XT-150-1-0302

A PLACEBO-CONTROLLED, DOUBLE-BLIND EVALUATION OF SAFETY, TOLERABILITY, AND EFFICACY OF XT-150 FOR THE TREATMENT OF FACET JOINT OSTEOARTHRITIS PAIN

STATISTICAL ANALYSIS PLAN

STATISTICAL ANALYSIS PLAN APPROVAL
PROTOCOL: XT-150-1-0302
VERSION 3.0

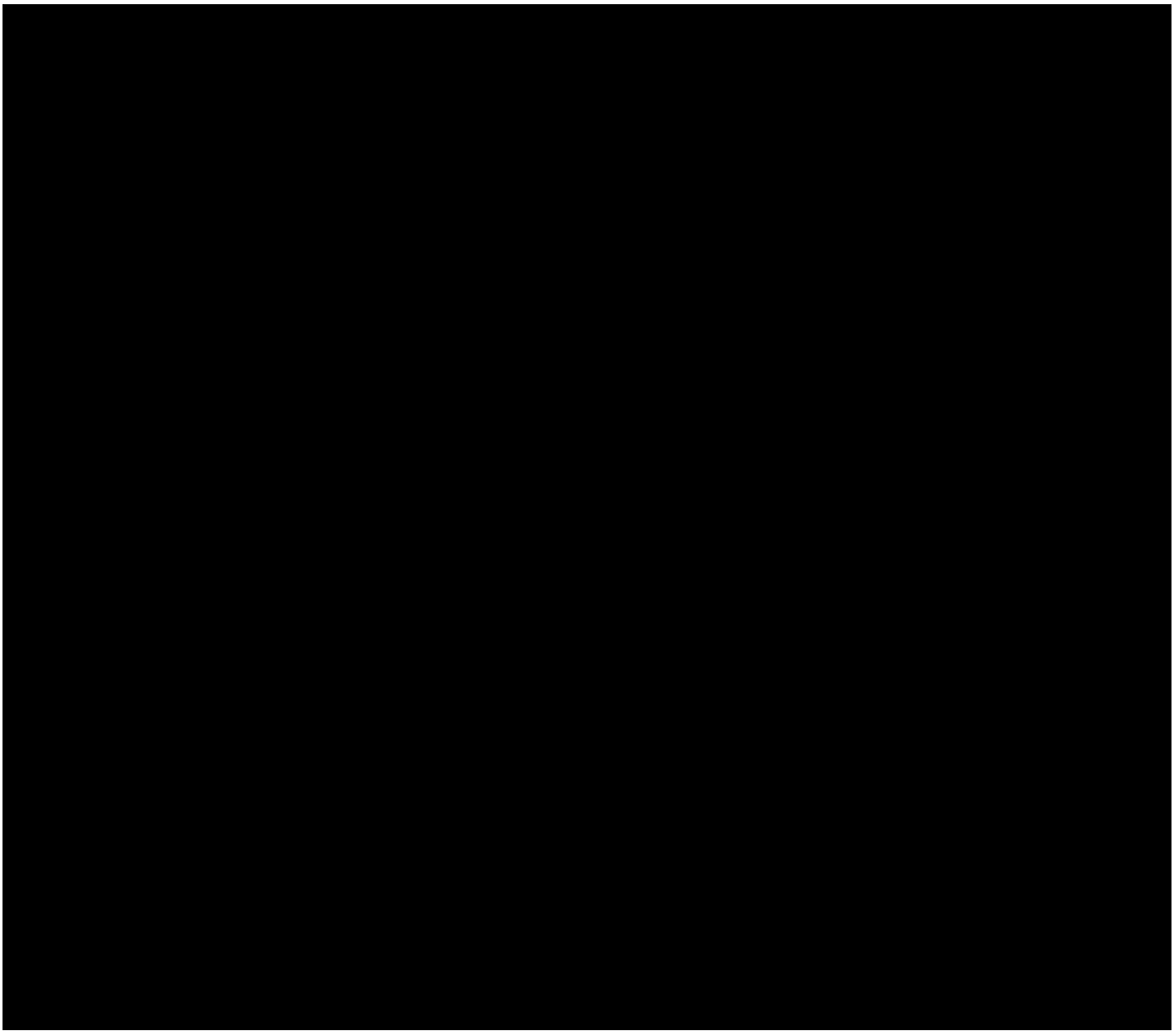

TABLE OF CONTENTS

LIST OF TABLES

VERSION HISTORY

1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Explanation
ADaM	analysis data model
AE	adverse event
ATC	Anatomical/Therapeutic/Chemical
BMI	body mass index
bpm	beats per minute
BP	blood pressure
C	Celsius
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
eCRF	electronic case report form
FJOA	Facet joint osteoarthritis
HR	heart rate
ICH	International Council for Harmonization
IPAQ	International Physical Activity Questionnaire
ITT	Intent-to-treat
IWGDF	International Working Group on the Diabetic Foot
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
N/A	not applicable
ND	not done
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SF12	Short Form Health Survey

SOC	standard of care, or system organ class
TEAE	treatment-emergent AE
TFLs	tables, figures, listings,
ULN	upper limit of normal
VAS	Visual Analog Scale
WHO	World Health Organization

2. INTRODUCTION

This Statistical Analysis Plan (SAP) provides the framework for the summarization and analysis of the clinical data from the study, "A Placebo-controlled, Double-blind Evaluation of Safety, Tolerability, and Efficacy of XT-150 for the Treatment of Facet Joint Osteoarthritis Pain." Changes made to the SAP after it has been signed but prior to the database lock will be documented in an SAP amendment. Any important changes made to the analysis will be described in the Clinical Study Report (CSR).

3. STUDY DESIGN

This is a phase 2a, randomized, double-blind, safety and efficacy study of XT-150 in adult participants experiencing back pain due to inflammation of the facet joint osteoarthritis (FJOA). Participants will receive XT-150 administered as a bilateral injection at Day 0 and Day 90, and then will be followed for safety and efficacy measures.

Up to 72 participants will be randomized 1:1:1 to placebo or one of two dose treatment groups[1]:

1. 0.15 mg XT-150 (1.0mL total delivered by two 0.5 mL injections)
2. 0.45 mg XT-150 (1.0mL total delivered by two 0.5 mL injections)
3. Placebo (Sterile saline) (1.0mL total delivered by two 0.5 mL injections)

