthritis, such as those in need of knee replacement; or the many patients who are not good surgical candidates for knee replacement. 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 GLP and non-GLP preclinical pharmacology and toxicology studies.

[redacted]

4.3 Clinical Experience

Three clinical trials with XT-150 are complete or 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) have been reported to date. The IB contains detailed summaries.

XT-150 is not marketed in any country.

Table 3. Human Clinical Trials 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]

Study	Design	Sites	Results Summary
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]
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]

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). Potential therapeutic benefits of XT-150 for the treatment of OA 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 3 clinical trials, 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, 2005; 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). [redacted] 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, 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. [redacted]

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-10 levels that exist transiently and at a much lower concentration.
- The IL-10 levels from XT-150 expression will be localized in the knee 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. Potential for local injection site infection is very low since 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-10var. 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, 1997), and van Deventer (1997).

None of these AEs have been recorded for any of the [redacted] patients in 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-10var 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 joint space of the knee reduces potential systemic adverse effects since it primarily localizes in the synovial tissues with very low, transient expression levels of IL-10var 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 pain, [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. Note that 2 ml injections are a routine intra-articular dose volume in current medical practice.

4.6 Population to be Studied

About 270 adult participants with a diagnosis of moderate to severe pain due to osteoarthritis of the knee 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), Human Research Ethics Committee (HREC) or Independent Ethics Committee (IEC) requirements.

5.0 STUDY PURPOSE AND OBJECTIVES

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 OA.

- The primary objective of this study is to confirm the safety and tolerability of a single intra-articular dose of XT-150.
- The secondary objective is to establish the analgesic efficacy of a single intra-articular dose of XT-150 as a treatment for pain in participants with OA of the knee.

6.0 STUDY DESIGN

6.1 Description of the Study

This is a Phase 2 safety, tolerability, and efficacy study of XT-150 in adult participants with pain due to osteoarthritis of the knee. The study will be conducted in 2 Stages, A and B.

Stage A is placebo controlled for six months following intra-articular injection in the Index Knee, which is defined by Kellgren-Lawrence grading and participant-reported pain. The primary efficacy endpoint is 30% response rate in WOMAC pain at Day 180.

Stage B continues for an additional six months of safety and efficacy monitoring during which participants can elect for a second injection to the Index Knee. Active 150 µg or 450 µg XT-150 will be randomly chosen for the second injection.

Participants will provide informed consent and meet all study eligibility criteria before any study procedures are initiated. FAST (Appendix 4: Focused Analgesia Selection Test) will be used to select patients who reliably report the magnitude of thermal stimulations.

Baseline confirmation of study eligibility will be completed within one day preceding study drug administration. Study drug will be administered by intra-articular (IA) injection into the joint space of the knee.

About 270 participants will be randomly enrolled into 1 of 3 treatment groups (approximately 90 participants/group). Treatment Groups:

1. Placebo (1 mL)
2. 150 µg XT-150 (1 mL)
3. 450 µg XT-150 (1 mL)

The study will be conducted in 2 stages, A and B:

A. Placebo controlled for 6 months
B. Continued follow up for 6 months with the option of randomly receiving a single 150 µg or 450 µg injection as the second injection to the Index Knee (knee dosed in Stage A).

Safety parameters and efficacy endpoints for each participant will be evaluated monthly for about 1 year from the first XT-150 dose (Stage A, Day 0)

The Schedules of Assessments and Procedures are presented in Table 1 and Table 2. 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. 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 the screening visit (WOMAC Pain Score for eligibility), then all measures at Baseline, on Day 7, Day 30, and approximately monthly thereafter for up to 1 year. 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 corona virus exposure concerns. Home services may be employed for blood collections.

6.3 Number of Participants

About 270 participants will be treated and evaluated.

6.4 Expected Duration of Subject Participation

Subject participation will require a commitment of approximately 1 year 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 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.

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

At any time in Stage B up to Day 330, inclusive, participants can elect for a single injection to the knee dosed in Stage A (Index Knee). The second injection dose will be randomized to be either 150 µg or 450 µg XT-150. There will be no placebo comparator in Stage B.

Instructions for study drug preparation and dosing are given in Section 8.0.

