# CLINICAL INVESTIGATION PLAN

| | |
|---|---|
| PRODUCT NAME/NUMBER: | CNTX-4975-05 |
| PROTOCOL NUMBER: | CNTX-4975i-OA-304 |
| IND NUMBER: | 132,999 |
| DEVELOPMENT PHASE: | Phase 3 |
| PROTOCOL TITLE: | A Randomized, Double-blind, Placebo-controlled, 2-Injection, 52-Week Study to Evaluate the Efficacy and Safety of Intra-articular Injections of CNTX-4975-05 in Subjects with Chronic, Moderate-to-severe Osteoarthritis Knee Pain |
| PROTOCOL DATE: | Version 1.0, 25 July 2018 |
| AMENDMENT 1 DATE | Version 2.0, 13 June 2019 |
| AMENDMENT 2 DATE | Version 3.0, 12 October 2020 |
| SPONSORED BY: | Centrexion Therapeutics Corp |
| | [redacted] |
| CONTRACT RESEARCH ORGANIZATION: | [redacted] |

## 1. APPROVAL SIGNATURES

| | |
|---|---|
| PROTOCOL NUMBER: | CNTX-4975i-OA-304 |
| PROTOCOL TITLE: | A Randomized, Double-blind, Placebo-controlled, 2-Injection, 52-Week Study to Evaluate the Efficacy and Safety of Intra-articular Injections of CNTX-4975-05 in Subjects with Chronic, Moderate-to-severe Osteoarthritis Knee Pain |
| PROTOCOL DATE: | Version 3.0, 12 October 2020 |

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

[redacted]

[redacted] Date

[redacted]

[redacted] Date

## 2. SYNOPSIS

| | |
|---|---|
| PRODUCT NAME/NUMBER | CNTX-4975-05 |
| PROTOCOL NUMBER | CNTX-4975i-OA-304 |
| DEVELOPMENT PHASE | Phase 3 |
| PROTOCOL TITLE | A Randomized, Double-blind, Placebo-controlled, 2-Injection, 52-Week Study to Evaluate the Efficacy and Safety of Intra-articular Injections of CNTX-4975-05 in Subjects with Chronic, Moderate-to-severe Osteoarthritis Knee Pain. |
| INDICATION | Knee pain due to osteoarthritis (OA) |
| OBJECTIVES | The objectives of this study in subjects with moderate-to-severe pain due to osteoarthritis of the knee are as follows:<br>*Primary Efficacy Objective:*<br>• To demonstrate the efficacy of CNTX-4975-05 [redacted] on OA pain in the index knee following an intra-articular (IA) injection at Baseline, and also to assess the impact of a repeat IA injection of CNTX-4975-05 at Week 26 on OA pain in the knee.<br>*Secondary Efficacy Objectives:*<br>• To assess the impact of a repeat IA injection of CNTX-4975-05 at Week 26 on OA pain in the knee at Week 38.<br>• To evaluate the overall improvement in OA of the index knee through Week 26.<br>*Exploratory Efficacy Objectives:*<br>• To explore the analgesic efficacy of CNTX-4975-05 on OA pain of the index knee through 52 weeks.<br>• To explore the overall benefit on OA of the index knee through 52 weeks.<br>• To explore the potential to delay the need for a total knee replacement surgery, based on the subjects' responses and the control of pain and improvement in function, quality of life, and on sleep.<br>• To explore the need for rescue and background analgesic medications for OA pain in the index knee.<br>*Supportive Efficacy Objective:*<br>• To explore the analgesic efficacy and overall benefit on OA of the index knee through Weeks 38 and 52, following a repeat IA injection of CNTX-4975-05 at Week 26.<br>*Safety Objective:*<br>• To evaluate the safety of an initial IA injection (at Baseline) and a repeat IA injection (at Week 26) of CNTX-4975-05, compared to placebo, in the index knee. |
| STUDY DESIGN | This is a randomized, double-blind, placebo-controlled, 2-injection, 52-week study to evaluate the efficacy and safety of an initial intra-articular injection (at Baseline) and a second intra-articular injection (at Week 26) of [redacted] of CNTX-4975-05, compared to placebo, in subjects with chronic, moderate-to-severe index knee pain from OA.<br>At randomization, subjects will be stratified to balance across treatment groups for: |

| | |
|---|---|
| | • K-L grades 2, 3 and 4, with a limit of approximately 20% of subjects having K-L grade 4,<br>• Body mass index (BMI) <30 or ≥30 kg/m$^2$, and<br>• Sex of subject<br><br>Subjects will be randomized to receive single IA injections of [redacted] of CNTX-4975-05, or matching placebo, injected into the index knee at Baseline and at Week 26. The second injection will consist of the original randomized investigational product (IP) (placebo or CNTX-4975-05). Subjects will continue to be followed for a further 26 weeks after the second injection (52 weeks total from the Baseline injection).<br><br>Injection of CNTX-4975-05:<br>[redacted]<br><br>Subjects should not take a hot bath or shower, or expose the injected knee to external heat, within 12 hours after the injection.<br><br>A provided tablet computer will be used to record the electronic patient-reported outcomes (ePRO). Entries will be made daily to evaluate the index knee pain (the primary endpoint) and use of rescue medication. All other assessments will be evaluated by telephone and/or clinic visits. Study staff will call subjects to assess OA pain, overall satisfaction with the treatment procedure, adverse events, and the use of rescue medication, on Day 3 after each injection. Subjects will return to the clinic at Weeks 4, 8, 12, 18, 26, 30, 38, 46, and 52 for study assessments. In case of technical issues, paper copies of the PROs will be provided for subject completion and filed at the site.<br><br>Efficacy will be assessed by OA index knee pain with walking, including durability of treatment response and cumulative responder analyses (cumulative and Outcome Measures in Rheumatology [OMERACT]-Osteoarthritis Research Society International [OARSI]; Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] knee pain, stiffness, and function [WOMAC A, B and C, respectively]; Patient Global Impression of Change [PGIC] for OA index knee pain; Knee Injury and Osteoarthritis Outcome Score [KOOS]; Medical Outcomes Study [MOS] sleep scale; SF-36 health questionnaire; EQ-5D-5L quality of life; Work Productivity and Activity Impairment Scale [WPAI]; assistive device usage questionnaire; and rescue medication use).<br><br>Safety will be assessed by injection site assessment (erythema and edema), assessment of treatment procedure pain, adverse events (AEs), physical examination findings, sensory testing, vital sign measurements, 12-lead electrocardiograms (ECG), clinical laboratory test results, and the stability of knee radiographs from Baseline to Week 52. |

| | |
|---|---|
| PLANNED NUMBER OF SUBJECTS | Approximately 325 subjects will be enrolled with a 2:3 allocation (placebo to active) (approximately 125 subjects assigned to placebo and 200 subjects assigned to [redacted] CNTX-4975-05). |
| STUDY ENTRY CRITERIA | Inclusion Criteria:<br>1. Male or female subjects between 40 and 95 years of age (inclusive) at the time of the Screening Visit with the ability to comply with answering the electronic diary using the study-provided tablet computers.<br>2. Confirmation of OA of the knee: radiography of both knees with a posterior-anterior, fixed-flexion view taken during the Pre-screening Period. The index knee must show evidence of chronic OA with a K-L grade of 2, 3 and 4. The IRT system will limit the number of K-L grade 4 subjects to approximately 55 subjects (approximately 20% of enrollment).<br>3. Confirmation of OA of the index knee: American College of Rheumatology (ACR) diagnostic criteria.<br>4. Moderate to severe pain in the index knee associated with OA must be stable for a minimum of 6 months prior to Screening, as assessed by the investigator.<br>5. For qualifying Baseline knee pain with walking, the Baseline score will be derived from the 14 days of pre-dose pain scores collected immediately preceding subject randomization on Day 1. The Baseline pain score will be calculated by the randomization algorithm as the mean of the scores from the 14 days (or at a minimum, 8 days) immediately preceding Day 1. Subjects must use a numeric pain rating scale (NPRS) (0-10; 0 = no pain, 10 = worst pain ever) to rate their index knee pain with walking, reported using the ePRO system. Pain in the index knee must be rated daily at bedtime (9:00 PM ± 3 hours) to determine the average knee pain with walking during the previous 24 hours. The site and subject training will target at least an 85% compliance rate, using ongoing assessment of compliance data, and site communication with the subject if compliance drops below 85%.<br>6. At Baseline only, pain with walking will also be collected and assessed for the non-index knee, as noted in the assessment above (5).<br>7. Compliance with diary entry to meet minimal acceptable criteria during Screening.<br>8. Understanding of the outcome measures, and the relationship among them, after subject training and testing.<br>9. BMI $\leq$45 kg/m$^2$.<br>10. Subjects must have failed 2 or more prior therapies. Failure is deemed to be inadequate relief in the opinion of the investigator. A therapy may be deemed to have been inadequate because of one or more of the following:<br>a) unacceptable adverse events (AEs);<br>b) inadequate response, or loss of response for chronic OA knee pain or<br>o pain in the index knee was minimally improved, not improved, or was worse and/or<br>o improvement function, and/or stiffness in the index knee was minimally improved, not improved, or was worse<br>c) medical condition resulting in contraindication to the standard of care appropriate to the severity of the index knee OA pain.<br>"Therapies" include, but are not limited to, each of the following:<br>o nonsteroidal anti-inflammatory drugs (NSAIDs) (including topical), opioids, duloxetine, other systemic therapy, IA corticosteroids, IA viscosupplements<br>o physical therapy, bracing, and orthotics.<br>11. Females not of childbearing potential, defined as post-menopausal for at least 1 year, or surgically sterile (bilateral tubal ligation, bilateral |

| | |
|---|---|
| | oophorectomy, or hysterectomy), or practicing one of the following medically acceptable methods of birth control throughout the study period:<br>• Hormonal methods such as oral, implantable, injectable, or transdermal contraceptives for a minimum of 1 full cycle (based on the subject's usual menstrual cycle period) before IP administration<br>• Total abstinence from sexual intercourse since the last menses before IP administration<br>• Intrauterine device<br>• Double barrier method (condoms, sponge, diaphragm, with spermicidal jellies or cream)<br>12. Able to speak, read, and understand the language of the study used for the informed consent and ePRO.<br>13. Willing and able to:<br>a) understand the study requirements,<br>b) abide by the study restrictions and requirements,<br>c) complete the study procedures,<br>d) be compliant and independently (ie, without assistance) record responses on the pain scales and make daily entries using ePRO (eg, have the ability to comply with answering the electronic diary using the study provided tablet computers),<br>e) independently communicate meaningfully with the study personnel.<br>14. Signed informed consent form approved by the institutional review board (IRB).<br>15. Subject agrees to stay on their current pain medication (including over the counter (OTC) medications) from the time of Pre-screening through Week 12. The current pain medication must be taken only for pain in the index knee, and not for another pain indication. Their current pain medication must be one of the allowed rescue medications and dosages, or hydrocodone at a dose up to 15 mg daily (or another opioid equivalent). The rescue medication is not allowed to be in the same drug class as the ongoing medication. For example, subjects will not be allowed to take tramadol as a rescue medication if they are taking an opioid as concomitant medication, or an NSAID as rescue if they are using an NSAID as concomitant medication. From Week 12 to completion of the study, subjects may stay on current pain medication as prescribed or OTC medication, but this is not required. If reducing or stopping background medications for the index knee OA pain, that information must be recorded by the site/subject.<br>16. Subject agrees to take only the allowed rescue medications for OA knee pain of the index knee from the time of the first Treatment Visit through study completion and agrees to use no topical medications for OA knee pain during the trial.<br>Exclusion criteria:<br>1. Joint replacement surgery of the index knee at any time (full or partial), or open surgery of the index knee in the past 24 months.<br>2. Prior arthroscopic surgery of the index knee within 6 months of Screening.<br>3. Any painful conditions of the index knee due to joint disease other than OA. For example, radicular or referred pain involving the index knee or from joint disease other than OA involving the index knee, such as, but not restricted to, inflammatory diseases, eg, rheumatoid arthritis, psoriatic arthritis, chondromalacia patella, metabolic diseases, gout/pseudogout, hemochromatosis, acromegaly, etc.<br>4. Periarticular pain from any cause, including referred pain, bursitis, tendonitis, soft tissue tenderness, or subacute/acute pain from injury.<br>5. Pain in the non-index knee that is >3 (NPRS 0-10) when walking or at rest. |

| | |
|---|---|
| | 6. Other chronic pain anywhere in the body that requires the use of analgesic medications, including, but not limited to, local painful areas, myofascial pain syndromes, fibromyalgia, genetic, metabolic abnormalities, hematologic or neuropathic pain, and any acute or chronic pain that may interfere with the study pain assessments by the subject.<br>7. Instability of the index knee (eg, cruciate ligament tear or rupture, significant protruding meniscus, substantial ligamentous laxity).<br>8. Misalignment (>10 degrees varus or valgus) of the index knee on standing.<br>9. Documented history of neuropathic arthropathy or finding of bony fragmentation in the index knee with imaging (radiographic, computed tomography, or magnetic resonance imaging).<br>10. Physical/occupational/chiropractic therapy for the lower extremities or acupuncture for the lower extremities within 30 days of Screening, or need for such therapy during the study.<br>11. Plans to have surgery, other invasive procedures, or IA injections (other than the IP) while participating in the study.<br>12. Has used topical capsaicin on the index knee within 90 days of Screening.<br>13. Current use of opioids for any condition other than for OA of the index knee (maximum dose of 15 mg of hydrocodone [or equivalent] per day).<br>14. Corticosteroid injection into the index knee within 90 days of Screening.<br>15. Received IA viscosupplementation (eg, Synvisc®, Hyalgan®) within 90 days of Screening.<br>16. History of allergic reaction to the planned local anesthesia/analgesic regimens, ethylenediaminetetraacetic acid (EDTA), Kolliphor HS 15, butylated hydroxytoluene (BHT), or capsaicin.<br>17. Presence of any medical condition or unstable health status that, in the judgment of the investigator, might adversely impact the safety of the subject, or the conduct of the study, or negatively affect the resulting data, including chronic conditions that are likely to alter the rate of healing or are likely to result in safety complications unrelated to the study medication, or significantly compromise key organ systems. For any question regarding eligibility, it is strongly recommended that the investigator discuss the subject with the medical monitor.<br>18. Is pregnant or is breast feeding.<br>19. Has a malignancy, a history of malignancy, or has received treatment for malignancy at any time, with exception of resected and cured basal cell carcinoma and squamous cell carcinoma of the skin.<br>20. Regular use of anticoagulant blood thinners (except low-dose aspirin, Dabigatran 150 mg once daily [qd], Enoxaparin 40 mg qd, Rivaroxaban 10 mg qd, Apixaban 2.5 mg twice daily [bid], or clopidogrel 75 mg qd, which are allowed).<br>21. Active cutaneous disease at the anticipated site of IP injection that would prevent the safe administration of IP.<br>22. Ulcer or open wound anywhere on the index knee.<br>23. Specific laboratory abnormalities:<br>• Hemoglobin <11.0 g/dL<br>• White blood cells (WBC) <2.5 X $10^9$/L<br>• Neutrophils <1.5 X $10^9$/L<br>• Platelets <100 X $10^9$/L<br>• Aspartate transaminase (AST) or alanine transaminase (ALT) >2 X upper limit of normal<br>• Creatinine >1.6 mg/dL<br>• Glucose (fasting) >250 mg/dL<br>• HgbA1c >9 |

| | |
|---|---|
| | 24. Clinically significant abnormal laboratory result at the Screening Visit (in the opinion of the investigator), or significant organ disease that would put the subject at undue risk or affect the ability of the subject to participate in the trial. For any question regarding eligibility, it is strongly recommended that the investigator discusses the subject with the medical monitor.<br>25. Use of an investigational medication within 30 days of Screening or 5 pharmacokinetic or pharmacodynamic half-lives (whichever is longer), or scheduled to receive such an agent while participating in the current study.<br>26. Prior participation in an ALGRX 4975 or CNTX-4975 study.<br>27. Has any of the following characteristics:<br>• Does not have a qualifying Baseline mean knee pain score of ≥5 and ≤9 out of 10 on the NPRS scale in the index knee<br>• Active or historic substance use disorder within the previous year as defined by the Diagnostic and Statistical Manual for Mental Health Disorders, fifth edition<br>• Test is positive upon urine drug screen for a substance of abuse (prescribed opioids acceptable)<br>• Has a history, at any time, or currently, of suicidal ideation, suicide attempt, or increased risk of suicide<br>• Has unacceptable level of depression or anxiety as measured by the Hospital Anxiety and Depression Scale (HADS) score of ≥11<br>• Has unacceptable chronic pain as measured by the Fibromyalgia Symptom Scale Score (FSS) of ≥13<br>• Has a positive pregnancy test at the Screening or Treatment Visit<br>• Has ongoing litigation for workers' compensation<br>• Has any condition, or is taking any medication, that would be contraindicated for study participation |
| INVESTIGATIONAL PRODUCT | Name: CNTX-4975-05 (trans-capsaicin injection), provided as a [redacted] |
| REFERENCE PRODUCT(S) | Name: Matching placebo, consisting of [redacted] saline for injection. |
| TREATMENT REGIMENS | All subjects will receive a single clinical or ultrasound-guided intra-articular injection of 2% lidocaine, followed by CNTX-4975-05 [redacted] or matching placebo, on Study Day 1 (Treatment Day 1) and at Week 26 (Treatment Day 2), along with controlled cooling. |
| PLANNED STUDY SITES | Approximately 30 concurrent study sites in the US |
| CRITERIA FOR EVALUATION | **Primary Efficacy Endpoints:**<br>The primary efficacy endpoint of this study, comparing results in subjects treated with [redacted] of CNTX-4975-05 or placebo, is as follows:<br>• Change from study baseline to Week 12 in the average pain in the index knee, using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) A (pain) subscale.<br>**Key Secondary Efficacy Endpoints:**<br>The key secondary efficacy endpoints of this study, comparing results in subjects treated with [redacted] of CNTX-4975-05 or placebo, are as follows:<br>• *First Key Secondary:* Change from study baseline to Week 38 in the average pain in the index knee, using the WOMAC A (pain) subscale. |