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

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

[1] The XT-150-1-0302 protocol provides XT-150 dosage levels in µg (150 µg and 450 µg XT-150), however Xalud requests dosage levels in mg. This is reflected throughout the SAP and TLF shells.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1. Study Objectives

Primary objectives:

- To evaluate the safety and tolerability of a repeat bilateral intra-articular dose of XT-150.

Secondary objectives:

- To establish the analgesic efficacy of a repeat bilateral intra-articular dose of XT-150 as a treatment for pain in participants with FJOA.

4.2. Study Endpoints

Safety Endpoints:

- Treatment-emergent adverse events (TEAE).
- Treatment-emergent serious adverse events (SAE).
- Abnormal clinical laboratory tests (chemistry and hematology).
- Vital signs (blood pressure, pulse, respiratory rate, and body temperature).
- Physical examination findings.

Primary Efficacy Endpoint:

- Change from baseline in pain intensity at Day 270 as recorded on a 0-100 VAS.

Secondary Efficacy Endpoints:

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

Exploratory Efficacy Endpoints:

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

5. [redacted] SAMPLE SIZE ESTIMATION

[redacted]

5.2. Sample Size Estimation

Up to 72 participants will be randomized, 24 to each group. The sample size is not based on any formal power calculations.

6. ANALYSIS POPULATIONS

For purposes of analysis, the following populations are defined:

Table 2: Analysis Populations

Population	Description
All Participants Population	All screened participants who signed the informed consent form. Screen failure information will be summarized using the All Participants Population.
Randomized Population	All participants who met screening criteria and are randomized in the study. This population will be used to determine the other analysis populations
Intent-To-Treat (ITT) Population	All participants who were randomized who received the treatment injection and will be analyzed according to randomized treatment. This population will be used for efficacy.
[redacted]	[redacted]
Safety Population	All participants who received any amount of study drug, analyzed according to their actual treatment received. This population will be used for safety.