7.0 SELECTION, DISCONTINUATION, AND WITHDRAWAL OF PARTICIPANTS

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. Symptomatic disease due to osteoarthritis, defined as a WOMAC Pain score ≥ 8 (worst possible = 20)
2. Focused Analgesia Selection Test (Analgesic Solutions, Wayland, MA) will be used to determine whether patients can report pain with sufficient consistency to enter the clinical trial (See Appendix 4)
3. Males and females between 45 and 85 years of age, inclusive.
4. Kellgren-Lawrence grading of 2 or 3 within the last 6 months (See Appendix 5)
5. Stable analgesic regimen during the 4 weeks prior to enrollment.
6. In the judgment of the Investigator, acceptable general medical condition
7. Life expectancy >6 months
8. 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.
9. Have suitable knee joint anatomy for intra-articular injection
10. Willing and able to return for the follow-up (FU) visits
11. Able to read and understand study instructions, and willing and able to comply with all study procedures

7.2 Participant Exclusion Criteria

Participants must NOT meet any of the following exclusion criteria:

1. Hypersensitivity, allergy, or significant reaction to any ingredient of the study drug, including double-stranded DNA, [redacted]
2. Previously received XT-150 injection(s)
3. Scheduled partial or complete knee replacement within 6 months; participant agrees not to schedule a knee replacement during Stage A of the study
4. History of knee arthroplasty on the Index Knee selected for study injection(s)
5. History of rheumatoid arthritis or other inflammatory disease
6. History of immunosuppressive therapy; systemic steroids in the last 3 months
7. Received knee injection with hyaluronic acid or stem-cells in the last 6 months
8. Knee injection of glucocorticoid in the last 3 months
9. Current treatment with systemic immunosuppressive (systemic corticosteroid therapy or other strong immunosuppressant)
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)
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/mm^3; <LLN - 0.8 x 10^9 /L, neutrophils <LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L)
13. Positive serology for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus

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 anticoagulant or anti-platelet treatment (e.g., warfarin, heparins, factor X inhibitors, clopidogrel, prasugrel, ticagrelor, or dipyridamole). Low-dose (≤ 325 mg/day) aspirin is permitted.
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 3 months 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 Investigator, 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.

7.4 Participant Withdrawal Criteria

7.4.1 Withdrawal from Study Protocol

Participants on study drug who wish to withdraw completely from this clinical study should be encouraged to complete the assessments for Day 360/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 and will be captured in CRFs:

- 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

Since the study treatment consists of a single dose of XT-150, and the participants should qualify for treatment before enrollment, no participants are anticipated to need to discontinue study drug unless they develop an SAE or need for excluded medications in the 24 hours prior to dosing.

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
- HREC/IRB decision to terminate or suspend approval for the investigation or the Investigator
- Investigator request to withdraw from participation
- Participant enrollment is unsatisfactory

8.0 STUDY DRUGS

Participants will be randomly enrolled into placebo or XT-150 (150 µg, or 450 µg) groups and will receive a single, 1 mL intra-articular injection on Day 0 of Stage A. Participants may receive a second injection (of either 150 µg or 450 µg) in Stage B.

[redacted]

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]

8.2 XT-150 administration

XT-150 will be administered as a bolus intra-articular injection into the joint space of the knee.

8.3 Placebo administration

Stage A only: placebo (1 mL sterile phosphate-buffered saline for injection) will be administered as a bolus intra-articular injection in the joint space of the knee.

8.4 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.

8.5 Comparator

Sterile phosphate-buffered saline (PBS) will be used as the placebo comparator. 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.

8.6 Compliance

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

8.7 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. Participants who received systemic treatment with a prohibited medication before enrolling may not receive study drug injection.

8.7.1 Prohibited medications

The following treatments are prohibited prior to study drug administration:

- Current treatment with antibiotics or antiviral agents, except as topical treatments.
- Current treatment with immunosuppressive agents
- Current treatment with anti-platelets or anticoagulants. Aspirin ≤325 mg/day is allowed
- Current use of systemic corticosteroids
- Alcohol or illicit drug abuse within 1 year before the screening visit

Concomitant medications for pain will be allowed at doses and frequencies prescribed prior to the study treatment. New medications or escalation of pre-study treatments will be captured on CRFs during the 360-day evaluation period.