| | |
|---|---|
| | • *Second Key Secondary*: Change from study baseline to Week 12 in the average function in the index knee, using the WOMAC C (function) subscale.<br><br>**Secondary Efficacy Endpoints:**<br>The secondary efficacy endpoints of this study, comparing results in subjects treated with [redacted] of CNTX-4975-05 or placebo, include the following:<br>• PGIC responders (scores of Very Much Improved or Much Improved) for the index knee at Week 12.<br>• Area under the curve (AUC) calculated based on the change from study baseline through Week 12 (Day 84) (i.e., Standardized $AUC_{Daily\text{-}Wk12}$) in the average pain with walking in the index knee over the previous 24 hours, using the NPRS (0-10)<br>• Change from study baseline (mean of most recent non-missing 8 out of 14 days, from Day -14 through Day -1) to Week 12 (mean of Day 78 through Day 84) in the average pain with walking in the index knee over the previous 24 hours, using the NPRS (0-10).<br>• AUC calculated on change from study baseline through Week 26 (Day 182) (i.e., Standardized $AUC_{Daily\text{-}Wk26}$) in the average pain with walking in the index knee over the previous 24 hours, using the NPRS (0-10).<br>• Change from study baseline to Week 26 in the average pain in the index knee, using the WOMAC A (pain) subscale.<br>• Change from study baseline to Week 26 in the average function in the index knee, using the WOMAC C (function) subscale.<br>• Change from study baseline to Week 26 in the average pain in the index knee with walking over the previous 24 hours, using the NPRS (0-10).<br>• PGIC responders (scores of Very Much Improved or Much Improved) for the index knee at Week 26.<br><br>**Exploratory Efficacy Endpoints:**<br>Exploratory efficacy endpoints of this study, comparing results in subjects treated with [redacted] of CNTX-4975-05 or placebo, include the following:<br>• Change from study baseline to each study visit through Week 52 in the average pain in the index knee, using the WOMAC A (pain) subscale.<br>• Change from study baseline to each study visit through Week 52 in the average stiffness in the index knee, using the WOMAC B (stiffness) subscale.<br>• Change from study baseline to each study visit through Week 52 in the average function in the index knee, using the WOMAC C (function) subscale.<br>• Change from study baseline to each study week through Week 52 in the average pain with walking in the index knee over the previous 24 hours, using the NPRS (0-10).<br>• AUC calculated on change from study baseline through Week 38 (Day 266) (i.e., Standardized $AUC_{Daily\text{-}Wk38}$) and Week 52 (Day 364) (i.e., Standardized $AUC_{Daily\text{-}Wk52}$) in the average pain with walking in the index knee over the previous 24 hours, using the NPRS (0-10).<br>• Total daily, standardized weekly, total weekly, rescue-adjusted total daily, and rescue-adjusted total daily AUC calculated on change from study baseline |

| | |
|---|---|
| | through Weeks 12, 26, 38, and 52 in the average pain with walking in the index knee over the previous 24 hours, using the NPRS (0-10).<br>• PGIC for the index knee for each study visit through Week 52.<br>• Change from study baseline to each study visit through Week 52 in the quality of life (QOL), as measured by the SF-36 Health Survey.<br>• Change from study baseline to each study visit through Week 52 in QOL, as measured by the five-level version of the EQ-5D-5L.<br>• Durability of efficacy of a first (up to Week 26) and a repeat IA injection (up to Week 52), as measured by the time from Day 1 (study baseline) to the return of study baseline (NPRS pain with walking) pain.<br>• Cumulative responder analysis for all subjects at each study visit, based on WOMAC A (pain), WOMAC B (stiffness), and WOMAC C (function) scores. Responders at each study visit (WOMAC) / study week (NPRS) will be defined using 1) percent change from study baseline, 2) the absolute change from study baseline, and 3) the observed value.<br>• Frequency of use of rescue and background analgesic medication for the index knee pain throughout the study period.<br>• OMERACT-OARSI criteria responders at each study visit through Week 52 (based on study baseline).<br>• Change from study baseline to each study visit through Week 52 in quality of sleep, as measured by the MOS sleep scale.<br>• Change from study baseline to each study visit through Week 52 in KOOS.<br>• Change from study baseline to each study visit through Week 52 in weight and body mass index (BMI).<br>• Change from study baseline to Week 52 in abdominal girth and HbA1c.<br>• Likelihood of subject need for joint replacement surgery, based on pain, function, and other patient-reported outcomes, from study baseline to each study visit through Week 52.<br>• Change from study baseline to each study visit through Week 52 in WPAI:OA results.<br>• To explore the effect of K-L grade, sex, BMI, and age on the analgesic efficacy of CNTX-4975-05, measured by WOMAC A (pain) scale, WOMAC C (function) scale, and average weekly pain with walking NPRS (0-10) score, through Week 52. Additionally, subjects with radiographic evidence of OA in the non-index (opposite) knee (K-L=2, 3, or 4) vs subjects with no radiographic evidence of OA in the non-index knee (K-L=0 or 1) will be analyzed.<br>• Subject's guess as to which treatment they think they received.<br>• Shift from study baseline to each study visit through Week 52 in worst case assistive device usage.<br>• Subject satisfaction with treatment procedure.<br><br>**Supportive Efficacy Endpoints:**<br>Supportive efficacy endpoints for the repeat injection, comparing results in subjects treated with [redacted] of CNTX-4975-05 or placebo, include the following:<br>• Change from Week 26 baseline to each study visit through Week 52 in the average pain in the index knee, using the WOMAC A (pain) subscale.<br>• Change from Week 26 baseline to each study visit through Week 52 in the average stiffness in the index knee, using the WOMAC B (stiffness) subscale.<br>• Change from Week 26 baseline to each study visit through Week 52 in the |

| | |
|---|---|
| | average function in the index knee, using the WOMAC C (function) subscale.<br>• Change from Week 26 baseline to each study week through Week 52 in the average pain with walking in the index knee over the previous 24 hours, using the NPRS (0-10).<br>• AUC calculated based on the change from Week 26 baseline through Week 38 and through Week 52 (i.e., Standardized $AUC_{Daily\text{-}Wk26Wk38}$ and Standardized $AUC_{Daily\text{-}Wk26Wk52}$) in the average pain with walking in the index knee over the previous 24 hours, using the NPRS (0-10).<br>• Total daily, standardized weekly, total weekly, rescue-adjusted total daily, and rescue-adjusted total daily AUC calculated on change from Week 26 baseline through Weeks 38 and 52 in the average pain with walking in the index knee over the previous 24 hours, using the NPRS (0-10).<br>• Change from Week 26 baseline to each study visit through Week 52 in the QOL, as measured by the SF-36 Health Survey.<br>• Change from Week 26 baseline to each study visit through Week 52 in QOL, as measured by EQ-5D-5L.<br>• OMERACT-OARSI criteria responders at each study visit through Week 52 (based on Week 26 baseline).<br>• Change from Week 26 baseline to each study visit through Week 52 in quality of sleep, as measured by the MOS sleep scale.<br>• Change from Week 26 baseline to each study visit through Week 52 in KOOS.<br>• Change from Week 26 baseline to each study visit through Week 52 in weight and BMI.<br>• Change from Week 26 baseline to each study visit through Week 52 on the WPAI:OA.<br><br>**Safety Endpoints:**<br>Safety endpoints in subjects treated with [redacted] of CNTX-4975-05 or placebo, include the following:<br>• AEs<br>• Vital signs<br>• Clinical laboratory evaluations (hematology, chemistry, and urinalysis)<br>• 12-lead electrocardiograms (ECG)<br>• Physical examination (including the presence or absence of an effusion in the index knee, periarticular pain/tenderness)<br>• Sensory testing using a 5-point Likert scale<br>• Concomitant medications and therapies (including background medications)<br>• Degree of procedure pain in the index knee on Day 1 and Week 26 (not recorded as AEs)<br>• Local physical findings after injection of the index knee<br>• Injection site assessment of erythema and edema.<br>• Stability of knee radiographs from pre-screening to Week 52, evaluated using Osteoarthritis Research Society International (OARSI) scoring criteria |
| STATISTICAL METHODS | The statistical analysis was developed to meet the requirements of the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA).<br>The primary and first key secondary efficacy endpoints are the change from study baseline to Week 12 and Week 38, respectively, in WOMAC A (pain) scores. An MMRM analysis will be performed that includes change from study baseline in |

| | |
|---|---|
| | WOMAC A (pain) scores as the dependent variable and terms for treatment, pooled site, baseline K-L grade category, study baseline BMI category, study baseline OA type, sex, study week, treatment by visit study week interaction, and study baseline WOMAC A (pain) score as a covariate, using an unstructured covariance structure. More details will be provided in the statistical analysis plan (SAP) on how to handle potential convergence issues.<br><br>The second key secondary efficacy endpoint is the change from study baseline to Week 12 in WOMAC C (function) scores; it will be analyzed in a manner similar to WOMAC A (pain) scores.<br><br>These analyses will be performed using the ITT population and will be repeated on additional populations for sensitivity, as specified in the SAP.<br><br>The PGIC will be summarized descriptively using frequencies and percentages by study week and treatment group. A responder analysis will be performed for each visit for the PGIC in which responders (PGIC of Very Much Improved or Much Improved) will be compared to non-responders.<br><br>Analysis of the change from study baseline to each study week in the average pain with walking in the index knee over the previous 24 hours (average weekly pain with walking NPRS [0-10]), will come from the MMRM used for the primary analysis and will be derived using contrast statements within that model. The MMRM analysis will be presented showing all study weeks. This analysis will be based on a worst observation carried forward (WOCF) approach that will replace scores occurring on a day where rescue medication was taken with the worst observation starting at Day 2. Details will be specified in the SAP.<br><br>Change from study baseline to Week 26 in WOMAC A (pain) and C (function) scores will be analyzed using an MMRM with the same terms as that described for the primary analysis.<br><br>All secondary efficacy analyses will be performed using the ITT population, unless otherwise specified. Sensitivity analyses of secondary efficacy endpoints will be specified in the SAP.<br><br>All supportive and exploratory efficacy analyses will be performed using the ITT population. Any *P* values provided in analyses in this section will be informational only and not used in the fixed-sequence testing.<br><br>The type I error rate of $\alpha = 0.05$ will be maintained for the study by using a fixed-sequence testing strategy for primary, key secondary, and secondary endpoints. If the primary endpoint has $P \leq 0.05$, then the full $\alpha = 0.05$ will be passed to the key secondary endpoints then secondary endpoints for continued fixed-sequence testing in the order listed; testing will stop at the first *P* value > 0.05. The fixed-sequence testing will be based on the order listed in the primary, key secondary, and secondary endpoints, in order to meet regulatory requirements.<br><br>All other continuous secondary and exploratory efficacy endpoints will be summarized using descriptive statistics by treatment group and week/visit, as appropriate, and analyzed using an MMRM analysis or by analysis of covariance, as appropriate. Categorical endpoints will be compared between treatments using Pearson's chi-square or Fisher's exact test, as appropriate.<br><br>Safety analyses will be conducted using data from the safety population. No formal inferential analyses will be conducted for safety variables unless otherwise noted.<br><br>Any data analyses included in the unblinded delivery will be considered final, and no changes to the analysis results will be permitted following unblinding. The entire project study team (including the project statistician) will remain blinded until the final database lock. |

| | |
|---|---|
| SAMPLE SIZE DETERMINATION | Approximately 325 subjects will be randomized to placebo (approximately 125 subjects) and to CNTX-4975-05 (approximately 200 subjects).<br><br>In the previous versions of the protocol (Versions 1.0 & 2.0), the primary endpoint was average weekly pain with walking NPRS (0-10) to Week 12. The sample size and power calculations were based on that endpoint.<br><br>Results from study CNTX-4975-OA-502 provided a standard deviation (SD) of 2.55 and mean changes from baseline of -3.02 and -4.42 for placebo and [redacted] of CNTX-4975, respectively. Assuming an effect size of 0.5, a sample size of 293 evaluable subjects at Week 12 with a 2:3 allocation (placebo to active) will achieve 98% statistical power for having a significant CNTX-4975-05 and placebo comparison, using a two-sided test at the 5% significance level. A power of 98% was used for the primary analysis at Week 12 in order to maintain adequate power for comparisons at later time points on the primary outcome and key secondary outcome measures.<br><br>Previous key secondary outcomes, WOMAC B (stiffness) and WOMAC C (function), are powered at 75% and 71%, respectively, at Week 12 (the primary endpoint) using an N of 293 for the trial. To account for dropouts and subjects for safety evaluation, the initial planned enrollment is approximately 325 subjects (approximately 125 subjects in placebo and 200 subjects in CNTX-4975-05).<br><br>In this version of the protocol (Version 3.0), the primary endpoint is the change from study baseline to Week 12 in WOMAC A (pain). In order to determine the approximate power for this primary endpoint, a post hoc analysis for change from baseline to Week 12 in WOMAC A (pain) from Centrexion's Phase 3 study in knee OA, CNTX-4975i-OA-301, was performed. The mean changes from baseline to Week 12 were -13.43 and -16.44 for placebo and [redacted] CNTX-4975-05, respectively, with a pooled SD of the population of 11.7794. With a calculated effect size of 0.256, a statistical power of 56% is predicted to detect a significant CNTX-4975-05 and placebo comparison, using a 2-sided test at the 5% significance level. |
| STUDY AND TREATMENT DURATION | The overall maximum study duration is expected to be approximately 58 weeks. The sequence and maximum duration of the study periods will be as follows:<br>• Pre-Screening (subjects should return for Screening as soon as feasible)<br>• Screening Period: up to 30 days +3-day window<br>• Treatment Period (double-blind, placebo-controlled): first dose at Day 1 (1 day); second dose at Week 26 (1 day)<br>• Post-Treatment Double-Blind period: 52 weeks<br>The maximum IP treatment period for each subject is 2 days.<br>The maximum study duration for each subject is approximately 58 weeks. |

## 3. TABLE OF CONTENTS

## 3.1. LIST OF TABLES

## REASONS FOR AMENDMENT (3.0)

[redacted]

## AMENDED PROTOCOL

The following are the amended protocol and appendices, including all revisions specified above.

## 4. LIST OF ABBREVIATIONS

| | |
|---|---|
| ACLS | Advanced Cardiac Life Support |
| ACR | American College of Rheumatology |
| ADL | activities of daily living |
| ADR | adverse drug reaction |
| AE | adverse event |
| AESI | adverse events of special interest |
| ALT | alanine transaminase |
| AST | aspartate transaminase |
| ATC | Anatomical Therapeutic Chemical class |
| AUC | area under the curve |
| BHT | butylated hydroxytoluene |
| bid | twice daily |
| BMI | body mass index |
| CNS | central nervous system |
| CRA | clinical research associate |
| CRF | case report form |
| CSR | clinical study report |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EDTA | ethylenediaminetetraacetic acid |
| EMA | European Medicines Agency |
| ePRO | electronic patient-reported outcomes |
| EQ-5D-5L | five-level version of the EuroQol five-dimensional questionnaire |
| FDA | Food and Drug Administration |
| FSS | Fibromyalgia Symptom Scales Score |
| GCP | Good Clinical Practice |
| h | hour |
| HADS | Hospital Anxiety and/or Depression Scale |
| HgbA1c | hemoglobin A1c |
| HR | heart rate |

| | |
|---|---|
| IA | intra-articular |
| IB | Investigator's brochure |
| ICF | informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IP | investigational product |
| IRB | Institutional Review Board |
| IRT | interactive web response system |
| ITT | intent-to-treat |
| K-L | Kellgren-Lawrence |
| KOOS | Knee Injury and Osteoarthritis Outcome Score |
| LOC | level of consciousness |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | mixed-model repeated measures |
| MOS | Medical Outcomes Study sleep scale |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NPRS | numeric pain rating scale |
| NSAID | nonsteroidal anti-inflammatory drug |
| OA | osteoarthritis |
| OARSI | Osteoarthritis Research Society International |
| OMERACT | Outcome Measures in Rheumatology |
| OTC | over the counter |
| PGIC | Patient Global Impression of Change |
| PK | pharmacokinetics |
| PO | per os (by mouth; oral) |
| PP | Per protocol |
| PRN | pro re nata (as needed) |
| qd | once daily |
| QID | four times daily |
| QOL | quality of life |
| RBC | red blood cells |
| RR | respiratory rate |
| SAE | serious adverse event |

| | |
|---|---|
| SAP | statistical analysis plan |
| SD | standard deviation |
| SOC | system organ class |
| Sport/Rec | Sport and Recreation |
| TRPV1 | transient receptor potential vanilloid subfamily member 1 |
| UADR | unexpected adverse drug reaction |
| UAE | unexpected adverse event |
| WBC | white blood cells |
| WHO-DD | World Health Organization Drug Dictionary |
| WOMAC | Western Ontario and McMaster Universities Osteoarthritis Index |
| WPAI | Work Productivity and Activity Impairment Scale |

# 5. INTRODUCTION

## 5.1. Background and Rationale

Osteoarthritis (OA) is one of the most common diseases seen in patients.[1] Osteoarthritis of the knee is characterized by pain, cartilage degradation, osteophyte formation, and joint space narrowing.[2] The pain can be debilitating. Patients are often impaired in their ability to perform simple daily tasks such as walking or climbing stairs. The pain may be felt even while sitting in a chair or lying in bed and may interfere with the ability to sleep.

Commonly prescribed medications for OA pain include acetaminophen/paracetamol, duloxetine, nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitors, and opioids. These drugs have serious potential side effects and often lack efficacy. When effective, they still have to be given frequently, and therefore, long-term systemic exposure is a potential issue from a safety perspective. CNTX-4975-05 is expected to provide long-term analgesia after a single injection into the index knee, with an elimination half-life in the order of hours, thus circumventing the need for long-term exposure. Successful relief of pain may forestall the need for a total joint replacement (total knee arthroplasty).