7. STATISTICAL METHODS

7.1. General Considerations

7.1.1. Standard Calculations

- Variables requiring calculation will be derived using the following formulas:
- Baseline: A baseline value, unless specified otherwise, is the last non-missing value recorded prior to the first dose of study drug (or placebo) on Day 0 as defined in the protocol (analysis Day 1). If an assessment has both a date and time that exactly match the date and time of first dose of study drug, the assessment will be counted as baseline.
- Change from Baseline: Change from baseline will be calculated for each participant at the specified time point as the value at the specified time point minus the baseline value.
- Study day: In the protocol, 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. However, CDISC standards require the first day of study drug administration to be Day 1 and therefore, study day will be calculated differently as outlined below for display in tables, figures, and listings (TFLs):
  - Study day = date – dose date + 1, where date ≥ dose date
  - Study day = date – dose date, where date < dose date
- Days: Durations, expressed in days, between one date (date1) and another later date (date2) are calculated according to the following formula: duration in days = (date2 - date1 + 1).
- Body Mass Index (BMI): BMI (kg/m2) = weight (kg) / [[height (cm)/100]2].

7.1.2. Summarization Groupings

The summary tables will be presented by randomization arm, visit, and timepoint (when applicable).

The following is a list of the abbreviations for treatment and ordering that will be used in the TFLs.

Table 3: Reporting Order

Cohort	Abbreviation for TLFS	Order on TFLs
0.150 mg XT-150	0.15mg XT-150	1
0.45 mg XT-150	0.45mg XT-150	2
Placebo	Placebo	3
Total	Total	4

7.2. General Comments on the Statistical Analyses

- Age will be provided in the EDC as reported at Informed Consent.
- Continuous variables will be summarized using number (n), mean, standard deviation (SD), median, minimum, and maximum.
- Categorical data will be reported with frequency counts and percentages.
- Non-safety listings will be sorted by planned randomization arm, participant number, and visit in ascending order, with the exception of certain listings pertaining to screening and randomization. Safety listings will be sorted by actual treatment received, participant number, and visit in ascending order. All relevant data captured on the electronic case report forms (eCRFs) and from external laboratories including specific descriptions of 'other' and comments fields will be included on the listings.
- If a clinical laboratory result is reported relative to a lower/upper range of detection for an assay, for example, "<10", the numeric portion of the result (10) will be used for statistical analyses and the full result, including any symbols, will be provided in the participant listings.
- Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1, and CDISC ADaM Implementation Guide Version 1.1. Pinnacle 21 Community Validator Version 3.0.1 or later will be utilized to ensure compliance with CDISC standards.
- Version 9.4 (or higher) of the SAS® statistical software package will be used to provide all tables, listings and figures.
- The analyses described in this plan are considered a priori, in that they have been defined prior to database lock. Any analyses added subsequently will be considered post-hoc and exploratory. Post-hoc analyses will be labelled as such on the output and identified in the CSR.
- Unless otherwise indicated, summaries will be performed by randomization arm.

7.3. Handling of Missing Data

- Unless otherwise specified, missing values for individual data points will remain as missing. Missing values will not be imputed and only observed values will be used in data analyses and presentations.
- For efficacy analyses, examining the number of participants with 30%, 50%, or 75% improvement in VAS, participants with missing data will be included in the analysis as participants who have not met the criteria for improvement.
- In all other cases, where individual data points are missing, categorical data will be summarized based on reduced denominators (ie, only participants with available data will be included in the denominators).
- Any partial dates will be presented using the CDISC standard ISO.8601 date format as shown in the SDTMIG v3.3 Section 4.4.2.

- All AEs with partial or missing dates and times will be considered treatment-emergent unless a partial start date indicates the AE began before the start of study medication or a stop date indicates the AE ended before the start of study medication.
  - For determination of treatment emergent AEs with partial start dates using the definition above, if the non-missing portion of the partial date is the same as the start of treatment or after (ex: same or later month and year), then it will be considered treatment emergent.

    Ex: If treatment begins March 12th, 2022 and an AE has a partial start date of March 2022 (missing day), it will be considered treatment emergent.
- All medications with partial or missing dates recorded on the concomitant medication eCRF will be considered concomitant unless a partial stop date clearly indicates it was stopped before the first dose of study treatment.
  - For determination of concomitant medications with partial stop dates using the definition above, if the missing part of the partial date is the same (same month or year) as the start of treatment or earlier, then it will be considered treatment emergent.

    Ex: If treatment begins March 12th, 2022 and a medication has a partial stop date of March 2022 (missing day), it will be considered concomitant.