8.7.2 Rescue Medications

Acetaminophen (≤ 3,000 mg in 24 hours) will be allowed as rescue medication.

[redacted]

8.8 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.

8.9 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.

9.0 STUDY PROCEDURES

Study procedures should be completed within the windows provided in the Schedule of Assessments and Procedures located in Table 1 (Stage A) and Table 2 (Stage B). However, if a participant is unable to attend a visit within the specified windows, the PI (or qualified designee) should discuss appropriate scheduling with the Medical Monitor (or appropriate designee).

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. 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)
- Kellgren-Lawrence grading (obtain a new radiograph if not done in 6 months prior to Screening (See Appendix 5: Kellgren-Lawrence Grading)
- Choice of Index Knee
    - Meets radiographic criteria: Kellgren-Lawrence grade 2 or 3

  - WOMAC Pain Subscore ≥ 8
  - If bilateral OA and both knees meet the first 2 criteria, the participant and investigator will jointly identify which knee will receive study drug
  - Record Left or Right knee as the Index Knee
- Obtain history of all pain medications and all other medications (prescription and over-the-counter [OTC]) and supplements)
- Conduct FAST assessment
- Participant training on accurate pain reporting
- Clinical assessments
  - Conduct complete physical examination, including height and weight (calculate body mass index [BMI])
  - Measure vital signs (temperature and the site collected [oral, rectal, temporal, or tympanic], heart rate, blood pressure, and respiratory rate)
  - Verify WOMAC Pain Subscore ≥ 8 attributable to the Index Knee.
- Laboratory assessments
  - Obtain blood samples for:
    - Hematology tests (complete blood count [CBC] with differential and platelets count),
    - coagulation laboratory tests (prothrombin time [PT] / international normalized ratio [INR] and either partial thromboplastin time [PTT] or activated partial thromboplastin time [aPTT]),
    - HIV, Hepatitis B and C
    - Serum pregnancy test for women of child-bearing potential
    - Serum chemistry tests (Appendix 1)
- Confirm participant qualification by inclusion/exclusion criteria

9.2 Baseline

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

[redacted]

- Training for accurate pain reporting
- Brief physical exam, including examination of Index Knee
- Obtain any changes from the complete medical history.
- Record any changes or updates in medications, including pain medications and therapies administered since Screening visit.
- Efficacy assessments

  - Record Baseline BPI scores (Appendix 2)
  - Record Baseline KOOS (Appendix 3)
  - Record participant's response to the OA question: "Considering all the ways the OA in your knee 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 baseline non-prescription pain therapies or practices
  - [redacted]
- 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 anti-IL-10 antibodies
- Confirm participant qualification by inclusion/exclusion criteria. Enroll participant prior to dosing

9.3 Day 0

- Before administering study drug:
  - Confirm that all study criteria are met (inclusion and exclusion)
  - Brief physical exam
  - Injection site examination of the Index Knee
  - 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 (Section 8.0 for details on preparation)
  - Aseptic techniques will be used in the preparation and administration of XT-150.
  - Injections to the knee space 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
  - Examine injection site for infections or reactions
- Clinical assessments

- Monitor Participant 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

- Refresh training on accurate pain reporting

[redacted]

[redacted]

9.4 Between clinic visits:

[redacted]

9.5 Follow up Visits – Stage A

(Day 7 [±1 day], 30 [±2 Days], 60 [±7 Days], 90 [±7 Days], 120 (±7 days) and 150 (±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
  - Record BPI scores (Appendix 2)
  - Record KOOS scores (Appendix 3)
  - Record participant's response to the question: "Considering all the ways the OA in your knee 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

[redacted]

[redacted]

- Laboratory assessments
  - Day 60: Obtain blood samples for hematology tests (complete blood count [CBC] with differential and platelets count), coagulation laboratory tests (prothrombin time [PT] / international normalized ratio [INR] and either partial thromboplastin time [PTT] or activated partial thromboplastin time [aPTT]), and serum chemistry tests (Appendix 1)
  - Days 7 (±1 day), 30 (±2 days) and 60 (±7 days): 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.
- Refresh training on accurate pain reporting
- [redacted]