### 5.1.1 Capsaicin for Injection (CNTX-4975-05)

CNTX-4975-05 (trans-capsaicin injection) is a long-acting, nonopioid analgesic drug candidate designed to provide pain relief for weeks to months after a single local application.[3] [redacted]

Capsaicin, the primary pungent agent in hot chili peppers, selectively activates sensory neurons (nociceptors, pain fibers) that convey information about noxious stimuli to the central nervous system by interacting with the capsaicin receptor, transient receptor potential vanilloid subfamily member 1 (TRPV1).[4] The initial effect is excitation (hence pain), which is followed by desensitization restricted to the TRPV1-expressing nociceptors.[5] The desensitization of nociceptors may last for weeks and is accompanied by degeneration of the nociceptor terminals, which then regenerate over a period of weeks.[6] The use of capsaicin has been the focus of many therapeutic applications, including the treatment of pain.[7] Topical capsaicin is approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) as a transdermal patch for treatment of post-herpetic neuralgia.[8] Nonclinical and clinical studies performed with capsaicin have demonstrated that it is a potent, long-lasting analgesic (reducing acute and chronic, moderate-to-severe pain for several weeks to months) with a short duration of systemic drug exposure (minimizing systemic side effects) following a single, localized application.[3]

## 5.2. Clinical Experience

The efficacy and safety of CNTX-4975 in subjects with moderate-to-severe OA knee pain has been investigated in 7 studies. In an initial dose-ranging study in 16 subjects (CNTX-4975-1-100-001), doses up to [redacted] were injected prior to subjects undergoing a total

knee joint replacement. No changes outside of those typically observed with OA were noted on pathological examination.

Clinical data from a randomized, double-blind, placebo-controlled OA clinical study (CNTX-4975-1-101-001) comparing [redacted] of CNTX-4975 to placebo (1:1 randomization, N = 12), showed that [redacted] of CNTX-4975 had a stronger efficacy signal than that of the lower doses [redacted]

Clinical data from an open-label study (CNTX-4975-2-006-2, N = 55) in which subjects with moderate-to-severe OA pain of the knee received [redacted] of CNTX-4975 via intra-articular (IA) injection [redacted]

In an open-label study (CNTX-4975-114-02P, N = 54), subjects received doses ranging from 0.2 mg to [redacted]

Study 4975-OA-502 was a phase 2, randomized, double-blind, placebo-controlled, dose-ranging, 24-week evaluation of the safety and efficacy of a single injection of CNTX-4975-04 [redacted] in subjects with chronic, moderate-to-severe OA knee pain. A significant difference for the decrease in pain with walking was apparent in the CNTX-4975-04 groups, relative to the placebo group, as early as 1 week after IP injection for the [redacted] dose; the pain reduction typically continued beyond [redacted] post-injection. Significant improvements in other associated endpoints similarly were observed beyond [redacted] post-injection. Multiple secondary and exploratory analyses showed meaningful improvement in knee function, knee stiffness, and Baseline pain with walking. The results of this study suggest that CNTX-4975-04 is an effective treatment for subjects with moderate-to-severe pain from OA in the knee.

During the trials of CTNX-4975 in subjects with OA, the incidence of serious adverse events (SAEs) was low, and none was thought to be related to the IP. Three of the studies reported no SAEs. In 1 study, an SAE was reported as possibly related (CNTX-4975-2-004-1, indication Morton's neuroma) and involved T-wave inversion. However, this event occurred in the placebo group and resolved without further treatment. Three other SAEs were listed as unrelated and involved chest pain (CNTX-4975-2-002-1, indication OA), femoral hernia (CNTX-4975-2-006-2, indication OA), and menorrhagia (CNTX-4975-2-005-2; indication lateral epicondylitis). One SAE was worsening of previous shoulder osteoarthritis in study CNTX-4975-OA-502, noted as unrelated, with the subject continuing in the trial.

Most of the systemic adverse events (AEs) occurred with similar frequency in capsaicin-treated (all doses combined) compared to placebo-treated subjects. The exception from this was the frequency of initial pain from the injection. Intra-articular injection into the knee of capsaicin produced short-term pain, most often for a period less than 30 minutes. In the preliminary analysis of Study 114-02P, subjects typically indicated that the pain was tolerable (mean peak pain, 5.4 on the 0-10 Numerical Pain Rating Scale [NPRS]). However, 4 of 40 subjects, asked to indicate whether the pain was tolerable, indicated that the pain was intolerable. In all instances

the procedure pain was short-lived (typically under 1 hour [h]) and was under satisfactory control at the time the patient was discharged from the clinic.

Study 4975-OA-501 included 30 subjects with OA of the knee whose index knee was treated with [redacted] CNTX-4975 IA. The focus of this study was to further manage procedural pain. The results suggested the best approach included a combination of opioid pre-medication, 15 mL of lidocaine (2%, without epinephrine) IA 15-30 minutes before IP injection, combined with joint cooling.

In Study 4975-OA-502, the safety profile of CNTX-4975-04 (regardless of dose) was similar to that of placebo from Day 2 through Week 24. On Day 1 (the day of IP injection) at 2 h post-injection, local, mild, or moderate edema was observed in 11.4%, 17.6%, and 16.9% of the subjects in the placebo, [redacted] CNTX-4975-04, and [redacted] CNTX-4975-04 groups, respectively. At the same time point, local, mild, or moderate erythema was observed in 5.7%, 5.9%, and 1.4% of the subjects in the placebo, [redacted] CNTX-4975-04, and [redacted] CNTX-4975-04 groups, respectively. There were no safety signals or adverse trends related to CNTX-4975-04 observed in any of the safety parameter assessments. Overall, both CNTX-4975-04 and the injection procedure were well tolerated by subjects 45 to 80 years of age with OA in the knee.

The present study, CNTX-4975i-OA-304, is 1 of 2 planned phase 3 pivotal studies and will be conducted in the US in approximately 325 subjects with moderate-to-severe OA knee pain. The study design is a randomized, double-blind, placebo-controlled, 2-injection, 52-week study to evaluate the efficacy and safety of an initial injection (at Baseline) and a second injection (at Week 26) of [redacted] of CNTX-4975-05, compared to placebo, delivered intra-articularly, to the index knee in subjects with chronic moderate-to-severe OA knee pain. The other 52 week phase 3 pivotal study, CNTX-4975i-OA-301, will also be conducted in the United States using a similar design to CNTX-4975i-OA-304, except there will be only a single injection (at Baseline) of [redacted] of CNTX-4975-05, compared to placebo.

### 5.3. Summary of Potential Risks and Benefits

The potential benefits of study participation are that subjects with painful OA of the knee 1) may experience a reduction in acute and chronic, moderate-to-severe pain as a result of treatment with CNTX-4975-05, in addition to functional improvements, improved quality of life, and a decrease in knee stiffness, and 2) will understand that they are contributing to the scientific knowledge that may lead to expansion of the treatment options for subjects with OA. No other benefits of participation are anticipated.

The potential risks of study participation include those associated with exposure to CNTX-4975-05 and the risks of medical evaluation, including venipuncture and IA injection. Subjects will be injected with 2% lidocaine (without epinephrine) to provide distension of the joint capsule for access to the whole joint for CNTX-4975-05 and secondarily for sensory blockade. In principle, subjects with substantial reduction of pain and improvement in function after injection could overuse the joint and subject the index joint to overuse and an acceleration of the knee OA.

A summary of the pharmaceutical properties and known potential risks of CNTX-4975-05 is provided in the current version of the investigator's brochure (IB).[3] The investigator must become familiar with all sections of the CNTX-4975 IB before the start of the study.

# 6. OBJECTIVES

The objectives of this study in subjects with moderate-to-severe pain due to OA of the knee are as follows:

## 6.1. Primary Efficacy Objective

- To demonstrate the efficacy of CNTX-4975-05 (1.0 mg) on OA pain in the index knee following an IA injection at Baseline, and also to assess the impact of a repeat IA injection of CNTX-4975-05 at Week 26 on OA pain in the knee.

## 6.2. Secondary Efficacy Objectives

- To assess the impact of a repeat IA injection of CNTX-4975-05 at Week 26 on OA pain in the knee at Week 38.
- To evaluate the overall improvement in OA of the index knee through Week 26.

## 6.3. Exploratory Efficacy Objectives

- To explore the analgesic efficacy of CNTX-4975-05 on OA pain of the index knee through 52 weeks.
- To explore the overall benefit on OA of the index knee through 52 weeks.
- To explore the potential to delay the need for a total knee replacement surgery, based on the subjects' responses and the control of pain and improvement in function, quality of life, and on sleep.
- To explore the need for rescue and background analgesic medications for OA pain in the index knee

## 6.4. Supportive Efficacy Objective

- To explore the analgesic efficacy and overall benefit on OA of the index knee through Weeks 38 and 52, following a repeat IA injection of CNTX-4975-05 at Week 26.

## 6.5. Safety Objective:

- To evaluate the safety of an initial IA injection (at Baseline) and a repeat IA injection (at Week 26) of CNTX-4975-05, compared to placebo, in the index knee.

# 7. STUDY DESIGN

## 7.1. Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled, 2-injection, 52-week study to evaluate the efficacy and safety of an initial intra-articular injection (at Baseline) and a second intra-articular injection (at Week 26) of [redacted] of CNTX-4975-05, compared to placebo, in subjects with chronic, moderate-to-severe index knee pain from OA (confirmed by the American College of Rheumatology (ACR) diagnostic criteria).

At randomization, subjects will be stratified to balance across treatment groups for:

- K-L grades 2, 3 and 4, with a limit of approximately 20% of subjects having K-L grade 4,
- Body mass index (BMI) <30 or ≥30 kg/m$^2$, and
- Sex of subject

Subjects will be randomized to receive single IA injections of [redacted] of CNTX-4975-05 or matching placebo injected into the index knee at Baseline and at Week 26. The second injection will consist of the original randomized investigational product (IP) (placebo or CNTX-4975-05). Subjects will continue to be followed for a further 26 weeks after the second injection (52 weeks total from the Baseline injection).

Injection of CNTX-4975-05:

[redacted]

Subjects should not take a hot bath or shower, or expose the injected knee to external heat, within 12 hours after the injection.

A provided tablet computer will be used to record the electronic patient-reported outcomes (ePRO). Entries will be made daily to evaluate the index knee pain (the primary endpoint) and use of rescue medication. All other assessments will be evaluated by telephone and/or clinic visits. Study staff will call subjects to assess OA pain, overall satisfaction with the treatment procedure, adverse events, and the use of rescue medication, on Day 3 after each injection. Subjects will return to the clinic at Weeks 4, 8, 12, 18, 26, 30, 38, 46, and 52 for study assessments. In case of technical issues, paper copies of the PROs will be provided for subject completion and filed at the site.

Efficacy will be assessed by OA index knee pain with walking, including durability of treatment response and cumulative responder analyses (cumulative and Outcome Measures in Rheumatology [OMERACT]-Osteoarthritis Research Society International [OARSI]; Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] knee pain, stiffness, and function [WOMAC A, B and C, respectively]; Patient Global Impression of Change [PGIC] for OA index knee pain; Knee Injury and Osteoarthritis Outcome Score [KOOS]; Medical Outcomes Study [MOS] sleep scale; SF-36 health questionnaire; EQ-5D-5L quality of life; Work Productivity and Activity Impairment Scale [WPAI]; assistive device usage; and rescue medication use).

Safety will be assessed by injection site assessment (erythema and edema), assessment of treatment procedure pain, adverse events (AEs), physical examination findings, sensory testing, vital sign measurements, 12-lead electrocardiograms (ECG), clinical laboratory test results, and the stability of knee radiographs from Baseline to Week 52.

All AEs observed by the study personnel or reported by the subject during the study (from the time of the signing of the informed consent through the post-treatment visit) will be documented.

### 7.2. Discussion of Study Design

This phase 3 study, CNTX-4975i-OA-304, is a randomized, double-blind, placebo-controlled, 2-injection, 52-week study to evaluate the efficacy and safety of 1 and 2 IA injections of CNTX-4975-05 in subjects with chronic, moderate-to-severe OA knee pain. Procedural pain associated with IA injection of IP will be controlled through pre-medication with IA lidocaine and adjunct controlled joint cooling. The planned safety and efficacy assessments are standard and appropriate.

### 7.3. Study Site(s)

The study will take place at approximately 30 concurrent sites in the US. Each site is anticipated to screen a sufficient number of subjects to be able to randomize approximately 325 subjects. A study site with an acceptable recruitment rate and acceptable quality metrics may be allowed to recruit more subjects if other sites have under enrollment.

### 7.4. Study Modifications for the COVID-19 Pandemic

On 24-April 2020, a memo was sent to all Principal Investigators and Study Staff detailing adjustments that were being made to allow for the safety of both study subjects and study staff following the onset of the COVID-19 pandemic (see Appendix D). At the time that this memo was sent to the study sites, all subjects had already been enrolled.

These adjustments included a widening of the window for the Week 52 final visit as well as the Week 52 radiograph. The original window of +/- 7 business days was increased to -14/+120 business days.

# 8. SUBJECT POPULATION

## 8.1. Selection of Study Population and Diagnosis

Based on the mechanism of action and use of trans-capsaicin for the treatment of pain, there are no gender-specific adverse effects known or to be expected. Thus, male and female subjects will be included in the study. A screening log of potential study candidates and/or an enrollment log of enrolled subjects must be maintained at each study site.

## 8.2. Study Entry Criteria

### 8.2.1 Inclusion Criteria

A subject will be eligible for study participation if the subject meets all of the following criteria:

1. Male or female subjects between 40 and 95 years of age (inclusive) at the time of the Screening Visit with the ability to comply with answering the electronic diary using the study-provided tablet computers.
2. Confirmation of OA of the knee: radiography of both knees with a posterior-anterior, fixed-flexion view taken during the Pre-screening Period. The index knee must show evidence of chronic OA with a K-L grade of 2, 3 and 4. The IRT system will limit the number of K-L grade 4 subjects to approximately 55 subjects (approximately 20% of enrollment).
3. Confirmation of OA of the index knee: American College of Rheumatology (ACR) diagnostic criteria.
4. Moderate to severe pain in the index knee associated with OA must be stable for a minimum of 6 months prior to Screening, as assessed by the investigator.
5. For qualifying Baseline knee pain with walking, the Baseline score will be derived from the 14 days of pre-dose pain scores collected immediately preceding subject randomization on Day 1. The Baseline pain score will be calculated by the randomization algorithm as the mean of the scores from the 14 days (or at a minimum, 8 days) immediately preceding Day 1. Subjects must use a numeric pain rating scale (NPRS) (0-10; 0 = no pain, 10 = worst pain ever) to rate their index knee pain with walking, reported using the ePRO system. Pain in the index knee must be rated daily at bedtime (9:00 PM ± 3 hours) to determine the average knee pain with walking during the previous 24 hours. The site and subject training will target at least an 85% compliance rate, using ongoing assessment of compliance data, and site communication with the subject if compliance drops below 85%.
6. At Baseline only, pain with walking will also be collected and assessed for the non-index knee, as noted in the assessment above (5).
7. Compliance with diary entry to meet minimal acceptable criteria during Screening.
8. Understanding of the outcome measures, and the relationship among them, after subject training and testing.
9. BMI $\leq$45 kg/m$^2$.

10. Subjects must have failed 2 or more prior therapies. Failure is deemed to be inadequate relief in the opinion of the investigator. A therapy may be deemed to have been inadequate because of one or more of the following:
    a) unacceptable adverse events (AEs);
    b) inadequate response, or loss of response for chronic OA knee pain or
        - pain in the index knee was minimally improved, not improved, or was worse and/or
        - improvement function, and/or stiffness in the index knee was minimally improved, not improved, or was worse
    c) medical condition resulting in contraindication to the standard of care appropriate to the severity of the index knee OA pain.

    "Therapies" include, but are not limited to, each of the following:
        - nonsteroidal anti-inflammatory drugs (NSAIDs) (including topical), opioids, duloxetine, other systemic therapy, IA corticosteroids, IA viscosupplements
        - physical therapy, bracing, and orthotics.
11. Females not of childbearing potential, defined as post-menopausal for at least 1 year, or surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy), or practicing one of the following medically acceptable methods of birth control throughout the study period:
    - Hormonal methods such as oral, implantable, injectable, or transdermal contraceptives for a minimum of 1 full cycle (based on the subject's usual menstrual cycle period) before IP administration
    - Total abstinence from sexual intercourse since the last menses before IP administration
    - Intrauterine device
    - Double barrier method (condoms, sponge, diaphragm, with spermicidal jellies or cream)
12. Able to speak, read, and understand the language of the study used for the informed consent and ePRO.
13. Willing and able to:
    a) understand the study requirements,
    b) abide by the study restrictions and requirements,
    c) complete the study procedures,
    d) be compliant and independently (ie, without assistance) record responses on the pain scales and make daily entries using ePRO (eg, have the ability to comply with answering the electronic diary using the study provided tablet computers),
    e) independently communicate meaningfully with the study personnel
14. Signed informed consent form approved by the institutional review board (IRB).
15. Subject agrees to stay on their current pain medication (including over the counter (OTC) medications) from the time of Pre-screening through Week 12. The current pain medication must be taken only for pain in the index knee, and not for another pain indication. Their current pain medication must be one of the allowed rescue medications and dosages, or hydrocodone at a dose up to 15 mg daily (or another opioid equivalent). The rescue

medication is not allowed to be in the same drug class as the ongoing medication. For example, subjects will not be allowed to take tramadol as a rescue medication if they are taking an opioid as concomitant medication, or an NSAID as rescue if they are using an NSAID as concomitant medication. From Week 12 to completion of the study, subjects may stay on current pain medication as prescribed or OTC medication, but this is not required. If reducing or stopping background medications for the index knee OA pain, that information must be recorded by the site/subject.

16. Subject agrees to take only the allowed rescue medications for OA knee pain of the index knee from the time of the first Treatment Visit through study completion and agrees to use no topical medications for OA knee pain during the trial.