[redacted]

7.5. Analysis Windows

For all measures that are summarized by visit, analysis visits will be assigned based on the analysis windows provided in Table 4. If more than one assessment falls into an assessment window, the assessment that is closest to the target day will be picked. If more than one assessment is equidistant from the target day, the earlier time will be picked.

Analysis windows are selected based on the midpoint between the upper bound of the previous window and the lower bound of the following window based on the protocol defined windows.

Analysis visits will be used in all summaries, figures, and efficacy analyses. Listings will not use analysis visits and instead use nominal visits based on the data. End of study visit will be summarized as a nominal visit as well as the analysis visit for which it falls under.

Table 4: Analysis Windows

Nominal Visit (Target Day)	Protocol Window	Analysis Window
0	0	≤0
7	[6, 8]	[1, 10]
14	[13, 15]	[11, 22]
30	[28, 32]	[23, 42]
60	[53, 67]	[43, 75]
90	[83, 97]	[76, 105]
120	[113, 127]	[106, 135]
150	[143, 157]	[136, 165]
180	[173, 187]	[166, 195]
210	[203, 217]	[196, 225]
240	[233, 247]	[226, 252]
270	[256, 284]	≥253

8. PROTOCOL VERSION 3.0 ANALYSIS IMPACT

Protocol version 3.0, dated June 8, 2022, made significant changes to the study design including adding a 2nd dose of study drug and two interim analyses. These changes are reflected in the SAP.

Due to this protocol version occurring during the study, some participants will receive only a single injection at baseline and complete the study at day 180 instead of day 270 as per the protocol prior to v3.0 if they did not sign informed consent for v3.0. In effect they will not complete the study under protocol v3.0 and will be considered pre-3.0 participants. These participants will be included in the ITT and Safety populations (if applicable) but will be excluded from the PP population.

Summary tables of the ITT and Safety populations will combine pre-3.0 and post-3.0 participants. Informed consent, disposition, and randomization tables and listings will delineate those who were considered pre-3.0 and those who were post-3.0. [redacted]

[redacted]

10. STATISTICAL ANALYSES

10.1. Informed Consent and Randomization

Informed consent, reconsent, enrolled or consented into protocol v3.0 prior to day 90, and randomization information will be summarized and listed by participant for the All Participants population.

10.2. Analysis Populations

Using the Randomized Population, the number and percent of participants in the ITT, Safety, [redacted] will be provided. [redacted]

10.3. Screened Participants

Using the All Participants population, the number of screened participants will be summarized as well as the number and percentage of participants who were enrolled and randomized and reasons for non-enrollment and not being randomized.

Inclusion/exclusion criteria that were failed for screen failures will be summarized at baseline and screening separately. Inclusion/exclusion findings will be listed, with screening and baseline screen failures listed separately.

10.4. Participant Disposition

Participant disposition will be summarized for the Randomized population. Due to this study only having a single dose of treatment at Day 0 and 90, no disposition related to treatment discontinuation is needed in this section as those reasons will be captured in the treatment administration section. Instead, due to protocol v3.0 and the addition of a 2nd dose at day 90, there are four "pathways" that a participant can take in the study and will be summarized from the Day 90 study administration form. Summaries will include:

- Total number of participants who withdrew from study and reason for withdrawal.
- Number of participants who passed day 90 prior to protocol v3.0 reconsent.
  - Number of participants who completed at day 180.
  - Number of participants who discontinued prematurely and reasons for discontinuation.
- Number of participants who were enrolled into protocol v3.0.
  - Number of participants who received the 2nd dose at day 90.
  - Number of participants who completed at day 270.
  - Number of participants who discontinued prematurely and reasons for discontinuation.
- Number of participants who reconsented to protocol v3.0 prior to day 90 to receive a 2nd dose at day 90.

  - Number of participants who received the 2nd dose at day 90.
  - Number of participants who completed at day 270.
  - Number of participants who discontinued prematurely and reasons for discontinuation.
- Number of participants who reconsented to protocol v3.0 prior to day 90 but did not consent to receive a 2nd dose at day 90.
  - Number of participants who completed at day 180.
  - Number of participants who discontinued prematurely and reasons for discontinuation.

A study flow diagram will be produced showing the total number of subjects screened, randomized, treated at day 0 and day 90, and the overall "pathway" of the study including reasons for discontinuation.

Participant disposition data will also be presented in listings.