9.6 Follow up Visit – Stage A, Day 180 [±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
  - Record BPI scores (Appendix 2)
  - Record KOOS scores (Appendix 3)
  - Record participant's response to the question: "Considering all the ways the OA in your knee 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
  - [redacted]
  - [redacted]
- Laboratory assessments: 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.
- Refresh training on accurate pain reporting
- [redacted]
- At participant's option, administer a second injection to the Index Knee after Day 180 efficacy and safety assessments have been recorded. The second injection will be XT-150 active drug, randomly assigned to be either 150 µg or 450 µg. Record reason provided by the participant for requesting the second injection.

9.7 Follow up Visits – Stage B

(Days 210 [±7 day], 240 [±7 Days], 270 [±7 Days], 300 [±7 Days], 330 [±7 Days], and 360 [± 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
  - Record BPI scores (Appendix 2)
  - Record KOOS scores (Appendix 3)
  - Record participant's response to the question: "Considering all the ways the OA in your knee 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
  - [redacted]
  - Obtain serum for analysis of anti-IL-10 antibodies (Day 360)
  - Obtain serum for pregnancy test (Day 360)
- Assess, identify, and record any AEs since last visit
- At participant's option, administer a second injection to the Index Knee. The second injection will be XT-150 active drug, randomly assigned to be either 150 µg or 450 µg. Record reason provided by the participant for requesting the second injection.
- Record any changes in concomitant medications including prescription, OTC, and herbal medications.
- [redacted]

10.0 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 Table 2 and assessment of anti-IL-10 antibodies is described in Section 12.0.

10.2 Adverse Events of Noted Interest in IL-10 Protein Trials

Safety will include the following reported IL-10 protein-associated toxicities as defined by Common Terminology Criteria for Adverse Events (CTCAE) criteria (version 5.0). Systemic levels of XT-150 produced IL-10 protein is 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 knee 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/mm^3; <1.5 to 1.0 x10^9/L

10.3 Adverse Events

Medical history will be collected for all participants at the time of informed consent. After consent, all AE's will be collected. The Investigator will assess all AEs and SAEs and will record the following information on the appropriate CRF page:

- 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.

10.4 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 by phone or email 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/HREC.

The study site will also transmit a Serious Adverse Event Report (SAER) to the site study monitor and sponsor by facsimile or email within 24 hours. Contact details will be provided to all sites. An optional initial report can be made via telephone, but a completed SAER must still be faxed or emailed within 24 hours of the site's knowledge of the event. The study sites will be provided with SAER 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 outcomes 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, SAERs should not indicate specific study drug assignments
- Indicate if the study drug was discontinued or the study drug administration schedule 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 SAER should be faxed or emailed 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, and an event or outcome. Supplemental information may be transmitted using a follow-up report and should not delay the initial report. The Sponsor 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.

10.5 Definitions

10.5.1 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.

Osteoarthritis-related events should not be considered or recorded as AEs unless the event fits the definition for an SAE (Section 10.5.4), in which case the SAE form must be submitted for safety reporting in the appropriate timeframe and entered as an AE into the CRF.

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 10.5.4.

10.5.2 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.

10.5.3 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.

10.5.4 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.

10.5.5 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.

10.6 Adverse Event Classification

10.6.1 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. Clinical failure that qualifies as an AE without evidence of study drug toxicity should be considered unrelated to study drug.

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

AE = adverse event

10.6.2 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) criteria (version 5.0). 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.

10.6.3 Serious Adverse Event

Any adverse experience occurring at any dose of study medication that occurs between the time of informed consent and the clinic visit on Day 360 that results in any of the following outcomes:

- Death
- Life-threatening situation (participant is at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a participant who received study drug
- Events that jeopardize the participant sufficiently that medical or surgical intervention may be required to prevent one of the above outcomes. Examples may include, but are not limited, to:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm
    - Blood dyscrasias that do not result in hospitalization
    - Seizures that do not result in hospitalization

10.6.3.1 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 FU visit on Day 90, 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 an 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 an 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.