### 8.2.2 Exclusion Criteria

A subject will be excluded from the study if the subject meets any of the following criteria:

1. Joint replacement surgery of the index knee at any time (full or partial), or open surgery of the index knee in the past 24 months.
2. Prior arthroscopic surgery of the index knee within 6 months of Screening.
3. Any painful conditions of the index knee due to joint disease other than OA. For example, radicular or referred pain involving the index knee or from joint disease other than OA involving the index knee such as, but not restricted to, inflammatory diseases, eg, rheumatoid arthritis, psoriatic arthritis, chondromalacia patella, metabolic diseases, gout/pseudogout, hemochromatosis, acromegaly, etc.
4. Periarticular pain from any cause, including referred pain, bursitis, tendonitis, soft tissue tenderness, or subacute/acute pain from injury.
5. Pain in the non-index knee that is >3 (NPRS 0-10) when walking or at rest.
6. Other chronic pain anywhere in the body that requires the use of analgesic medications, including, but not limited to, local painful areas, myofascial pain syndromes, fibromyalgia, genetic, metabolic abnormalities, hematologic or neuropathic pain, and any acute or chronic pain that may interfere with the study pain assessments by the subject.
7. Instability of the index knee (eg, cruciate ligament tear or rupture, significant protruding meniscus, substantial ligamentous laxity).
8. Misalignment (>10 degrees varus or valgus) of the index knee on standing.
9. Documented history of neuropathic arthropathy or finding of bony fragmentation in the index knee with imaging (radiographic, computed tomography, or magnetic resonance imaging).
10. Physical/occupational/chiropractic therapy for the lower extremities or acupuncture for the lower extremities within 30 days of Screening, or need for such therapy during the study.
11. Plans to have surgery, other invasive procedures, or IA injections (other than the IP) while participating in the study.
12. Has used topical capsaicin on the index knee within 90 days of Screening.
13. Current use of opioids for any condition other than for OA of the index knee (maximum dose of 15 mg of hydrocodone [or equivalent] per day).

14. Corticosteroid injection into the index knee within 90 days of Screening.
15. Received IA viscosupplementation (eg, Synvisc®, Hyalgan®) within 90 days of Screening.
16. History of allergic reaction to the planned local anesthesia/analgesic regimens, [redacted] or capsaicin.
17. Presence of any medical condition or unstable health status that, in the judgment of the investigator, might adversely impact the safety of the subject, or the conduct of the study, or negatively affect the resulting data, including chronic conditions that are likely to alter the rate of healing or are likely to result in safety complications unrelated to the study medication, or significantly compromise key organ systems. For any question regarding eligibility, it is strongly recommended that the investigator discuss the subject with the medical monitor.
18. Is pregnant or is breast feeding.
19. Has a malignancy, a history of malignancy, or has received treatment for malignancy at any time, with exception of resected and cured basal cell carcinoma and squamous cell carcinoma of the skin.
20. Regular use of anticoagulant blood thinners (except low-dose aspirin, Dabigatran 150 mg once daily [qd], Enoxaparin 40 mg qd, Rivaroxaban 10 mg qd, Apixaban 2.5 mg twice daily [bid], or clopidogrel 75 mg qd, which are allowed).
21. Active cutaneous disease at the anticipated site of IP injection that would prevent the safe administration of IP.
22. Ulcer or open wound anywhere on the index knee.
23. Specific laboratory abnormalities:
    - Hemoglobin <11.0 g/dL
    - White blood cells (WBC) <2.5 X $10^9$/L
    - Neutrophils <1.5 X $10^9$/L
    - Platelets <100 X $10^9$/L
    - Aspartate transaminase (AST) or alanine transaminase (ALT) >2 X upper limit of normal
    - Creatinine >1.6 mg/dL
    - Glucose (fasting) >250 mg/dL
    - HgbA1c >9
24. Clinically significant abnormal laboratory result at the Screening Visit (in the opinion of the investigator), or significant organ disease that would put the subject at undue risk or affect the ability of the subject to participate in the trial. For any question regarding eligibility, it is strongly recommended that the investigator discusses the subject with the medical monitor.
25. Use of an investigational medication within 30 days of Screening or 5 pharmacokinetic (PK) or pharmacodynamic (PD) half-lives (whichever is longer), or scheduled to receive such an agent while participating in the current study.
26. Prior participation in an ALGRX 4975 or CNTX-4975 study.
27. Has any of the following characteristics:

- Does not have a qualifying Baseline mean knee pain score of ≥5 and ≤9 out of 10 on the NPRS scale in the index knee
- Active or historic substance use disorder within the previous year as defined by the Diagnostic and Statistical Manual for Mental Health Disorders, fifth edition
- Test is positive upon urine drug screen for a substance of abuse (prescribed opioids acceptable)
- Has a history, at any time, or currently, of suicidal ideation, suicide attempt, or increased risk of suicide
- Has unacceptable level of depression or anxiety as measured by the Hospital Anxiety and Depression Scale (HADS) score of ≥11
- Has unacceptable chronic pain as measured by the Fibromyalgia Symptom Scale Score (FSS) of ≥13
- Has a positive pregnancy test at the Screening or Treatment Visit
- Has ongoing litigation for workers' compensation
- Has any condition, or is taking any medication, that would be contraindicated for study participation

### 8.3. Premature Subject Withdrawal

All subjects will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. Every reasonable attempt should be made by the investigator to keep subjects in the study. However, subjects must be withdrawn from the study if they withdraw consent to participate. Investigators must attempt to contact subjects who fail to attend scheduled visits by telephone or other means to exclude the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 11.2.

The sponsor reserves the right to request the withdrawal of a subject due to protocol deviations or other reasons.

The investigator also has the right to withdraw subjects from the study at any time for lack of therapeutic effect that is intolerable or otherwise unacceptable to the subject, and at any time for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or in the investigator's opinion, to protect the subject's best interest.

If a subject is withdrawn before completing the study, the reason for withdrawal and the date of discontinuation will be recorded on the appropriate page of the electronic case report form (eCRF). Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the study should be performed at the time of premature discontinuation.

### 8.4. Subject Replacement Criteria

Withdrawn subjects will not be replaced. If a substantial number of subjects are withdrawn from the study, the sponsor will evaluate the need for developing replacement criteria.

Randomized subjects withdrawn from the study may not reenter. The subject number for a withdrawn subject will not be reassigned to another subject.

# 9. TREATMENTS

## 9.1. Identification of Investigational Product(s)

Investigational product (IP) will be provided in the form of pre-filled syringes.

Investigational product will be supplied as [redacted]

## 9.2. Labeling and Packaging

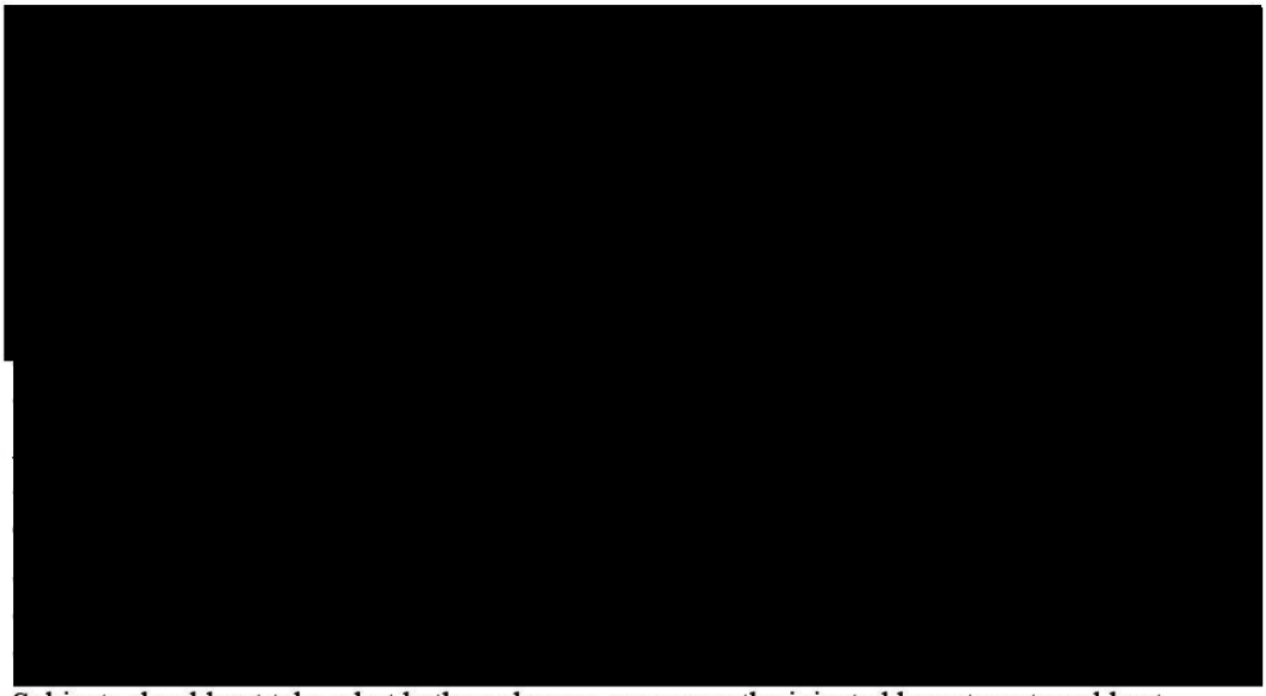
Labeling and packaging of IP will be performed by [redacted]

Investigational product will be packaged as individual double-blinded pre-filled syringes. IP will be packaged so as to be blinded to the investigator, the study clinic personnel, and subjects.

## 9.3. Treatments Administered

Subjects will be randomized to receive a single IA injection of 1.0 mg of CNTX-4975-05 or matching placebo, injected into the index knee on Treatment Day 1. On Treatment Day 2 (Week 26), subjects will receive a second injection of their original randomized IP (placebo or CNTX-4975-05).

[redacted]



Subjects should not take a hot bath or shower, or expose the injected knee to external heat, within 12 hours after the injection.

### 9.4. Dispensing and Storage

The IP supplied by Berkshire Sterile Manufacturing is to be used exclusively in the clinical study according to the instructions of this protocol. The investigator is responsible for dispensing the IP according to the dosage scheme and for ensuring proper storage of the IP.

The investigator must confirm the receipt of the IP with his/her signature. A copy of this receipt must be kept by the investigator and another copy will be stored at Centrexion Therapeutics Corp. and/or . Until the IP is dispensed to the subjects, it must be stored in a securely locked, temperature-controlled room with limited access.

The key to the storage area is to be kept by the investigator or designee responsible for the IP. The store will be accessible only to those persons authorized by the investigator to dispense the IP.

### 9.5. Method of Assigning Subjects to Treatment Groups

In this parallel-group randomized study, subjects who meet study entry criteria will be randomly assigned to placebo (approximately 125) or CNTX-4975-05 (approximately 200) (in a 2:3 allocation [placebo to active]). The randomization schedule will be computer generated using a permuted block algorithm and will randomly allocate IP to randomization numbers. The randomization numbers will be assigned sequentially through a central IRT as subjects are entered into the study. The randomization schedule will be stratified as follows:

- K-L grades 2, 3 and 4, with a limit of approximately 20% of subjects having K-L grade 4,
- BMI $<30$ or $\geq 30$ kg/m$^2$, and

- Sex of subject

Study center will be a blocking factor in the randomization schedule.

The specific numeric requirements for some Inclusion/Exclusion criteria into the study will be blinded for the investigator and study site staff. Blinding of the specific numeric requirements is done to reduce bias introduced into the trial for subjects who may not quite meet the study requirements for randomization. The study sites will enter into the IRT a set of values from specific Inclusion/Exclusion criteria, which will be evaluated by the Centrexion Randomization Algorithm. Those subjects who fulfill the randomization requirements may be enrolled into the study.

The randomization schedule will be prepared by [redacted] before the start of the study. No one involved in the study performance will have access to the randomization schedule before the official unblinding of treatment assignment. No subject will be randomized into this study more than once.

### 9.6. Blinding and Unblinding Treatment Assignment

All subjects, investigators, and study personnel involved in the conduct of the study, including data management and the site pharmacist, will be blinded to treatment assignment, with the exception of a specified unblinded statistician and programmer from [redacted], who will have access to the randomization code. The unblinded study personnel will not participate in study procedures or data analysis prior to unblinding of the study data. If an interim analysis is to be conducted, then unblinded personnel who are not otherwise involved in the study will prepare the data for review.

Study personnel will endeavor to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment.

Unblinding should be discussed in advance with the medical monitor, if possible. For emergency unblinding, study personnel will use the IRT. If the investigator is not able to discuss treatment unblinding in advance, then he/she must notify the medical monitor as soon as possible about the unblinding incident, without revealing the subject's treatment assignment.

The investigator, or designee, must record the date and reason for study discontinuation on the appropriate CRF for that subject. In all cases that are not emergencies, the investigator should discuss the event with the medical monitor prior to unblinding the subject's treatment assignment.

If treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study. Thus, the overall study blind will not be compromised. If a subject's treatment assignment is unblinded, he/she may or may not be asked to withdraw from the study. The investigator should make this decision after consultation with the medical monitor.

At the final visit, subjects will be asked which treatment they think they received.

### 9.7. Selection of Dose in the Study

The objective of this study is to determine the efficacy and safety of [redacted] of CNTX-4975-05, compared to matching placebo, administered by a single IA injection into the index knee of subjects with moderate-to-severe pain from OA in the knee. The results of a previous OA Phase 2 study, CNTX-4975-OA-502, conducted by the sponsor, demonstrated that [redacted] is an effective and well-tolerated treatment for subjects with moderate-to-severe pain from OA in the index knee. A dose of [redacted] resulted in a significant decrease in pain with walking relative to placebo as early as 1 week after IP injection, and the pain reduction typically continued beyond 12 weeks post-injection. In addition, multiple secondary and exploratory analyses showed meaningful improvement in knee function, knee stiffness, and Baseline pain. In addition, the safety profile of CNTX-4975-05 was similar to that of placebo throughout the 24-week study.

### 9.8. Dose Adjustment Criteria

Dose adjustment is not allowed in this study.

### 9.9. Selection of Timing of Dose for Each Subject

All subjects will receive a single clinical or ultrasound-guided IA injection of CNTX-4975-05 or, matching placebo, into the index knee at the study site under the surveillance of appropriate study personnel on Study Day 1 (Treatment Day 1) and at Week 26 (Treatment Day 2).

### 9.10. Drug Accountability

The site pharmacist must maintain adequate records showing the receipt, dispensing, return, or other disposition of the IP including the date, quantity, batch or code number, and identification of subjects (subject number) who received the IP. The site pharmacist will not supply the IP to any person except those named as the investigator or sub-investigators, designated study personnel, and subjects in this study. The site pharmacist will not dispense the IP from any study sites other than those listed. Investigational product(s) may not be relabeled or reassigned for use by other subjects. If any of the IP is not dispensed, is lost, stolen, spilled, unusable, or is received in a damaged container, this information must be documented and reported to Centrexion Therapeutics Corp. and appropriate regulatory agencies, as required.

Upon completion of the study, the IP (partly used, unused, and empty packaging) must be left in the original packaging and returned to the sponsor or designee for destruction.

### 9.11. Treatment Compliance

On Treatment Day 1 and Treatment Day 2 (Week 26), all subjects will receive the single IA investigational product injection. It is recommended to use ultrasound-guided injection, but it is not required. Intra-articular injection without imaging guidance should assure that the needle is in the joint by aspirating joint fluid before injecting IP. All injections at the study site should be under the surveillance of appropriate study personnel. Injection procedure details will be recorded in the subject's eCRF.

All concomitant medications used (including OTC medications) will be recorded in the source document and on the appropriate eCRF.

## 9.12. Permitted and Prohibited Therapies

All concomitant medications used (including OTC medications) will be recorded in the source document and on the appropriate eCRF.

### 9.12.1 Rescue Medication for OA Knee Pain

From Pre-screening through Week 12, subjects are to stay on their current pain medication (prescription or OTC). The current pain medication must be taken only for pain in the index knee, and not for another pain indication. The current pain medication must be either one of the allowed medications listed in Table 9-1 (maximum dose as noted in Table 9-1) or hydrocodone at a dose up to 15 mg daily (or another opioid equivalent). From Week 12 through completion of the study, subjects are permitted to change or discontinue their doses of these background pain medications to treat the index knee OA pain.

Starting with the first Treatment Visit, one of the rescue medications shown in Table 9-1 may be added for the index knee OA pain. If the subject's background medication is one of the allowed medications in Table 9-1, they may continue that therapy and use one of the other classes of rescue medication along with their background medication. The rescue medication is not allowed to be in the same drug class as the ongoing medication. For example, subjects will not be allowed to take tramadol as a rescue medication if they are taking an opioid as concomitant medication, or an NSAID as rescue if they are using an NSAID as a concomitant medication. Details of all rescue medication will be recorded daily by the subject in the ePRO system.

Subjects are not to take rescue medication within 24 h of any post-treatment planned study visit.

Rescue medications may include one of the following:

- acetaminophen,
- a single NSAID, or
- Tramadol, up to 200 mg/day

**Table 9-1: Rescue Medication Ladder for Pain Relief**

| Rescue Tier | Rescue Medication | Maximum daily dosage | Recommended Dose for Rescue Pain Relief |
|---|---|---|---|
| 1 | Acetaminophen | 650 mg × 4 = 2.6 gm | 325 mg, 2 tablets PO, QID, PRN |
| 2 | Ibuprofen | 600 mg × 4 = 2400 mg | 600 mg PO, QID, PRN |
| 2 | Naproxen | 500 mg × 2 = 1000 mg | 500 mg PO, BID, PRN |
| 2 | Celecoxib | 200 mg | 100 mg PO, BID, PRN |
| 2 | Meloxicam | 15 mg | 7.5 mg, PO, BID or 15 mg QD, PRN |
| 3 | Tramadol | 200 mg | 25 – 50 mg PO, QID, PRN<br>Caution subjects of possible adverse events of dizziness, nausea, and somnolence. |

BID = twice daily; PO = by mouth (orally); PRN = as needed; QD = once daily; QID = four times daily

### 9.12.2 Prohibited Therapies

The following therapies are prohibited both prior to and during the study:

- Injection of corticosteroids in the index knee from 90 days prior to Screening through study completion.
- Topical medications applied to the index knee for OA pain (including capsaicin, lidocaine, prescription, or OTC medications) from 90 days prior to Screening through study completion.
- Current use of opioids for any condition other than for OA of the index knee (maximum dose of 15 mg of hydrocodone [or equivalent] per day as background medication allowed at entry). Permitted analgesics, taken occasionally for conditions other than index knee OA (not rescue analgesics) should be avoided within 24 h of any post-IP treatment planned study visit, and are to be recorded as concomitant medications.
- Regular use of anticoagulant blood thinners (except low-dose aspirin, Dabigatran 150 mg once daily [qd], Enoxaparin 40 mg qd, Rivaroxaban 10 mg qd, Apixaban 2.5 mg twice daily [bid], or clopidogrel 75 mg qd, which are allowed).
- Use of an investigational medication within 30 days prior to Screening, or 5 PK or PD half-lives (whichever is longer), or scheduled to receive such an agent while participating in the study.
- Physical/occupational/chiropractic therapy for the lower extremities or acupuncture for the lower extremities within 30 days of Screening, or need for such therapy during the course of the study.
- Joint replacement surgery of the index knee at any time (full or partial), or open surgery of the index knee in the past 24 months prior to Screening, or prior arthroscopic surgery of the index knee within 6 months of Screening.
- Surgery, or other invasive procedures, or IA injections (other than the IP) while participating in the study.