10.5. Protocol Deviations

In accordance with International Council for Harmonisation (ICH) E3, Sponsor-defined eligibility violations and important (major versus minor) protocol deviations will be identified and summarized by type of deviation in the ITT population.

All protocol deviations will also be listed by participant and including the type of deviation.

10.6. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized descriptively for the ITT and Safety populations. The following demographic and baseline data will be summarized: sex, age, race, ethnicity, height, weight, BMI, [redacted]. Age is provided in the EDC at date of informed consent.

A demographic listing will also be provided.

Screening and on-study pregnancy serum/urine test results will also be listed.

10.7. Medical and Surgical History

Medical and Surgical history collected at screening will be coded using Medical Dictionary for Regulatory Activities (MedDRA), version 24.1. Medical and Surgical history will be summarized for the Safety Population by system organ class and preferred term.

Medical and Surgical history will be listed, with FJOA related history highlighted.

10.7.1. FJOA Related Medical History

Medical and surgical history related to FJOA collected at screening will be coded using Medical Dictionary for Regulatory Activities (MedDRA), version 24.1. FJOA related medical and surgical history will be summarized for the Safety population by system organ class and preferred term.

10.8. Prior and Concomitant Medications

Verbatim terms on case report forms will be mapped to Anatomical/Therapeutic/Chemical (ATC) class and generic drug name using the World Health Organization (WHO) drug dictionary, WHO Drug – Global B3, September 2021.

Prior medications are those medications started before the start of study drug. Concomitant medications are those medications taken after the start of study drug. As such, prior medications continued after the use of study drug are also considered concomitant medications. Prior and concomitant medications will be summarized for the Safety population by ATC class (level 3) and preferred term. Participants receiving the same medication more than once are counted only once for each ATC class and preferred term.

In addition, separate summaries including only back pain medication will be provided using the same format.

Prior and concomitant medications will be listed by participant, and a separate listing with medications taken for back pain will also be provided.

10.9. Study Drug Treatment Administration

Participants will receive a single dose of XT-150 (or placebo) consisting of two injections bilaterally into the facet joint at baseline and another at Day 90. The following information will be summarized for the Randomized population at each visit:

- Site of injections (L3-L4, L4-L5, L5-S1).
- Number of participants receiving any XT-150 or placebo.
- Reasons participants did not receive any XT-150 or placebo.
- Number of participants receiving the full dose of XT-150 or placebo (both injections) at each timepoint individually.
- Reasons that the full dose was not administered.
- Number of participants receiving the full dose at both timepoints.

Treatment administrations will be listed, with information about each bilateral injection listed separately.

10.10. Confirmation of FJOA and Lidocaine Facet Selection

Confirmation of FJOA by imaging and lidocaine facet selection will be performed at screening. The following information will be summarized in the Safety population: number of participants with FJOA confirmation by scan type, number of lidocaine tests performed to select target facet joint, and the selected facet joint location for treatment.

FJOA imaging and lidocaine facet selection details will be listed.

10.11. Assessment of IL-10 Antibodies and IL-10 Protein

IL-10 protein and anti-IL-10 antibodies results will be summarized for the Safety population across study visits.

IL-10 related information will be listed for each participant.

10.12. Plasma DNA Biodistribution

Sample collection and presence of plasmid DNA in whole blood will be summarized across study visits for the Safety population.

Plasmid DNA related information will be listed for each participant.

10.13. Efficacy Analysis

All efficacy analyses will be conducted on the ITT [redacted] Population as randomized. [redacted]

10.13.1. VAS Pain Indicator Chart Score

10.13.1.1. Primary Efficacy Analysis

The VAS Pain indicator chart is a score from 0-100 with 100 being the worst score and is collected at each study visit.

The VAS Pain score will be summarized at each visit, including change from baseline at each visit. [redacted]

All VAS pain scores will be listed for each participant by visit.

[redacted]

If ≥7 participants receive only a single dose as per the pre[redacted]

[redacted]

[redacted]

10.13.2. Oswestry Disability Index (ODI)

The Oswestry Disability Index (ODI) is a 10-category index where each score is given an ordinal integer between 0-5, where 5 is the worst score. The Oswestry disability score is a composite 0%-100% disability score that will be summarized based on the composite of the individual scores as (Total score from individual components / (# of questions completed * 5)) x 100. Typically, this will be (Total Score / 50) x 100 if a participant completes the entire questionnaire.