10.7 Adverse Event Follow-up

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

10.8 Adverse Events of Special Interest

10.8.1 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.

10.9 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.

10.10 Risks for Women of Child-Bearing 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.

11.0 ASSESSMENT OF EFFICACY PARAMETERS

Efficacy assessments will be recorded throughout the study (up to Study Day 360) per the Schedules of Assessments and Procedures in Table 1 and Table 2.

The primary efficacy outcome measure is:

- Whether the subject achieves at least a 30% improvement from baseline in WOMAC Pain Score at Day 180, as recorded on a 0 to 20 point scale with 20 being the maximum (worst) score

Secondary efficacy outcome measures:

- Change from baseline in the WOMAC Function Score at Day 180
- Change from baseline in patient response, at Day 180, to the question: "Considering all the ways the OA in your knee affects you, how are you doing today?", using a scale of 1 – 5, 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)

Additional outcome measures include:

- [redacted]
- Total and individual parameter scores for the Brief Pain Inventory of Intensity and Interference (BPI)
- The Knee Outcome and Osteoarthritis Scores (KOOS)

[redacted]

12.0 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/Day1, then on Days 7, 30, 60, 180, and 360, 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.

13.0 STATISTICAL METHODS

Efficacy will be assessed at baseline (before XT-150 injection) and at each study visit, starting at Day 7 [±1 day].

All participants will be included in the safety analysis.

A comprehensive Statistical Analysis Plan (SAP) will be prepared and finalized before database lock. 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.

13.1 Determination of Sample Size

A total of 270 subjects will be randomized to the 3 treatment groups in a 1:1:1 ratio. The sample size of 90 subjects per group provides more than 90% power to detect a greater responder rate in at least one XT-150 group compared to placebo and 85% power to detect both arms superior to placebo, assuming the responder rate is 30% in each XT-150 group and 10% in the placebo group. As a sensitivity analysis of different assumptions on the response rates in the placebo and XT-150 groups, Table 7 shows the statistical power to detect that at least one treatment group provides greater response than placebo and to detect that both treatment groups provide greater responses.

Table 7. Treatment Effect That Can Be Detected

Placebo response rate (%)	XT-150 response rate (%) in both treatment arms	Statistical Power (%)	
		To detect at least one treatment arm superior to placebo	To detect both treatment arms superior to placebo
10	25	78	57
	30	95	85
	35	99	97
15	25	38	18
	30	70	46
	35	91	77

13.2 Analysis Populations

The Intent-to-Treat (ITT) Population will comprise all enrolled participants who received the treatment injection, analyzed according to randomized treatment. The ITT Population will be the primary analysis population for efficacy.

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

13.3 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, WOMAC Pain Score, BPI, and KOOS), clinical signs and symptoms, and administration of study drug will be summarized in the ITT and Safety Populations.

13.4 Safety Analyses

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 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 18 or higher. AEs will be collected for each participant from the signing of the informed consent through the last study visit on Day 360.

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.

13.5 Analysis of Efficacy

All inferential analyses of efficacy will be based on the first 180 days after dose administration (Stage A) and on the analysis of time from Day 0 until patient request for a second injection (see Section 13.5.4). Other analyses of data from Stage B and comparisons between Stage A and B will be descriptive; such analyses will be specified in the SAP.

13.5.1 Multiplicity of endpoints

The statistical analysis of the primary endpoint will preserve a familywise error rate of 0.025 (one-sided), accounting for statistical tests of each of the two XT-150 doses to placebo with respect to the primary endpoint.

P-values from analyses of other endpoints may be interpreted as descriptive statistics.

13.5.2 Statistical methods for the binary outcomes

Whether the subject achieves at least a 30% improvement from baseline in WOMAC Pain Score at Day 180 will be coded as a binary outcome: responder or non-responder. Subjects who withdraw from study before Day 180 or otherwise do not provide a response at that time point will be considered non-responders. The response outcome will be analyzed in a logistic regression model with treatment as the main factor and baseline WOMAC pain as a covariate. Within this model, z-tests will be used to compare the two XT-150 doses to placebo, with step-down Dunnett-like adjustments for multiplicity of doses. Handling of special cases, such as zero responders in a treatment group, will be addressed in the SAP.