The subject should be excluded from study participation if they have taken any medication prior to randomization that would indicate that the subject has a serious or unstable illness, is not in good general health, or has a condition that would contraindicate study participation.

Subjects receiving excluded therapies will be ineligible for study enrollment. If subjects receive excluded therapies after enrollment, continuation in the study will be at the discretion of the sponsor/investigator/medical monitor.

## 9.13. Treatment After End of Study

After the end of the study, each subject will be treated according to standard clinical practice.

# 10. STUDY PROCEDURES

Subjects must provide written informed consent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

For the timing of assessments and procedures throughout the study, refer to the schedule of events (Section 17.1). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the schedule of events for each subject. If a subject misses a study visit for any reason, the visit should be rescheduled as soon as possible.

## 10.1. Study Periods and Visits

### 10.1.1 Pre-Screening and Screening, Day -30 to Day 1

Once the Pre-Screening Visit has been performed, including the knee radiograph, subjects should be scheduled to return to the study center for the Screening Visit as soon as is feasible. The subject must have the Screening Visit performed within 30 days before enrollment into the study. The following procedures will be performed at pre-screening and screening.

#### 10.1.1.1 Pre-Screening Visit

1. Written informed consent
2. Investigator pre-screening assessment of knee for preliminary eligibility using fixed flexion radiographic imaging (both knees)[9,10]
3. Confirmation of OA (K-L grade 2, 3 or 4) of the knee: radiograph K-L grade by central reader is the only assessment used for randomization
4. Height and weight (BMI)
5. History of cancer
6. Knee pain (clinic, NPRS)

#### 10.1.1.2 Screening Visit, Visit 1

1. Confirmation of OA of the index knee: American College of Rheumatology (ACR) diagnostic criteria
2. Inclusion/exclusion criteria
3. Demographics
4. Medical history, current knee OA medications (eg, prescription and nonprescription medications) and treatment history (including all previous pharmacologic, noninvasive or invasive treatments)
5. HADS
6. FSS
7. Knee circumference
8. Abdominal girth
9. Complete physical examination
10. ECG
11. Clinical laboratory testing (fasting for at least 8 hours)

12. Urine drug screen
13. Urine pregnancy test
14. Vital signs
15. Set up subject's account in ePRO to record daily knee pain diary (NPRS)
16. Training and assessment of knowledge on pain ratings, allowable rescue medication, other patient-reported outcomes ratings, and entering data into the ePRO system
17. AEs
18. Concomitant medications and therapies

### 10.1.2 Treatment 1, Day 1, Visit 2

As 2 cases of severe allergic reactions have occurred in the entire CNTX-4975 program, a crash cart and personnel certified in advanced cardiac life support (ACLS) should be immediately available. See Section 11.2.1 for details.

The following procedures will be performed on Day 1:

1. Verify that ePRO compliance meets requirements for randomization
2. Inclusion/exclusion criteria
3. Partial physical examination
4. Clinical laboratory testing
5. Urine drug screen
6. Urine pregnancy test
7. Vital signs (standing and sitting vital signs within approximately 5 minutes before the injection of IP, and sitting-only vital signs within approximately 5, 15, and 30 minutes after injection of IP) and weight
8. Sensory testing at the knee and foot using a 5-point Likert scale
9. Randomization
10. Daily knee pain diary (NPRS) by ePRO
11. Review daily ePRO pain scores (NPRS)
12. Review ePRO compliance with subject; retrain as needed
13. Knee pain, stiffness and physical function at study visits (WOMAC A, B, and C)
14. Joint replacement questionnaire
15. KOOS
16. MOS sleep scale
17. Health status questionnaire (SF-36)
18. Quality of life EQ-5D-5L
19. WPAI questionnaire
20. Injection site assessments (erythema, edema) before injection, and after the injection 1 and 2 hours post-dose IP
21. Subject procedure pain assessments (1) at rest prior to pre-medication; (2) prior to full 15 ml of intra-articular 2% lidocaine (without epinephrine); (3) at rest 10 minutes (± 2 minutes) after full 15 mL intra-articular 2% lidocaine (without epinephrine); (4) at 30 minutes

(± 5 minutes) after intra-articular injection of 2 mL of the IP and (5) at rest at the 1 h and 2 h time points after intra-articular injection of the IP (± 10 minutes)

22. Treatment procedure, including cooling, intra-articular 15 mL 2% lidocaine (without epinephrine), intra-articular IP injection, and post-injection cooling
23. All subjects must be monitored for at least 30 minutes (or longer, as required by the protocol) after study drug injection to ensure that they do not have a hypersensitivity reaction/anaphylaxis
24. AEs
25. Training and assessment of knowledge on rescue medication use and logging of rescue medication into ePRO system
26. Concomitant medications and therapies

### 10.1.3 Double-blind Post-treatment 1 Assessment and Observation Period, Day 3 to Week 18, Visit 3 to Visit 7

#### 10.1.3.1 Day 3, Telephone Visit 3

1. Training and assessment of knowledge, as needed, on pain ratings, allowable rescue medication, all other patient-reported outcomes ratings, and entering data into the ePRO system
2. Remind subject to continue daily entry of ePRO pain scores (NPRS) and rescue medication use (9:00 PM ± 3 hours)
3. Review daily ePRO pain scores (NPRS) and rescue medication use recall
4. Review ePRO compliance with subject; retrain as needed
5. Subject assessment of satisfaction with the treatment procedure
6. Patient Global Impression of Change (PGIC) in the index knee
7. AEs
8. Concomitant medications and therapies

#### 10.1.3.2 Week 4, Visit 4

1. Partial physical examination
2. Vital signs and weight
3. Training and assessment of knowledge, as needed, on pain ratings, allowable rescue medication, all other patient-reported outcomes ratings, and entering data into the ePRO system
4. Injection site assessment (erythema, edema)
5. Daily knee pain diary (NPRS) by ePRO
6. Review daily ePRO pain scores (NPRS) and rescue medication use recall
7. Review ePRO compliance with subject; retrain as needed
8. Knee pain, stiffness and physical function at study visits (WOMAC A, B, and C)
9. PGIC
10. KOOS
11. Assistive device usage

12. AEs
13. Rescue medication use
14. Concomitant medications and therapies

#### 10.1.3.3 Week 8, Visit 5

1. Training and assessment of knowledge, as needed, on pain ratings, allowable rescue medication, all other patient-reported outcomes ratings, and entering data into the ePRO system
2. Daily knee pain diary (NPRS) by ePRO
3. Review daily ePRO pain scores (NPRS) and rescue medication use recall
4. Review ePRO compliance with subject; retrain as needed
5. Knee pain, stiffness and physical function at study visits (WOMAC A, B, and C)
6. PGIC
7. MOS sleep scale
8. Health status questionnaire (SF-36)
9. WPAI questionnaire
10. Assistive device usage
11. AEs
12. Rescue medication use
13. Concomitant medications and therapies

#### 10.1.3.4 Week 12, Visit 6

1. Complete physical examination
2. Clinical laboratory testing
3. Urine drug screen
4. Urine pregnancy test
5. Vital signs and weight
6. Sensory testing at the knee and foot using a 5-point Likert scale
7. Training and assessment of knowledge, as needed, on pain ratings, allowable rescue medication, all other patient-reported outcomes ratings, and entering data into the ePRO system
8. Daily knee pain diary (NPRS) by ePRO
9. Review daily ePRO pain scores (NPRS) and rescue medication use recall
10. Review ePRO compliance with subject; retrain as needed
11. Knee pain, stiffness and physical function at study visits (WOMAC A, B, and C)
12. PGIC
13. Joint replacement questionnaire
14. KOOS
15. EQ-5D-5L
16. Assistive device usage

17. AEs
18. Rescue medication use
19. Concomitant medications and therapies

#### 10.1.3.5 Week 18, Visit 7

1. Vital signs
2. Training and assessment of knowledge, as needed, on pain ratings, allowable rescue medication, all other patient-reported outcomes ratings, and entering data into the ePRO system
3. Daily knee pain diary (NPRS) by ePRO
4. Review daily ePRO pain scores (NPRS) and rescue medication use recall
5. Review ePRO compliance with subject; retrain as needed
6. Knee pain, stiffness and physical function at study visits (WOMAC A, B, and C)
7. PGIC
8. Joint replacement questionnaire
9. KOOS
10. MOS sleep scale
11. SF-36
12. EQ-5D-5L
13. WPAI
14. Assistive device usage
15. AEs
16. Rescue medication use
17. Concomitant medications and therapies

### 10.1.4 Treatment 2, Week 26, Visit 8

As 2 cases of severe allergic reactions have occurred in the entire CNTX-4975 program, a crash cart and personnel certified in advanced cardiac life support (ACLS) should be immediately available. See section 11.2.1 for details.

The following procedures will be performed on Day 1 of Treatment 2:

1. Complete physical examination
2. ECG
3. Clinical laboratory testing
4. Urine drug screen
5. Urine pregnancy test
6. Vital signs (standing and sitting vital signs within approximately 5 minutes before the injection of IP, and sitting-only vital signs within approximately 5, 15, and 30 minutes after injection of IP) and weight
7. Sensory testing at the knee and foot using a 5-point Likert scale

8. Training and assessment of knowledge, as needed, on pain ratings, allowable rescue medication, all other patient-reported outcomes ratings, and entering data into the ePRO system
9. Daily knee pain diary (NPRS) by ePRO
10. Review daily ePRO pain scores (NPRS) and rescue medication use recall
11. Review ePRO compliance with subject; retrain as needed
12. Knee pain, stiffness and physical function at study visits (WOMAC A, B, and C)
13. PGIC
14. Joint replacement questionnaire
15. KOOS
16. MOS sleep scale
17. SF-36
18. EQ-5D-5L
19. WPAI
20. Assistive device usage
21. Injection site assessments (erythema, edema) before injection, and after the injection 1 and 2 hours post-dose IP
22. Subject procedure pain assessments (1) at rest prior to pre-medication; (2) prior to full 15 mL of intra-articular 2% lidocaine (without epinephrine); (3) at rest 10 minutes (± 2 minutes) after full 15 mL of intra-articular 2% lidocaine (without epinephrine); (4) at 30 minutes (± 5 minutes) after intra-articular injection of 2 mL of the IP and (5) at rest at the 1 h and 2 h time points after intra-articular injection of the IP (± 10 minutes)
23. Treatment procedure, including cooling, intra-articular 15 mL 2% lidocaine (without epinephrine), intra-articular IP injection, and post-injection cooling
24. All subjects must be monitored for at least 30 minutes (or longer, as required by the protocol) after study drug injection to ensure that they do not have a hypersensitivity reaction/anaphylaxis
25. AEs
26. Concomitant medications and therapies

### 10.1.5 Double-blind Post-treatment 2 Assessment and Observation Period, Day 3 to Week 46, Visit 9 to Visit 12

#### 10.1.5.1 Day 3, Telephone Visit 9

1. Training and assessment of knowledge, as needed, on pain ratings, allowable rescue medication, all other patient-reported outcomes ratings, and entering data into the ePRO system
2. Daily knee pain diary (NPRS) by ePRO
3. Review daily ePRO pain scores (NPRS) and rescue medication use recall
4. Review ePRO compliance with subject; retrain as needed
5. PGIC in index knee
6. AEs

7. Rescue medication use
8. Concomitant medications and therapies
9. Subject assessment of satisfaction with the treatment procedure

#### 10.1.5.2 Week 30, Visit 10

1. Vital signs
2. Training and assessment of knowledge, as needed, on pain ratings, allowable rescue medication, all other patient-reported outcomes ratings, and entering data into the ePRO system
3. Daily knee pain diary (NPRS) by ePRO
4. Review daily ePRO pain scores (NPRS) and rescue medication use recall
5. Review ePRO compliance with subject; retrain as needed
6. Knee pain, stiffness and physical function at study visits (WOMAC A, B, and C)
7. PGIC
8. Joint replacement questionnaire
9. KOOS
10. Injection site assessment (erythema, edema)
11. Assistive device usage
12. AEs
13. Rescue medication use
14. Concomitant medications and therapies

#### 10.1.5.3 Week 38, Visit 11

1. Partial physical examination and weight
2. Clinical laboratory testing
3. Training and assessment of knowledge, as needed, on pain ratings, allowable rescue medication, all other patient-reported outcomes ratings, and entering data into the ePRO system
4. Daily knee pain diary (NPRS) by ePRO
5. Review daily ePRO pain scores (NPRS) and rescue medication use recall
6. Review ePRO compliance with subject; retrain as needed
7. Knee pain, stiffness and physical function at study visits (WOMAC A, B, and C)
8. PGIC
9. Joint replacement questionnaire
10. MOS sleep scale
11. SF-36
12. EQ-5D-5L
13. WPAI
14. Assistive device usage
15. AEs

16. Rescue medication use
17. Concomitant medications and therapies

#### 10.1.5.4 Week 46, Visit 12

1. Vital signs
2. Training and assessment of knowledge, as needed, on pain ratings, allowable rescue medication, all other patient-reported outcomes ratings, and entering data into the ePRO system
3. Daily knee pain diary (NPRS) by ePRO
4. Review daily ePRO pain scores (NPRS) and rescue medication use recall
5. Review ePRO compliance with subject; retrain as needed
6. Knee pain, stiffness and physical function at study visits (WOMAC A, B, and C)
7. PGIC
8. Joint replacement questionnaire
9. KOOS
10. Assistive device usage
11. AEs
12. Rescue medication use
13. Concomitant medications and therapies

### 10.1.6 Final/Early Termination (ET) Visit, Week 52, Visit 13

1. Fixed flexion radiographic imaging (both knees)[9,10]
2. Abdominal girth
3. Complete physical examination
4. ECG
5. Clinical laboratory testing
6. Urine drug screen
7. Urine pregnancy test
8. Vital signs and weight
9. Sensory testing at the knee and foot using a 5-point Likert scale
10. Daily knee pain diary (NPRS) by ePRO
11. Review daily ePRO pain scores (NPRS) and rescue medication use recall
12. Review ePRO compliance with subject
13. Knee pain, stiffness and physical function at study visits (WOMAC A, B, and C)
14. PGIC
15. Joint replacement questionnaire
16. KOOS
17. MOS sleep scale
18. SF-36
19. EQ-5D-5L

20. WPAI
21. Assistive device usage
22. AEs
23. Rescue medication use
24. Concomitant medications and therapies
25. Subject termination form
26. A question asking subjects which treatment they think they received
27. A question asking if the subject would undergo the procedure again if their knee pain returned

## 10.2. Study Duration

### 10.2.1 Overall Study Schedule

The overall study duration is expected to be 25 months, with 12 months of active enrollment.

The planned sequence and maximum duration of the study periods will be as follows:

1. Pre-Screening Period (after the Pre-Screening Visit has been performed, including the knee radiograph, subjects should be scheduled to return to the study center to have the Screening Visit performed as soon as is feasible)
2. Screening Period: up to 30 days + 3-day window
3. Treatment Period (double-blind, placebo-controlled): first dose at Day 1 (1 day); second dose at Week 26 (1 day)
4. Post-Treatment Double-Blind period: 52 weeks

The maximum treatment duration for each subject is 2 days.

The maximum study duration for each subject is approximately 58 weeks.

## 10.3. Assessments

### 10.3.1 Efficacy

#### 10.3.1.1 Knee Pain, Stiffness and Function: Western Ontario and McMaster Universities Arthritis Index (WOMAC)

The Western Ontario and McMaster Universities developed the WOMAC score in use among patients with knee and/or hip OA. The WOMAC is a validated, multidimensional measure of pain, stiffness, and physical functional disability that is sensitive to the effects of drugs or other intervention. It is available in 5-point Likert, 100 mm Visual Analogue and 11-box Numerical Rating Scale formats. This study will use the 11-box Numerical Pain Rating Scale (NPRS) format (see Appendix A). The NRS uses end points of 0="None" (or "No pain/stiffness/difficulty") and 10="Extreme."

The WOMAC is a self-administered index and contains 24 items asked in relation to the index knee joint. The WOMAC has 3 dimensions: Pain (Section A), Stiffness (Section B), and Physical Function (Section C).

- The pain section includes 5 items about the amount of pain experienced doing various activities (walking, stair climbing, nocturnal, at rest, weight bearing).

- The stiffness section has 2 items: joint stiffness upon wakening and joint stiffness later in the day.
- The function section asks about the degree of difficulty in doing 17 activities due to the reference joint (descending stairs, ascending stairs, rising from sitting position, standing, bending to the floor, walking on a flat surface, getting into or out of a car, going shopping, putting on socks, lying in bed, taking off socks, rising from bed, getting into or out of the bath, sitting, getting onto or off the toilet, heavy domestic duties, and light domestic duties).

#### 10.3.1.2 Patient Global Impression of Change in Knee Pain

Subjects will rate their change in knee pain as compared to Baseline (before IP injection) by completing the PGIC.

The PGIC is a 7-point categorical scale, where the patient rates their change in overall status compared to Baseline as follows: 1 = Very much improved; 2 = Much improved; 3 = Minimally improved; 4 = No change; 5 = Minimally worse; 6 = Much worse; and 7 = Very much worse.

#### 10.3.1.3 Average Walking OA Knee Pain (NPRS)

From the Screening Visit until the Week 52 Visit, subjects will use an ePRO at bedtime (9:00 PM ± 3 hours) to record on a daily basis their average daily OA knee pain score with walking during the previous 24 hours. Average daily OA knee pain with walking will be evaluated using a 0-10 NPRS (0 = "no pain" and 10 = "worst possible pain").