[redacted]

Oswestry Disability individual raw scores and the Oswestry disability score (%) will be listed for each participant by visit.

[redacted]

[redacted]

10.13.3. Participant Global Assessment

The participant global assessment is a score from 1-5, where 5 is the worst score. The score will be summarized at each visit, including shifts from baseline for each score and descriptive statistics with changes from baseline.

[redacted]

Participant global assessment scores will be listed for each participant by visit.

10.13.4. International Physical Activity Questionnaire (IPAQ)

The IPAQ is a questionnaire with multiple categories that will be summarized across study visits. The following measures will be summarized as continuous by randomization arm (sub-bullets use reduced N based on how many answer the previous question as >0):

- During the last 7 days, how many did you do vigorous physical activities? (0-7 days)
  - How much time did you spend per day doing vigorous physical activities on those days? (hours)
- During the last 7 days, how many did you do moderate physical activities? (0-7 days)
  - How much time did you spend per day doing moderate physical activities on those days? (hours)
- During the last 7 days, how many did you walk at least 10 minutes at a time? (0-7 days)
  - How much time did you spend walking on those days? (hours)
- During the last 7 days, how much time did you spend sitting on a weekday? (hours)

[redacted]

IPAQ values will be listed for each participant by visit.

10.13.5. Quality of Life (SF-12v2)

The SF-12v2 questionnaire has multiple sections with multiple-choice questions based on physical and mental quality of life. The answers to the SF-12v2 questionnaire will be scored through QualityMetric PRO CoRE standard software as standardized scores or "T scores". With

T scores, scoring is standardized across the Short Form adult surveys using the means and SDs from the 2009 U.S. general population, with a mean of 50 and SD of 10.

Missing data estimation methods of "Maximum Data Recovery" from the PRO CoRE software will be used in generation of the T scores. This method allows the software to use partial information to make calculations of scores for respondents who have answered only a part of the multi-item scales. This allows the Physical Component Summary (PCS) and Mental Component Summary (MCS) to be calculated with at least 7 of the 8 categories completed. However, PCS will not be calculated if the Physical Functioning (PF) scale is missing and MCS is not calculated if the Mental Health (MH) scale is missing. These T scores will be categorized into the following scales:

- Physical Component Summary (PCS): All scores contribute; physical-related scores are more heavily weighted. T score range: 4.62 – 76.36.
- Mental Component Summary (MCS): All scores contribute; mental-related scores are more heavily weighted. T score range: 1.32 – 79.48.
- Physical Functioning (PF): Items 2a, 2b. T score range: 22.1 – 56.47.
- Role-Physical (RP): Items 3a, 3b. T score range: 20.32 – 57.18.
- Bodily Pain (BP): Item 5. T score range: 16.68 – 57.44.
- General Health (GH): Item 1. T score range: 18.87 – 61.99
- Vitality (VT): Item 6b. T score range: 27.62 – 67.88.
- Social Functioning (SF): Item 7. T score range: 16.18 – 56.57.
- Role-Emotional (RE): Items 4a, 4b. T score range: 11.35 – 56.08.
- Mental Health (MH): Items 6a, 6c. T score range: 15.77 – 64.54.

[redacted]

SF-12 T scores categories will be listed for each participant by visit.

10.14. Safety Analyses

All safety analyses will be conducted on the safety population. Participants will be summarized by treatment arm, visit (where applicable), and time (where applicable). For all safety analyses, in cases where participants received the wrong study medication, participants will be summarized based on the treatment received.

10.14.1. Adverse Events

AEs will be coded to system organ class (SOC) and preferred term according to MedDRA, version 24.1. Pretreatment AEs are defined as AEs that have an onset on or after the date the informed consent was signed but before the date of the first dose of study drug. Treatment-emergent adverse events (TEAEs) are defined as AEs that start or worsen after the first dose of study drug. Adverse event severity will be graded using CTCAE v5.0.

Summaries will be provided for TEAEs, with the number and percentage of participants reporting each type of event presented. If a participant reports the same preferred term more than once, it is counted only once within that category. Similarly, if a participant has AEs of two or more preferred terms under the same SOC, then that participant only counts once for that SOC. Furthermore, for a given summary, the preferred term will only be counted once at its worst severity and strongest relationship to study drug.