[redacted]

13.5.3 Statistical methods for the continuous or graded endpoints

Continuous or graded responses, including changes from baseline in WOMAC Function and patient response, as well as KOOS and BPI items, will be analyzed in a repeated-measures analysis of covariance model with treatment, Study Day and their interactions as the main factors and the baseline value of the endpoint as a covariate. Missing data will not be imputed before such analyses. Within this model, t-tests will be used to compare the two XT-150 doses to placebo, with step-down Dunnett-like adjustments for multiplicity of doses. Within such models, changes from baseline may be analyzed at other time points (Days 7 [±1 day], 30 [±2 days], 60 (±7 days), 90 [±7 days], 120 [±7 days], and 150 [±7 days]). Additional efficacy analyses may be performed using alternate models.

[redacted]

[redacted]

13.6 Bioanalytical Analyses

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

13.7 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.

13.8 Termination Criteria

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

13.9 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.

14.0 INVESTIGATOR REQUIREMENTS

14.1 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/HREC. The Investigator will be responsible for enrolling only those participants who have met the protocol inclusion and exclusion criteria.

14.1.1 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.

14.2 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.

14.3 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.

14.4 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 (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.

14.5 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 until Day 360
- 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/HREC approval and notification, if appropriate
- A summary of the study prepared by the Investigator (an IRB/IEC summary letter is acceptable)

15.0 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

16.0 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, FDA GCP guidelines, and any additional national or IRB/IEC-required procedures, particularly those related to the Corona Virus Disease 2019 (COVID-19) pandemic.

16.1 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.

16.2 IRB/HREC Approval

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

The Investigator is responsible for informing the IRB/HREC 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/HREC of any significant AEs that occur during the study.

17.0 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.

17.1 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/IEC 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.

17.2 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.

17.3 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.

18.0 FINANCING AND INSURANCE

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

19.0 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 contributions to study design, enrollment, data analysis, and interpretation of results.

20.0 REFERENCES

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21.0 APPENDICES

Appendix 1: Clinical Laboratory Tests

Hematology Hemoglobin hematocrit total and differential leukocyte count red blood cell count platelet count
Coagulation Prothrombin time/ International Normalized Ratio Partial thromboplastin time or activated partial thromboplastin time
Serum Chemistry bilirubin (total and direct) alkaline phosphatase aspartate aminotransferase (AST) alanine aminotransferase (ALT)

Appendix 2: BPI

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Brief Pain Inventory (Short Form)

Date:____/____/____ Time:_____

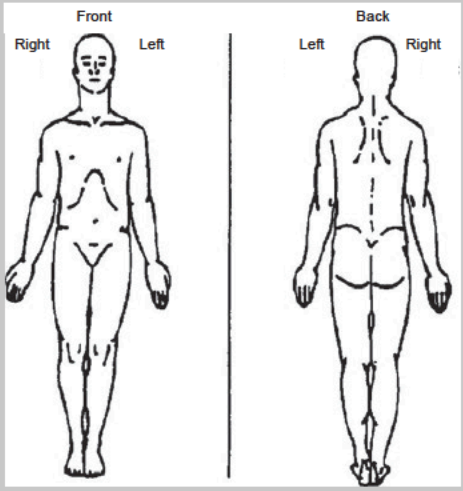
Name:_____ _____ __

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

   1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Date:___/___/____ Time:_____

Name:_____ _____ _____

Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
No Relief — Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

C. Walking Ability

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

F. Sleep

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

Appendix 3: KOOS

KOOS KNEE SURVEY

Today's date: _____/_____/_____ Date of birth: _____/_____/_____

Name: _____

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to perform your usual activities.
Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms

These questions should be answered thinking of your knee symptoms during the **last week**.

S1. Do you have swelling in your knee?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S3. Does your knee catch or hang up when moving?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S4. Can you straighten your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

S5. Can you bend your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

Stiffness

The following questions concern the amount of joint stiffness you have experienced during the **last week** in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

S6. How severe is your knee joint stiffness after first wakening in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

S7. How severe is your knee stiffness after sitting, lying or resting **later in the day**?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Pain

P1. How often do you experience knee pain?