#### 10.3.1.4 Knee Injury and Osteoarthritis Outcome Score (KOOS)

The KOOS was developed as an extension of the WOMAC Osteoarthritis Index with the purpose of evaluating short-term and long-term symptoms and function in subjects with knee injury and OA. The KOOS holds 5 separately scored subscales: Pain, other symptoms, Function in Daily Living (ADL), Function in Sport and Recreation (Sport/Rec), and knee-related Quality of Life (QOL). The KOOS has been validated for several orthopedic interventions such as anterior cruciate ligament reconstruction, meniscectomy, and total knee replacement. In addition, the instrument has been used to evaluate physical therapy, nutritional supplementation, and glucosamine supplementation. The effect size is generally largest for the subscale QOL followed by the subscale Pain. The KOOS is a valid, reliable, and responsive self-administered instrument that can be used for short-term and long-term follow-up of several types of knee injury, including OA.

#### 10.3.1.5 Medical Outcomes Study (MOS) Sleep Scale

Intended to assess the extent of sleep problems, the MOS sleep scale measures 6 dimensions of sleep, including initiation, maintenance (eg, staying asleep), quantity, adequacy, somnolence (eg, drowsiness), and respiratory impairments (eg, shortness of breath, snoring). Disturbed sleep has a major impact on quality of life and is often a common symptom of many other chronic conditions, such as chronic pain and mood disorders.

The reliability and validity of the MOS sleep scale have been evaluated in a number of disease areas, including neuropathic pain, restless leg syndrome, overactive bladder, and rheumatoid arthritis.

Intended for adults 18 years of age and older, the forms are available in a fixed form mode of administration, with a standard 4-week recall period (Appendix A).

#### 10.3.1.6 Quality of Life (EQ-5D-5L)

The EQ-5D-5L is a generic, preference-based patient-reported outcome measure, which measures health-related quality of life.[11] In patients with chronic pain, the construct validity of the EQ-5D-5L differentiates between patient subgroups with different severities of AEs and analgesic efficacy. When anchoring the EQ-5D-5L measures to a disease-specific questionnaire such as the WOMAC, both questionnaires could differentiate between WOMAC severity levels.[12]

- The first part of the EQ-5D-5L asks the subject to grade the degree of problems associated with performing a series of 5 aspects of daily functioning (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) by selecting 1 of 5 descriptive categories: no/none, slight, moderate, severe, or extremely.
- The second part of the EQ-5D-5L asks the subject to answer the question "We would like to know how good or bad your health is TODAY" by marking an X on a 100-cm, graduated scale, where 100 corresponds to "the best health you can imagine" and 0 corresponds to "the worst health you can imagine." The scale is graduated by units, with each 5-unit increment from zero labeled with the corresponding value (ie, 0, 5, 10, 15, etc.). The subject is then asked to record the value for the location of X on the scale.

Quality of life will be assessed using the EQ-5D-5L scale (Appendix A) according to the schedule of events, Table 17-1.

#### 10.3.1.7 Short Form-36 Health Status Questionnaire

The Short Form-36 Health Survey is a 36-item, patient-reported survey of patient health, and is commonly used in health economics as a variable in the quality-adjusted life year calculation to determine the cost-effectiveness of a health treatment. The original SF-36 came out from the MOS.

The SF-36 measures 8 health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Physical functioning covers limitations in daily life due to health problems. The role physical scale measures role limitations due to physical health problems. The bodily pain scale assesses pain frequency and pain interference with usual roles. The general health scale measures individual perceptions of general health. The vitality scale assesses energy levels and fatigue. The social functioning scale measures the extent to which ill health interferes with social activities. The role emotional scale assesses role limitations due to emotional problems, and the mental health scale measures psychological distress (Appendix A).

#### 10.3.1.8 Work Productivity and Activity Impairment Scale (WPAI)

The Work Productivity and Activity Impairment (WPAI) questionnaire is an instrument to measure impairments in both paid work and unpaid work. It measures absenteeism, presenteeism as well as the impairments in unpaid activity because of health problem during the past seven days (Appendix A). The WPAI is a valid questionnaire for assessing impairments in paid work and activities in OA patients and for measuring the relative differences between OA patients with different health status.

#### 10.3.1.9 Assistive Device Usage

The Assistive Device Usage questionnaire is an instrument to measure any changes in the types of devices used to assist with walking during the study period. Subjects who use assistive devices at the start of the study are asked to identify the type of device used. This question is then asked again at specified visits during the study. The frequency of device use is also captured (Often; Seldom; or Not at All).

The choice of devices is as follows:

- Cane
- Crutch
- Walker
- Gait Trainer
- Seated walking scooter
- Wheelchair
- Stairlift
- Other (if other, specify in the space provided)

#### 10.3.1.10 Rescue Medication Use

Subjects may take allowed rescue medication for pain of the index knee as needed, except that they should not use rescue medication within 24 hours of a planned study visit. Permitted rescue medications are listed in Section 9.12.1. Data on the type of rescue medication, and the daily dose, will be reported daily by the subject using the ePRO from Screening through Week 52 or for Early Termination. Additional rescue medication details will be collected at study visits and follow-up telephone calls in the source documents and in the eCRF.

### 10.3.2 Clinical Pharmacology

Not applicable for this study.

### 10.3.3 Safety

Safety will be assessed by injection site assessment (erythema and edema), assessment of procedure pain, AEs, physical examination findings, sensory testing, vital sign measurements, 12-lead ECG, clinical laboratory test results, and the stability of the radiographic knee OA, based on Pre-screening and Week 52 radiographs.

#### 10.3.3.1 Laboratory Safety Assessments

##### 10.3.3.1.1 Laboratory Tests to be Performed

Samples for the following laboratory tests will be collected at the time points specified in the schedule of events (Section 17.1).

| | |
|---|---|
| Hematology | hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count (or estimate), white blood cell count including differential |
| Serum Chemistry | albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea |

| | |
|---|---|
| | nitrogen, creatinine, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, uric acid |
| Coagulation Panel | Prothrombin time, partial thromboplastin time, fibrinogen |
| Urinalysis | pH, specific gravity, occult blood, leukocyte esterase, glucose, protein, ketones |
| Urine Pregnancy Test | for all female subjects |
| Urine Drug Screen | amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and tetrahydrocannabinol |
| Other | HbA1c, serum pregnancy test for female subjects |
| Knee Radiographs | Stability of the radiographic knee OA joint damage, compared to placebo or no treatment, based on Pre-screening and Week 52 radiographs. Scoring will use the OARSI criteria |

Blood and urine samples for hematology, serum chemistry, and urinalysis will be sent to a central laboratory for analyses. Urine drug screens and urine pregnancy tests may be conducted at the study sites. Knee radiographs will be obtained at the sites, and images will be evaluated by a central reader.

#### 10.3.3.1.2 Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all study personnel involved in the collection of blood and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

#### 10.3.3.1.3 Evaluation of Laboratory Values

The normal ranges of values for the laboratory assessments in this study will be provided by the responsible laboratory and submitted to Centrexion Therapeutics Corp. prior to the beginning of the study. They will be regarded as the reference ranges on which decisions will be made.

If a laboratory value is out of the reference range, it is not necessarily clinically relevant. The investigator must evaluate the out-of-range values and record his/her assessment of the clinical relevance in the appropriate eCRF.

All laboratory values which, in the investigator's opinion, show clinically relevant or pathological changes during or after termination of the treatment have to be reported as AEs and followed as described in Section 11.2.6.

All measurements described in this section are recognized standard methods.

#### 10.3.3.2 Clinical Examinations

##### 10.3.3.2.1 Vital Signs

Vital signs measurements will include systolic and diastolic blood pressure, heart rate (HR) and respiratory rate (RR). At each office visit, except on the days of injection, vital signs will be measured after the subject has been standing for approximately 2 minutes, and after the subject has been in a sitting position for approximately 5 minutes. On the days of injection, both standing and sitting vital signs will be measured within approximately 5 minutes before the injection of IP, and sitting-only vital signs will be measured within approximately 5, 15, and 30 minutes after the injection.

Temperature will also be measured at all office visits, except the Pre-Screening Visit.

##### 10.3.3.2.2 Electrocardiogram

A standard 12-lead ECG will be performed at rest, with the subject lying down for approximately 5 minutes before the ECG is obtained. The ECG will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety during the trial. The principal investigator or qualified designee will review, sign, and date each ECG reading, noting whether or not any abnormal results are of clinical significance. The ECG will be repeated if any results are considered to be clinically significant. All ECG recordings will be identified with the subject number, initials, date, and time of the recording.

##### 10.3.3.2.3 Physical Examination

Complete (excluding a genitourinary exam) or partial physical examinations will be conducted according to the schedule of events, Table 17-1. The investigator should also assess periarticular tenderness and pain in the soft tissue of the index knee at each physical exam and record the results on the eCRF. Height will be measured at the Pre-screening Visit. Body weight will be measured at Pre-screening, Day 1 (pre-dose), and Weeks 4, 12, 26, 38, and 52/Early Termination Visit. Knee circumference will be measured at Screening and pre-dose at Week 26, and abdominal girth will be measured at Screening and at the End-of-Study Visit (Week 52).

In addition to periarticular pain (assessed at all visits), the partial physical examination should include vital signs (blood pressure and heart rate) and temperature. The investigator should also listen to the heart and lungs at a minimum and follow up any symptoms with a targeted physical exam, as appropriate.

The principal investigator or his/her appointed designee is primarily responsible for performing the physical examination. Whenever possible, the same individual should perform all physical examinations if feasible.

##### 10.3.3.2.4 Injection Site Assessment

The injection site will be examined and assessed for erythema and edema (separately by an investigator using a categorical scale of none, mild, moderate, or severe) on Treatment Day 1 before injection, after the injection at 1 and 2 hours post-dose, and at the Week 4 study visit. The procedure will be repeated on Treatment Day 2 (Week 26) and Week 30. Significant bruising or other clinically significant injection site reactions (other than erythema or edema) will be recorded as AEs.

#### 10.3.3.2.5 Sensory Testing

Sensory testing will be performed at Baseline and at Weeks 12, 26, and 52/Early Termination Visit. The following sensory tests will be performed bilaterally:

- Position sense at the knee and great toe
- Vibratory sense at the patella (measured via 128 Hz tuning fork)
- Light touch assessed over the patella, popliteal area, and the top of the foot
- Pinprick sensibility tested at the top of the foot and over the patella

Each of the above sensory tests will be graded using the following 5-point Likert scale:

| Finding | Score | Definition |
|---|---|---|
| Normal | 4 | Normal sensory function, sensory response as expected in a normal subject |
| Mild Deficit | 3 | Defined as a possible, inconsistent deficit |
| Moderate Deficit | 2 | Defined as a clear, consistent deficit |
| Severe Deficit | 1 | Defined as a major impairment |
| Absent Sensation | 0 | Defined as a complete loss of sensation |

The use of the 5-point Likert scale (0-4) will be based on the clinician's assessment.

### 10.3.3.3 Assessment of Procedure Pain

Procedure pain will be assessed by asking subjects to rate their index knee for pain (1) at rest prior to pre-medication; (2) prior to intra-articular 2% lidocaine (without epinephrine); (3) at rest 10 minutes (± 2 minutes) after intra-articular 2% lidocaine (without epinephrine); (4) at 30 minutes (± 5 minutes) after intra-articular injection of the IP and (5) at rest at the 1 h and 2 h time points after intra-articular injection of the IP (± 10 minutes). Categorical scoring will be used: none, mild, moderate, moderately severe, or severe.

### 10.3.3.4 Assessment of Satisfaction with the Treatment Procedure

Subjects will be asked to rate their overall satisfaction with the treatment procedure using the following 7-point scale at the two telephone visits 3 days after each treatment (TV3 and TV 9).

1 – Completely dissatisfied

2 – Mostly dissatisfied

3 – Somewhat dissatisfied

4 – Neither satisfied or dissatisfied

5 – Somewhat satisfied

6 – Mostly satisfied

7 – Completely satisfied

### 10.3.3.5 Assessment of Stability of Knee Radiographs (index and non-index knees)

Knee radiographs will be taken of each knee at Pre-screening (Baseline) and Week 52 (or early termination) using the fixed flexion method. For the safety assessment, both knees will be assessed for a change from Pre-screening to Week 52 in radiographic classification using the OARSI scoring criteria.

#### 10.3.3.6 Adverse Events

The definitions and management of and special considerations for AEs are provided in Section 11.

# 11. ADVERSE EVENTS

## 11.1. Definitions

### 11.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease, temporally associated with the product, whether or not related to the product.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality of the disease or condition (worsening of a pre-existing condition is considered an AE).

Events occurring in subjects treated with placebo or active comparator or during treatment-free periods of the study are also considered AEs.

### 11.1.2 Adverse Drug Reaction

All noxious and unintended responses to an investigational product related to any dose should be considered adverse drug reactions (ADRs).

The phrase "responses to an investigational product" means that a causal relationship between an investigational product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to an investigational product qualify as ADRs.

All AEs for which the judgment of relationship to IP is "possible" or higher will be considered ADRs. If a relationship to IP is not given, then the AE must be treated as if the relationship to IP were "possible."

### 11.1.3 Unexpected Adverse Event/Adverse Drug Reaction

An expected AE or ADR is one for which the nature or severity is consistent with the known AE profile of the product. For an IP, the known information is contained in the IB. For a marketed product, the known information is contained in the current package insert for the product.

An unexpected adverse event (UAE) or unexpected adverse drug reaction (UADR) is one for which the specificity or severity is not consistent with the current IB. For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected events. Examples would be (a) acute renal failure as an expected adverse reaction with a subsequent new occurrence of interstitial nephritis (interstitial nephritis would be unexpected) and (b) hepatitis with a first occurrence of fulminant hepatitis (fulminant hepatitis would be unexpected).

### 11.1.4 Serious Adverse Events/Drug Reaction

A serious adverse event (SAE) is any untoward medical occurrence that at any dose

- results in death
- is life-threatening
  NOTE: *The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*
- requires inpatient hospitalization or prolongation of existing hospitalization
  NOTE: *Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the test drug, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization, or accommodation problems and without medical background does not need to be considered an SAE.*
- results in persistent or significant disability/incapacity
- is a congenital anomaly
  NOTE: *A congenital anomaly in an infant born to a mother who was exposed to the IP during pregnancy is an SAE. However, a newly diagnosed pregnancy in a subject that has received an IP is not considered an SAE unless it is suspected that the IP(s) interacted with a contraceptive method and led to the pregnancy.*
- is an important medical event
  NOTE: *Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, development of drug dependency, or drug abuse. The occurrence of malignant tumors is also to be considered serious.*

### 11.1.5 Significant Adverse Events

Other significant AEs are defined as marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of IP, dose reduction, or significant additional concomitant therapy.

### 11.1.6 Treatment-Emergent Adverse Events

An AE is defined as treatment emergent if the first onset or worsening is after the first administration of IP.

## 11.2. Management of Adverse Events

Adverse events will be collected from the time of signing the ICF through the Follow-up Visit or Early Termination Visit, whichever occurs first.

### 11.2.1 Adverse Event of Special Interest: Severe Allergic Reaction – Anaphylaxis/ Anaphylactoid Reaction

***Only study sites with crash carts or equivalent and ACLS-certified personnel immediately available are permitted to treat subjects with study drug.***

A case of laryngospasm was observed during a hip replacement operation after capsaicin was instilled into the surgical wound, requiring the subject to be intubated during the procedure.

A case of severe allergic reaction was seen immediately after CNTX-4975-05 was injected into the knee of a subject in study CNTX-4975i-OA-303, with the subject complaining of dyspnea and tachycardia. Epinephrine 0.5 mg and IM solumedrol were given, and the subject recovered in minutes, with no subsequent adverse events.

**Anaphylactic Reaction**

An anaphylactic reaction is a rapid onset serious allergic reaction that has a variety of symptoms and outcomes, which can include death. An anaphylactic reaction typically has symptoms and signs starting over minutes to hours. Anaphylaxis causes more than one of the following: low blood pressure, lightheadedness, shortness of breath, an itchy rash, throat or tongue swelling, and vomiting.

**Anaphylactoid reaction**

These reactions produce the same clinical signs and symptoms anaphylactic reactions, but are not IgE mediated, but instead occur through a direct non-immune-mediated release of mediators from basophils and/or mast cells or can manifest from direct complement activation.

All subjects must be monitored for at least 30 minutes (or longer, as required by the protocol) after study drug injection to ensure that they do not have a hypersensitivity reaction/anaphylaxis. Vital signs (VS) are to be done pre-injection and 5 minutes after the injection, standing and sitting, and then vital signs must now be taken at 15 and 30 minutes (sitting only) after injection of study drug

Any subject that meets the criteria for anaphylaxis or anaphylactoid reactions, as described in the paper by Sampson et al. (2006)[13] (see Appendix C) following the first/prior injection is prohibited from being re-treated with study drug.

**Clinical Criteria for Diagnosing Anaphylaxis**

Anaphylaxis is highly likely when any **<u>one</u> of the following 3 criteria** are fulfilled:

1. **Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula), AND AT LEAST ONE OF THE FOLLOWING**:
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. **Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours)**:
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)

| |
|---|
| b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) |
| c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) |
| d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting) |
| **3. Reduced BP after exposure to known allergen for that patient (minutes to several hours)**: |
| a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP* |
| b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline |
| Source: Sampson et al. (2006) |
| Abbreviations: PEF, Peak expiratory flow; BP, blood pressure. |
| * Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 × age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years. |

In the event of an anaphylactic reaction or anaphylactoid event, institute treatment immediately, as outlined in Appendix C. Note also that a serum tryptase blood level must be obtained using the Vacutainer tube provided.

All anaphylactic and anaphylactoid events (e.g. rash, dyspnea, gastrointestinal symptoms) must be recorded with the time that the events occurred and resolved, and treatments (e.g. epinephrine) should be recorded with their time of administration.

### 11.2.2 Collection

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. At each visit, the subject will be allowed time to spontaneously report any issues since the last visit or evaluation. The investigator will then monitor and/or ask about or evaluate AEs using nonleading questions, such as

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs.

### 11.2.3 Evaluation

#### 11.2.3.1 Severity of Adverse Events

The clinical severity of an AE will be classified as

| | |
|---|---|
| Mild | Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. |
| Moderate | Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject. |

| | |
|---|---|
| Severe | Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. |

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity, whereas an SAE is an AE that meets serious criteria, as described in Section 11.1.4.

#### 11.2.3.2 Seriousness

The investigator is to evaluate whether the AE meets serious criteria, as described in Section 11.1.4.