AEs of special interest will be identified programmatically and reviewed by the study team prior to unblinding. AEs of special interest include:

- (Unexplained) fever
- Grade 2+ allergic, cytokine release, or infusion-related reactions - Therapy or infusion interruption indicated but responds promptly to either:
  - symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids)
  - prophylactic medications indicated for ≤24 hours
- Grade 2+ injection site reactions
- Grade 2+ neutropenia

The following summaries and listings for AEs will be provided:

- An overall summary table of AEs summarizing the number and percent of participants, in the following categories: any AE, any TEAE, TEAEs by highest severity grade, any TEAEs of special interest, TEAEs by relationship to study drug (related, not related), any serious TEAE, TEAEs leading to drug withdrawal, and TEAEs leading to premature withdrawal from the study, any TEAEs with a fatal outcome
- Incidence of TEAEs by MedDRA SOC and preferred terms
- Incidence of TEAEs by MedDRA SOC, preferred terms, and maximum severity grade
- Incidence of TEAEs by MedDRA SOC, preferred terms, and relationship to study drug.

- Incidence of TEAES of special interest, by SOC, preferred terms, and maximum severity grade.
- Incidence of SAEs by SOC, preferred terms, and maximum severity grade
- Listing of all AEs (with non-treatment-emergent events flagged and AEs of special interest highlighted).
- Listing of all AEs of special interest
- Listing of AEs leading to drug withdrawal
- Listing of all SAEs

In addition, all deaths will be listed with the primary cause of death and whether an AE is associated with the death.

10.14.2. Clinical Laboratory Evaluations

Descriptive statistics for chemistry and hematology parameters at screening will be summarized for the safety population by treatment arm. Post-baseline laboratory parameters collected as part of AEs or at unscheduled visits will be included in listings.

Listings will be provided by treatment arm. Values for any hematology, chemistry, and serology results that are outside the laboratory reference ranges will be flagged on the individual participant data listings as high or low.

10.14.3. Clinical Examination of the Back (Injection Site)

Clinical examinations of the back and injection site will be performed regularly during the study. The following examination criteria will be assessed and the proportion of participants with symptoms will be summarized by visit:

- Pain
- Erythema
- Swelling
- Pruritus
- Warmth
- Hematoma
- Induration
- Other skin reactions

Injection site reactions will also be recorded as AEs.

10.14.4. Vital Signs

Systolic and diastolic blood pressures (mmHg), heart rate (bpm), respiratory rate (breaths/minute), and temperature (°C), as well as height, weight, and BMI, will be summarized using descriptive statistics at all scheduled time points. Descriptive statistics of the change from

baseline to each post-baseline time point will also be provided. Abnormal and clinically significant vital signs will be summarized at each timepoint, with abnormal vitals being described in the table below.

Table 5: Abnormal Vital Threshold Values

Vital Sign	Threshold
Diastolic blood pressure	> 20 mmHg increase from baseline
Systolic blood pressure	≥ 140 mmHg
Heart rate	< 60 beats/min
Heart rate	> 120 beats/min
Temperature	>102.3 F

All vital signs will be displayed in by-participant listings. Clinical interpretations that highlight clinically significant vital signs are included.

11. DEPARTURES FROM PROTOCOL PLANNED ANALYSES

Table 6: Departures from Protocol Analyses

Analysis Endpoint and SAP Section	Protocol Original Analysis	Updated Analysis	Rationale
Safety: Clinical Laboratories Section 10.14.2	Change from Baseline summaries for hematology and chemistry labs will be presented	Summary of screening labs, only listing of post-baseline labs if collected.	No post-baseline clinical labs are collected, just screening. Change from baseline will not be possible.
Safety: Abnormal Physical Exam Section 10.14	A summary of abnormal physical exams will be presented.	No physical examination summary or listing	Abnormal physical exams are collected as AEs, so they will be captured there.
[redacted]	[redacted]	[redacted]	[redacted]
Quality of Life (SF-12v2) Section 10.13.5	The SF-12 scores would be scored using the 1998 US norms.	The SF-12 scores will be scored using the 2009 US norms	The 2009 norms should better fit the population than the 1998 norms.

APPENDICES

Appendix 1 Schedule of Events

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

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

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

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

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

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

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

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

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

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

[i] Pain therapy and concomitant medications are recorded [redacted]

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

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

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

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

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