Never ☐ Monthly ☐ Weekly ☐ Daily ☐ Always ☐

What amount of knee pain have you experienced the **last week** during the following activities?

P2. Twisting/pivoting on your knee

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

P3. Straightening knee fully

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

P4. Bending knee fully

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

P5. Walking on flat surface

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

P6. Going up or down stairs

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

P7. At night while in bed

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

P8. Sitting or lying

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

P9. Standing upright

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A1. Descending stairs

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A2. Ascending stairs

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A3. Rising from sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A4. Standing

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A5. Bending to floor/pick up an object

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A6. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A7. Getting in/out of car

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A8. Going shopping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A9. Putting on socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A10. Rising from bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A11. Taking off socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A12. Lying in bed (turning over, maintaining knee position)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A13. Getting in/out of bath

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A14. Sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A15. Getting on/off toilet

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A17. Light domestic duties (cooking, dusting, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, sports and recreational activities

The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the **last week** due to your knee.

SP1. Squatting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP2. Running

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP3. Jumping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP4. Twisting/pivoting on your injured knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP5. Kneeling

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Quality of Life

Q1. How often are you aware of your knee problem?

Never	Monthly	Weekly	Daily	Constantly
☐	☐	☐	☐	☐

Q2. Have you modified your life style to avoid potentially damaging activities to your knee?

Not at all	Mildly	Moderately	Severely	Totally
☐	☐	☐	☐	☐

Q3. How much are you troubled with lack of confidence in your knee?

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

Q4. In general, how much difficulty do you have with your knee?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Thank you very much for completing all the questions in this questionnaire.

Appendix 4: Focused Analgesia Selection Test (FAST)

FAST is based on recording a subject's pain reports in response to repeated administration of thermal noxious stimuli of various intensities to assess subject's pain reporting skills.

Specifically, FAST utilizes the MEDOC TSA II device. The Thermal Sensory Analyzer II incorporates a Peltier element-based thermode (30×30 mm^2). The thermode is applied to the ventral surface of the subject's nondominant arm and the temperature is raised from a baseline of 32°C, peaked for 3 seconds at 1 of 7 designated temperatures (43°C, 45°C, 47°C, 48°C, 49°C, 50°C, or 51°C), and then decreased down to the baseline. Stimulus duration is always 8 seconds, meaning that the rate of rise and fall varies from 3.3 to 9°C/seconds depending on the destination temperature.

Subjects are asked to rate the peak pain intensity of each stimulus by using a computerized visual analog scale (CoVAS): a box attached to the computer with a (0–100 mm) slider that moves along a line from "no pain" to "worst pain imaginable".

Each temperature is presented 7 times in a random block-ordered design (total of 49 stimuli). Stimuli are triggered manually, allowing the subject sufficient time to rate the pain they perceived during each stimulus, resulting in interstimulus intervals of 10–20 seconds. The location of the thermode is adjusted every 14 stimuli to minimize sensitization and/or habituation effects. The duration of the FAST procedure is ~25 minutes.

Data is sent electronically to Analgesic Solutions (AS) evaluators. Within 48-72 hours, AS reports back to the clinical site the acceptability of results for enrollment into the clinical trial.

Appendix 5: Kellgren-Lawrence Grading

References:

Kellgren JH, Lawrence JS. Radiological Assessment of Osteo-arthrosis. Ann. Rheum Dis. 1957, 16:494-502.

Kohn MD, Sassoon, AA, Fernando ND. Classifications in Brief: Kellgren-Lawrence Classification of Osteoarthritis. Clin Orthop Relat Res. 2016, 474:1886-1893.

Grades 2 and 3 OA of the knee are eligible for the study

Grade 0: no radiographic features of OA are present

Grade 1: doubtful joint space narrowing (JSN) and possible osteophytic lipping

Grade 2: definite osteophytes and possible JSN on anteroposterior weight-bearing radiograph

Grade 3: multiple osteophytes, definite JSN, sclerosis, possible bony deformity

Grade 4: large osteophytes, marked JSN, severe sclerosis and definite bony deformity

Appendix 6: Investigator Signature

I have read and understand the current version of protocol XT-150-2-0204 and the 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/HREC.

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]