#### 11.2.3.3 Action(s) Taken

Action(s) taken with regard to IP may consist of the following:

| | |
|---|---|
| Dose increased | An indication that a medication schedule was modified by addition; either by changing the frequency, strength or amount. |
| Dose not changed | An indication that a medication schedule was maintained. |
| Dose reduced | An indication that a medication schedule was modified by subtraction, either by changing the frequency, strength or amount. |
| Drug interrupted | An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication. |
| Drug withdrawn | An indication that a medication schedule was modified through termination of a prescribed regimen of medication. |
| Not applicable | Determination of a value is not relevant in the current context. |
| Unknown | Not known, not observed, not recorded, or refused. |

#### 11.2.3.4 Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Fatal*
- Unknown

*Only select fatal as an outcome when the AE results in death. If more than one AE is possibly related to the subject's death, the outcome of death should be indicated for each such AE. Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

#### 11.2.3.5 Adverse Event Relationship to Investigational Product

The investigator must make an assessment of each AE's relationship to the IP. The categories for classifying the investigator's opinion of the relationship are listed below.

| | |
|---|---|
| Not related | An AE with sufficient evidence to accept that there is no causal relationship to IP administration (eg, no temporal relationship to drug administration, because the drug was administered after onset of event; investigation shows that the drug was not administered; another cause was proven). |
| Unlikely related | An AE, including laboratory test abnormality, with a temporal relationship to IP administration that makes a causal relationship improbable, and in which other drugs, events or underlying disease provide plausible explanations. |
| Possibly related | An AE with a reasonable time sequence to administration of the IP, but which could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear. |
| Related | An AE occurring in a plausible time relationship to IP administration and which cannot be explained by a concurrent disease or other drugs or events. The response to withdrawal of the drug (dechallenge) is clinically reasonable. |

### 11.2.4 Documentation

All AEs occurring within the period of observation for the study must be documented in the CRF with the following information, where appropriate. (The period of observation for the study is described in Section 11.2.)

- AE name or term
- When the AE first occurred (start date and time)
- When the AE stopped (stop date and time or an indication of "ongoing")
- Severity of the AE
- Seriousness (hospitalization, death, etc.)
- Actions taken
- Outcome
- Investigator opinion regarding the AE relationship to the IP(s)

### 11.2.5 Treatment of Adverse Events

Adverse events that occur during the study will be treated, if necessary, by established standards of care. The decision about whether the subject may continue in the study will be made by the sponsor after consultation with the investigator and/or medical monitor.

If AEs occur in a subject that are not tolerable, the investigator must decide whether to stop the subject's involvement in the study and/or treat the subject. Special procedures may be recommended for the specific IP, such as the collection of a serum sample for determining blood concentrations of IP, specific tapering procedures, or treatment regimens, as appropriate.

For double-blinded studies, it is not necessary to unblind a subject's treatment assignment in most circumstances, even if an SAE has occurred. In the case of CNTX-497505, systemic exposure is complete in less than 24 hours after injection. If unblinding is necessary, see Section 9.6 for a description of the unblinding procedures.

### 11.2.6 Follow-up

Any AE will be followed to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause(s) (ie, concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. Potentially related AEs that are ongoing at the Week 52 clinic visit will be followed until they are stable, resolved, or no longer clinically significant, in the opinion of the investigator, or until 4 weeks after the study is completed. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the eCRF page.

### 11.2.7 Notification

#### 11.2.7.1 Serious Adverse Events

The investigator or designee must report all SAEs promptly to [redacted] within 24 hours of first becoming aware of the event, and sending the SAE form to [redacted] by one of the following methods:

[redacted]

The written report should be submitted on the SAE form provided for this purpose. At the time of first notification, the investigator or designee should provide the following information, if available:

- Protocol number
- Reporter (study site and investigator)
- Suspect IP
- Subject's study number
- Subject's year of birth
- Subject's sex
- Date of first dose of IP(s)
- Date of last dose of IP(s), if applicable
- Adverse event term
- Date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria(on) that were met
- Concomitant medication at onset of the event
- Relevant medical history information

- Relevant laboratory test findings
- Investigator's opinion of the relationship to IP(s). ("Is there a reasonable possibility that the IP caused the SAE? Yes or No?")
- Whether and when the investigator was unblinded as to the subject's treatment assignment

Within 24 hours of the initial notification, the investigator must provide a written SAE Report Form that describes the SAE to [redacted], who will forward a de-identified copy of the information to [redacted]

Any missing or additional relevant information concerning the SAE should be provided to the recipient(s) of the initial information as soon as possible on a follow-up SAE Report Form, together with the following information (adverse event, date of occurrence, patient ID, study ID, IP, and site number); this will allow the follow-up information to be linked to the initial SAE report. Ensure that any additional information requested about the event (e.g., hospital reports, autopsy reports) is provided to the designated individual(s) as soon as it is available.

Specific information may be requested by the [redacted] Department using a follow-up request form.

The investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of his/her health authorities, IRB, principal and coordinating investigators, study investigators, and institutions. The detailed reporting duties and division of responsibilities between the sponsor and [redacted] will be provided in a separate document (see CNTX-4975i-OA-304 Safety Management Plan). The study monitor may be able to assist with this.

#### 11.2.7.2 Adverse Drug Reactions

See Safety Management Plan.

#### 11.2.7.3 Non-Serious Adverse Events

Non-serious AEs will be recorded in the eCRF and reported by Premier Research to Centrexion Therapeutics Corp.

### 11.3. Special Considerations

#### 11.3.1 Pregnancy

All women of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation. Women should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted prior to administration of IP on every woman of childbearing potential. A woman who is found to be pregnant at the Screening Visit will be excluded from the study and considered to be a Screening failure.

A woman who becomes pregnant within 2 days of treatment with the IP will be immediately discontinued from study participation. The investigator must report the pregnancy as if it were an SAE within 24 hours of learning of the pregnancy, to Premier Research Pharmacovigilance using

the Pregnancy Data Collection Form via the same fax number and/or email address as for SAE reporting. The investigator should contact the designated individual(s) who receive SAE notification and record information related to the pregnancy on an SAE and AE form (entering the event temporarily as non-serious on both forms) provided by the sponsor or its designee.

Early Termination Visit assessments are required as soon as possible after learning of the pregnancy. The investigator is also responsible for following the pregnancy until delivery or termination. These findings must be reported on the SAE and AE form and forwarded to the designated individual(s). The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.

### 11.3.2 Overdose

The maximal dose of IP should not be exceeded during the study.

Overdose that occurs during the study will be treated and documented as an AE/UAE/SAE if it fulfills the criteria. If the overdose does not result in an AE, it should be reported in written form to the designated individual(s) who receive SAE notification. The information contained therein should include study site identification, reporter identification, subject identification, IP, dose, action taken, and any comments.

## 12. DATA SAFETY MONITORING BOARD

A Data Safety Monitoring Board (DSMB) will not be used in this study.

# 13. STATISTICS

The statistical analysis was developed to meet the requirements of the United States FDA and the EMA.

## 13.1. Study Endpoints

### 13.1.1 Primary Efficacy Endpoints

The primary efficacy endpoint of this study, comparing results in subjects treated with [redacted] of CNTX-4975-05 or placebo, is as follows:

- Change from study baseline to Week 12 in the average pain in the index knee, using the WOMAC A (pain) subscale.

### 13.1.2 Key Secondary Efficacy Endpoints:

The key secondary efficacy endpoints of this study, comparing results in subjects treated with [redacted] of CNTX-4975-05 or placebo, are as follows:

- *First Key Secondary:* Change from study baseline to Week 38 in the average pain in the index knee, using the WOMAC A (pain) subscale.
- *Second Key Secondary*: Change from study baseline to Week 12 in the average function in the index knee, using the WOMAC C (function) subscale.

### 13.1.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study, comparing results in subjects treated with [redacted] of CNTX-4975-05 or placebo, include the following:

- PGIC responders (scores of Very Much Improved or Much Improved) for the index knee at Week 12.
- Area under the curve (AUC) calculated based on the change from study baseline through Week 12 (Day 84) (i.e., Standardized $AUC_{Daily\text{-}Wk12}$) in the average pain with walking in the index knee over the previous 24 hours, using the NPRS (0-10)
- Change from study baseline (mean of most recent non-missing 8 out of 14 days, from Day -14 through Day -1) to Week 12 (mean of Day 78 through Day 84) in the average pain with walking in the index knee over the previous 24 hours, using the NPRS (0-10).
- AUC calculated on change from study baseline through Week 26 (Day 182) (i.e., Standardized $AUC_{Daily\text{-}wk26}$) in the average pain with walking in the index knee over the previous 24 hours, using the NPRS (0-10).
- Change from study baseline to Week 26 in the average pain in the index knee, using the WOMAC A (pain) subscale.
- Change from study baseline to Week 26 in the average function in the index knee, using the WOMAC C (function) subscale.
- Change from study baseline to Week 26 in the average pain in the index knee with walking over the previous 24 hours, using the NPRS (0-10).

- PGIC responders (scores of Very Much Improved or Much Improved) for the index knee at Week 26.

### 13.1.4 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints of this study, comparing results in subjects treated with [redacted] of CNTX-4975-05 or placebo, include the following:

- Change from study baseline to each study visit through Week 52 in the average pain in the index knee, using the WOMAC A (pain) subscale.
- Change from study baseline to each study visit through Week 52 in the average stiffness in the index knee, using the WOMAC B (stiffness) subscale.
- Change from study baseline to each study visit through Week 52 in the average function in the index knee, using the WOMAC C (function) subscale.
- Change from study baseline to each study week through Week 52 in the average pain with walking in the index knee over the previous 24 hours, using the NPRS (0-10).
- AUC calculated on change from study baseline through Week 38 (Day 266) (i.e., Standardized $AUC_{Daily\text{-}Wk38}$) and Week 52 (Day 364) (i.e., Standardized $AUC_{Daily\text{-}Wk52}$) in the average pain with walking in the index knee over the previous 24 hours, using the NPRS (0-10).
- Total daily, standardized weekly, total weekly, rescue-adjusted total daily, and rescue-adjusted total daily AUC calculated on change from study baseline through Weeks 12, 26, 38, and 52 in the average pain with walking in the index knee over the previous 24 hours, using the NPRS (0-10).
- PGIC for the index knee for each study visit through Week 52.
- Change from study baseline to each study visit through Week 52 in the quality of life (QOL), as measured by the SF-36 Health Survey.
- Change from study baseline to each study visit through Week 52 in QOL, as measured by the five-level version of the EQ-5D-5L.
- Durability of efficacy of a first (up to Week 26) and a repeat IA injection (up to Week 52), as measured by the time from Day 1 (study baseline) to the return of study baseline (NPRS pain with walking) pain.
- Cumulative responder analysis for all subjects at each study visit, based on WOMAC A (pain), WOMAC B (stiffness), and WOMAC C (function) scores. Responders at each study visit (WOMAC) / study week (NPRS) will be defined using 1) percent change from study baseline, 2) the absolute change from study baseline, and 3) the observed value.
- Frequency of use of rescue and background analgesic medication for the index knee pain throughout the study period.
- OMERACT-OARSI criteria responders at each study visit through Week 52 (based on study baseline).

- Change from study baseline to each study visit through Week 52 in quality of sleep, as measured by the MOS sleep scale.
- Change from study baseline to each study visit through Week 52 in KOOS.
- Change from study baseline to each study visit through Week 52 in weight and body mass index (BMI).
- Change from study baseline to Week 52 in abdominal girth and HbA1c.
- Likelihood of subject need for joint replacement surgery, based on pain, function, and other patient-reported outcomes, from study baseline to each study visit through Week 52.
- Change from study baseline to each study visit through Week 52 in WPAI:OA results.
- To explore the effect of K-L grade, sex, BMI, and age on the analgesic efficacy of CNTX-4975-05, measured by WOMAC A (pain) scale, WOMAC C (function) scale, and average weekly pain with walking NPRS (0-10) score, through Week 52. Additionally, subjects with radiographic evidence of OA in the non-index (opposite) knee (K-L=2, 3, or 4) vs subjects with no radiographic evidence of OA in the non-index knee (K-L=0 or 1) will be analyzed.
- Subject's guess as to which treatment they think they received.
- Shift from study baseline to each study visit through Week 52 in worst case assistive device usage.
- Subject satisfaction with treatment procedure.

### 13.1.5 Supportive Efficacy Endpoints

Supportive efficacy endpoints for the repeat injection, comparing results in subjects treated with [redacted] of CNTX-4975-05 or placebo, include the following:

- Change from Week 26 baseline to each study visit through Week 52 in the average pain in the index knee, using the WOMAC A (pain) subscale.
- Change from Week 26 baseline to each study visit through Week 52 in the average stiffness in the index knee, using the WOMAC B (stiffness) subscale.
- Change from Week 26 baseline to each study visit through Week 52 in the average function in the index knee, using the WOMAC C (function) subscale.
- Change from Week 26 baseline to each study week through Week 52 in the average pain with walking in the index knee over the previous 24 hours, using the NPRS (0-10).
- AUC calculated based on the change from Week 26 baseline through Week 38 and through Week 52 (i.e., Standardized $AUC_{Daily\text{-}Wk26Wk38}$ and Standardized $AUC_{Daily\text{-}Wk26Wk52}$) in the average pain with walking in the index knee over the previous 24 hours, using the NPRS) (0-10).
- Total daily, standardized weekly, total weekly, rescue-adjusted total daily, and rescue-adjusted total daily AUC calculated on change from Week 26 baseline through Weeks 38

and 52 in the average pain with walking in the index knee over the previous 24 hours, using the NPRS (0-10).

- Change from Week 26 baseline to each study visit through Week 52 in the QOL, as measured by the SF-36 Health Survey.
- Change from Week 26 baseline to each study visit through Week 52 in QOL, as measured by EQ-5D-5L.
- OMERACT-OARSI criteria responders at each study visit through Week 52 (based on Week 26 baseline).
- Change from Week 26 baseline to each study visit through Week 52 in quality of sleep, as measured by the MOS sleep scale.
- Change from Week 26 baseline to each study visit through Week 52 in KOOS.
- Change from Week 26 baseline to each study visit through Week 52 in weight and BMI.
- Change from Week 26 baseline to each study visit through Week 52 on the WPAI:OA.

### 13.1.6 Safety Endpoints

Safety endpoints in subjects treated with 1.0 mg of CNTX-4975-05 or placebo, include the following:

- AEs
- Vital signs
- Clinical laboratory evaluations (hematology, chemistry, and urinalysis)
- 12-lead ECG
- Physical examination (including the presence or absence of an effusion in the index knee, periarticular pain/tenderness)
- Sensory testing using a 5-point Likert scale
- Concomitant medications and therapies (including background medications)
- Degree of procedure pain in the index knee on Day 1 and Week 26 (not recorded as AEs)
- Local physical findings after injection of the index knee
- Injection site assessment of erythema and edema
- Stability of knee radiographs from Pre-screening to Week 52, evaluated using OARSI scoring criteria

## 13.2. Sample Size Determination

Approximately 325 subjects will be randomized to placebo (approximately 125 subjects) and to CNTX-4975-05 (approximately 200 subjects).

In the previous versions of the protocol (Versions 1.0 and 2.0), the primary endpoint was average weekly pain with walking NPRS (0-10) to Week 12. The sample size and power calculations were based upon that endpoint.

Results from study CNTX-4975-OA-502 provided a standard deviation (SD) of 2.55 and mean changes from baseline of -3.02 and -4.42 for placebo and [redacted] of CNTX-4975, respectively. Assuming an effect size of 0.5, a sample size of 293 evaluable subjects at Week 12 with a 2:3 allocation (placebo to active) will achieve 98% statistical power for having a significant CNTX-4975-05 and placebo comparison, using a two-sided test at the 5% significance level. A power of 98% was used for the primary analysis at Week 12 in order to maintain adequate power for comparisons at later time points on the primary outcome and key secondary outcome measures. Previously key secondary outcomes, WOMAC B (stiffness) and WOMAC C (function), are powered at 75% and 71%, respectively, at Week 12 (the primary endpoint) using an N of 293 for the trial. To account for dropouts and subjects for safety evaluation, the initial planned enrollment is approximately 325 subjects (approximately 125 subjects in placebo and 200 subjects in CNTX-4975-05).

In this version of the protocol (Version 3.0), the primary endpoint is the change from study baseline to Week 12 in WOMAC A (pain). In order to determine the approximate power for this primary endpoint, a post hoc analysis for change from baseline to Week 12 in WOMAC A (pain) from Centrexion's Phase 3 study in knee OA, CNTX 4975i-OA-301, was performed. The mean changes from baseline to Week 12 were -13.43 and -16.44 for placebo and [redacted] CNTX-4975-05, respectively, with a pooled SD of the population of 11.7794. With a calculated effect size of 0.256, a statistical power of 56% is predicted to detect a significant CNTX-4975-05 and placebo comparison, using a 2-sided test at the 5% significance level.

### 13.3. Analysis Populations

The following analysis populations are planned for this study: The following analysis populations are planned for this study:

- Safety: all subjects who receive any amount of planned IP.
- Safety (Single Injection Received) Population: all subjects who receive only 1 IP injection but continue in the study past Week 26.
- Week 26 Safety Population: all subjects who receive any amount of IP from a repeat IP injection at the Week 26 visit.
- Intent-to-Treat (ITT): all randomized subjects who receive any amount of IP. Additional subgroups of the ITT may be specified according to K-L grades, BMI values, sex, and other subgroups as indicated.
- Week 26 Intent-to-Treat Population; all randomized subjects who receive the repeat IP injection at the Week 26 visit.
- Per Protocol for Week 12: all subjects in the ITT population who receive IP and do not have any critical protocol violations as determined prior to database lock. Critical violations will include general critical violations (e.g., prohibited medication that could affect the primary endpoint outcomes) or critical violations specifically related to the Week 12 WOMAC A (pain) or C (function) primary endpoints.
- Per Protocol for Week 38: all subjects in the Week 26 ITT population who receive a repeat IP injection and do not have any critical protocol violations as determined prior to

database lock. Critical violations will include general critical violations (e.g., prohibited medication that could affect the primary endpoint outcomes) or critical violations specifically related to the Week 38 WOMAC A (pain) primary endpoint.

Membership in the analysis populations will be determined prior to database lock.

If a subject is randomized incorrectly or is administered the incorrect IP, analyses of the ITT and Week 26 ITT populations will be based on the assigned treatment whereas all other analyses will be based on the actual treatment.

## 13.4. Statistical Analyses

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) that describes the details of the analyses to be conducted will be written prior to database lock.

For analyses involving study site, if the number of subjects per site is small, sites may be pooled for analysis, or omitted from statistical models. The final determination will be made prior to database lock.

Summary statistics will be provided for the variables described below. For continuous variables, these statistics will typically include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, these statistics will typically include the number and percentage of subjects in each category.

Study baseline will be defined with respect to the first injection; Week 26 baseline will be defined with respect to the repeat injection. Study baseline is the primary baseline definition used in analyses, whereas Week 26 baseline is supportive. More details will be provided in the SAP.

### 13.4.1 Study Subjects and Demographics

#### 13.4.1.1 Disposition and Withdrawals

The numbers of subjects randomized, completing, and withdrawing, along with reasons for withdrawal, will be tabulated overall and by treatment group. The number of subjects in each analysis population will be reported.

#### 13.4.1.2 Protocol Deviations

Protocol deviations will be identified and classified as minor or major for statistical analysis purposes before unblinding, and will be summarized or listed as appropriate. Critical protocol deviations will be used to exclude subjects from the per protocol populations for Week 12 and/or Week 38 analyses.

#### 13.4.1.3 Demographics and Other Baseline Characteristics

These analyses will be conducted for all analysis populations.

Demographic variables will include age, sex, height, and weight. Information on race and ethnicity will be collected for any eventual analysis of differences in response to the IP[s], in accordance with local regulatory requirements. Baseline subject characteristics will include

medical history, including confirmation of OA diagnosis and time since diagnosis, and physical examination findings.

Prior and concomitant medications will be summarized by treatment group, by the number and percentage of subjects taking each medication, classified using World Health Organization Drug Dictionary (WHO-DD) Anatomical Therapeutic Chemical (ATC) classes and preferred terms.

### 13.4.2 Exposure and Compliance

All subjects will receive 1 or 2 IP injections at the study site under the surveillance of appropriate study personnel and, therefore, no compliance will be calculated. Injection procedure details and IP batch or lot number(s) will be recorded in the subject's eCRF/electronic data capture (EDC) system and summarized or listed as appropriate.

### 13.4.3 Efficacy Analyses

Efficacy variables will be summarized and analyzed using the ITT population, unless otherwise specified in the statistical analysis plan (SAP).

The type I error rate of $\alpha = 0.05$ will be maintained for the study by using a fixed-sequence testing strategy for primary, key secondary, and secondary endpoints. If the primary endpoint has $P \leq 0.05$, then the full $\alpha = 0.05$ will be passed to the key secondary endpoints then secondary endpoints for continued fixed-sequence testing in the order listed; testing will stop at the first $P$ value $> 0.05$. The fixed-sequence testing will be based on the order listed in the primary, key secondary, and secondary endpoints, in order to meet regulatory requirements.

Sites will be pooled for statistical analysis as follows: sites should have a minimum of 20 randomized subjects. The smallest sites will be grouped sequentially in order of smallest to largest, until each pooled site has a minimum of 20 subjects. If a site had 2 site numbers due to additional randomization numbers required (if needed), those site numbers will be considered as 1 site before pooling.

#### 13.4.3.1 Primary Efficacy Endpoint Analysis

The primary endpoint efficacy analysis, the change from study baseline to Week 12 in WOMAC A (pain) scores, will be based on the ITT population.

A mixed model for repeated measures (MMRM) analysis will be performed that includes change from study baseline in WOMAC A (pain) scores as the dependent variable and terms for treatment, pooled site, baseline K-L grade category, study baseline BMI category, study baseline OA type, sex, study week, treatment by visit study week interaction, and study baseline WOMAC A (pain) score as a covariate, using an unstructured covariance structure. Least squares estimates of the treatment differences at Week 12, along with 95% confidence intervals, will be derived from this model and reported. More details will be provided in the SAP on how to handle potential convergence issues.

Sensitivity analyses of the primary endpoints will be performed on other populations, as specified in the SAP. Further sensitivity analyses on the primary endpoints to explore the impact of missing data will be performed and will be described in a detailed SAP. Descriptive summaries (such as mean, standard error, median, minimum, and maximum) will also be

provided for the primary endpoint. Results from the MMRM primary analyses will be used to determine study success based on the fixed-sequence approach.

#### 13.4.3.2 Key Secondary Efficacy Endpoints Analyses

The key endpoint efficacy analyses, change from study baseline to Week 38 in WOMAC A (pain) scores and change from study baseline to Week 12 in WOMAC C (function) scores, will be based on the ITT population.

The key secondary efficacy endpoints will be analyzed in a manner similar to change from study baseline to Week 12 in WOMAC A (pain) scores.

Sensitivity analyses of the primary endpoints will be performed on other populations, as specified in the SAP. Further sensitivity analyses on the primary endpoints to explore the impact of missing data will be performed and will be described in a detailed SAP. Descriptive summaries (such as mean, standard error, median, minimum, and maximum) will also be provided for the primary endpoint. Results from the MMRM primary analyses will be used to determine study success based on the fixed-sequence approach.

#### 13.4.3.3 Secondary Efficacy Endpoints Analyses

The PGIC will be summarized descriptively using frequencies and percentages by study week and treatment group. A responder analysis will be performed for each visit for the PGIC in which responders (PGIC of Very Much Improved or Much Improved) will be compared to non-responders. The responder analysis will be presented for all study visits; however, only results at Week 12 and Week 26 will be included in the fixed-sequence testing strategy.

Analysis of the change from study baseline to each study week in the average pain with walking in the index knee over the previous 24 hours (average weekly pain with walking NPRS [0-10]), will come from the MMRM used for the primary analysis and will be derived using contrast statements within that model. The MMRM analysis will be presented showing all study weeks; however, only results at Week 12 and Week 26 will be included in the fixed-sequence testing strategy. This analysis will be based on a worst observation carried forward (WOCF) approach that will replace scores occurring on a day where rescue medication was taken with the worst observation starting at Day 2. Details will be specified in the SAP. Area under the curve (AUC) as calculated on change from study baseline through Week 12 (Day 84) and through Week 26 (Day 182) in the average pain in the index knee with walking over the previous 24 hours, using the NPRS (0-10), in subjects treated with [redacted] of CNTX-4975-05, compared with placebo, will be analyzed using an analysis of covariance (ANCOVA) model with terms for pooled site, baseline K-L grade category, study baseline BMI category, sex, treatment, and study baseline daily pain with walking NPRS (0-10) score as a covariate, based on the ITT population.

Change from study baseline to Week 26 in WOMAC A (pain) and C (function) scores will be analyzed using an MMRM with the same terms as that described for the primary analysis.

All secondary efficacy analyses will be performed using the ITT population, unless otherwise specified. Sensitivity analyses of secondary efficacy endpoints will be specified in the SAP if required.

#### 13.4.3.4 Exploratory Efficacy Analyses

All continuous exploratory efficacy endpoints will be summarized using descriptive statistics by treatment group and week/visit, as appropriate, and analyzed using an MMRM analysis or by ANCOVA, as appropriate. Categorical endpoints (responder analyses) will be compared between treatments using Pearson's chi-square or Fisher's exact test, as appropriate; other categorical endpoints (including shift from study baseline) will be summarized descriptively using frequencies and percentages. *P* values from supportive efficacy endpoints will be considered nominal and no adjustments for multiplicity will be made.

#### 13.4.3.5 Supportive Efficacy Analyses

Unless otherwise specified in the SAP, all supportive efficacy analyses for the repeat injection will be based on the Week 26 baseline, to assess the effect of the repeat injection on efficacy. All continuous exploratory efficacy endpoints will be summarized using descriptive statistics by treatment group and week/visit, as appropriate, and analyzed using an MMRM analysis or by ANCOVA, as appropriate. Categorical endpoints (responder analyses) will be compared between treatments using Pearson's chi-square or Fisher's exact test, as appropriate; other categorical endpoints (including shift from Week 26 baseline) will be summarized descriptively using frequencies and percentages. *P* values from exploratory efficacy endpoints will be considered nominal and no adjustments for multiplicity will be made.

### 13.4.4 Safety and Tolerability Analyses

Safety analyses will be conducted using data from the safety population (as defined in Section 13.3). Safety variables include injection site assessment (erythema and edema), assessment of procedure pain, AEs, physical examination findings, sensory testing, vital sign measurements, 12-lead ECG findings, clinical laboratory test results, and stability of knee radiographs over time. No formal inferential analyses will be conducted for safety variables unless otherwise noted.

#### 13.4.4.1 Adverse Events

All AEs will be coded using MedDRA, Version 20.0.

Treatment-emergent AEs are defined as:

- AEs with onset at the time of or following the start of treatment with IP through the Follow-up Visit or Early Termination Visit, whichever occurs first

The number and percentage of subjects with AEs will be displayed for each treatment group by system organ class (SOC) and preferred term (PT). Summaries of AEs by severity and relationship to IP will also be provided. Serious adverse events and AEs resulting in discontinuation of IP will be summarized separately in a similar manner. Subject listings of AEs, SAEs and AEs causing discontinuation of IP will be produced.

#### 13.4.4.2 Clinical Laboratory Evaluations

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual (absolute) values and changes from Baseline values will be presented for clinical laboratory values for each treatment group at each time point.

The number of subjects with clinical laboratory values categorized as below, within, or above normal ranges, will be tabulated showing change from study baseline and Week 26 baseline (shift tables) for each clinical laboratory analyte by treatment group and by study visit. Pre- and post-treatment values will also be presented with analysis summary of mean changes from study and Week 26 baseline.

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will be reported as AEs.

#### 13.4.4.3 Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from study and Week 26 baseline will be calculated for systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and respiratory rate (RR).

Vital signs will be tabulated showing change from study and Week 26 baseline (shift tables) for each parameter by treatment group and by study visit. Pre- and post-treatment values may also be presented with a summary of mean changes from study and Week 26 baseline.

#### 13.4.4.4 Electrocardiograms

The number and percentage of subjects with normal and abnormal ECG findings will be summarized for each treatment group at each time point. A comparison of QT results will be presented. Summary statistics for study baseline values and at study visits according to the schedule of events will be displayed by treatment group for QT and the QT interval corrected for heart rate (QTc) calculated using Bazett's and Fridericia's QT correction methods. In addition, the number and percent of subjects in each treatment group who experienced a change >30 ms or a change >60 ms will be presented.

Descriptive summaries (mean, SD, median, minimum, and maximum) will be presented for ECG measures of PR interval, QRS interval, QT interval, QTc interval (both correction methods), and HR for each treatment group at each time point.

#### 13.4.4.5 Physical Examination Findings

The number and percentage of subjects with normal and abnormal findings in the complete physical examination will be displayed for each treatment group.

#### 13.4.4.6 Injection Site Assessment

The number and percentage of subjects with erythema and edema findings separately categorized as none, mild, moderate, or severe will be summarized for each treatment group at each time point.

#### 13.4.4.7 Sensory Testing

The number and percentage of subjects with each sensory assessment, categorized from normal to absent, using the 5-point Likert scale, where 0 is absent sensation and 4 is normal sensation (see Section 10.3.3.2.5), will be summarized for each treatment group at each time point.

#### 13.4.4.8 Procedure Pain

The number and percentage of subjects with pain assessments categorized as none, mild, moderate, moderately severe, or severe (0-4) will be summarized by treatment group at each time point.

#### 13.4.4.9 Satisfaction with the Treatment Procedure

The number and percentage of subjects with each satisfaction assessment categorization (1-7) will be summarized for each treatment group at each time point.

#### 13.4.4.10 Knee Radiographs

Assessments of abnormality (normal or abnormal) will be provided by a central reader for subchondral insufficiency, osteonecrosis, attrition, and sclerosis in the medial femoral, lateral femoral, medial tibial, and lateral tibial locations; additionally, an assessment of joint space narrowing (none, mild, moderate, or severe) will be provided for medial and lateral locations. The number and percentage of subjects with each knee radiograph abnormality assessment will be summarized for each treatment group.

### 13.4.5 Interim Analysis

No interim analysis is planned for this study.

# 14. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits, and meticulous data management.

## 14.1. Sponsor and Investigator Responsibilities

### 14.1.1 Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 15). The sponsor reserves the right to withdraw a subject from the study, to terminate participation of a study site at any time (Section 14.7), and/or to discontinue the study (Section 14.6).

Centrexion Therapeutics Corp. agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

### 14.1.2 Investigator Responsibilities

By signing the Investigator's Agreement (Section 17.2), the investigator indicates that he/she has carefully read the protocol, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The investigator also agrees to conduct this study in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities, including the April 1996 International Council for Harmonisation (ICH) Guidance for Industry E6 Good Clinical Practice (GCP), and in agreement with the 2013 version of the Declaration of Helsinki. While delegation of certain aspects of the study to sub investigators and study coordinators is appropriate, the investigator will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The investigator is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (e.g., sub investigators and study coordinators) and their specific study-related duties.

Investigators should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, IPs, and their specific duties within the context of the study. Investigators are responsible for providing Centrexion Therapeutics Corp. with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study may be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

## 14.2. Site Initiation

Study personnel may not screen or enroll subjects into the study until after receiving notification from the sponsor or its designee that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

1. The study site has received the appropriate IRB approval for the protocol and the appropriate ICF.
2. All GCP documents have been submitted to and approved by the sponsor or its designee.
3. The study site has a Clinical Trial Agreement in place.
4. Study site personnel, including the investigator, have participated in a study initiation meeting.

### 14.3. Screen Failures

Subjects who fail inclusion and/or exclusion criteria may be rescreened for the study. Subjects may only be rescreened once 30 days or more after the original Screening Visit. If a subject is eligible to enter the study after having previously failed Screening, the subject will be assigned a new subject identification number.

### 14.4. Study Documents

All documentation and material provided by Centrexion Therapeutics Corp. for this study are to be retained in a secure location and treated as confidential material.

#### 14.4.1 Good Clinical Practice Documents

The GCP documents are listed below:

- Signed original protocol (ie, Investigator's Agreement)
- Curricula vitae of all investigators and sub investigators
- Name and address of the laboratories
- List of laboratory reference ranges, and if available, a quality certificate
- Form Signature Log/Delegation of Study-related Duties
- Any other relevant GCP documents

The GCP documents must be received from the investigator and reviewed and approved by Centrexion Therapeutics Corp. or its designee before the study site can initiate the study and before Centrexion Therapeutics Corp. will authorize shipment of IP to the study site. Copies of the investigator's GCP documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the IP IB, eCRF completion guidelines, copies of regulatory references, copies of IRB correspondence, and IP accountability records should also be retained as part of the investigator's GCP documents. It is the investigator's responsibility to ensure that copies of all required GCP documents are organized, current, and available for inspection.

#### 14.4.2 Case Report Forms

By signing the Investigator's Agreement (Section 17.2), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all subjects who sign an ICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the

specific eCRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the CRF/EDC system according to the completion guidelines provided by the sponsor or its designee.

The eCRFs must be signed by the investigator or a sub investigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

### 14.4.3 Source Documents

Information recorded in the CRF/EDC system should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

Clinical laboratory data required by the protocol will be electronically transferred from the central/local laboratory to the sponsor or its designee. A paper copy of the laboratory results will be provided to the study site and should be retained with each subject's source data.

## 14.5. Data Quality Control

Centrexion Therapeutics Corp. and its designees will perform quality control checks on this clinical study.

### 14.5.1 Monitoring Procedures

Centrexion Therapeutics Corp. and/or its designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRAs) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized Centrexion Therapeutics Corp. personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRA(s) will review

- regulatory documents, directly comparing entries in the CRF/EDC system with the source documents
- consenting procedures
- AE procedures
- storage and accountability of IP and study materials

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRF are described in the study manual. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 17.2), the investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator

agrees to allow Centrexion Therapeutics Corp. or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

### 14.5.2 Data Management

Centrexion Therapeutics Corp. or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and [redacted] standard operating procedures (SOPs). A comprehensive data management plan (DMP) will be developed including a data management overview, description of database contents, annotated CRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the study manual.

### 14.5.3 Quality Assurance/Audit

This study will be subject to audit by Centrexion Therapeutics Corp. or its designee. Audits may be undertaken to check compliance with GCP guidelines, and can include:

- site audits
- Trial Master File audits
- database audits
- document audits (eg, protocol and/or clinical study report [CSR])

Centrexion Therapeutics Corp. or its designee may conduct additional audits on a selection of study sites, requiring access to subject notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify Centrexion Therapeutics Corp. immediately.

## 14.6. Study Termination

The study may be terminated the discretion of Centrexion Therapeutics Corp. at any time and for any reason.

## 14.7. Study Site Closure

At the end of the study, all study sites will be closed. Centrexion Therapeutics Corp. may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines
- Inadequate patient enrollment

### 14.7.1 Record Retention

The investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential until

- At least 2 years after the last marketing authorization for the IP has been approved or the sponsor has discontinued its research with the IP, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the IP

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of her/his intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

## 14.8. Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Centrexion Therapeutics Corp. The protocol amendment must be signed by the investigator and approved by the IRB before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(ies) having jurisdiction over the conduct of the study.

## 14.9. Use of Information and Publication

All information concerning IP, Centrexion Therapeutics Corp.'s operations, patent applications, formulae, manufacturing processes, basic scientific data, and formulation information supplied by Centrexion Therapeutics Corp. or its designee to the investigator and not previously published, is considered confidential and remains the sole property of Centrexion Therapeutics Corp. Case report forms also remain the property of Centrexion Therapeutics Corp. The investigator agrees to use this information for purposes of study execution through finalization and will not use it for other purposes without the written consent of the sponsor.

The information developed in this study will be used by Centrexion Therapeutics Corp. in connection with the continued development of IP and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of Centrexion Therapeutics Corp. Publication or other public presentation of IP data resulting from this study requires prior review and written approval of Centrexion Therapeutics Corp. Abstracts, manuscripts, and presentation materials should be provided to Centrexion Therapeutics Corp. for review and approval at least 30 days prior to the relevant submission deadline. Data from individual study sites must not be published separately.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition or publication by the investigator until Centrexion Therapeutics Corp. has reviewed and commented on such a presentation or manuscript for publication.

# 15. ETHICAL AND LEGAL CONSIDERATIONS

## 15.1. Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry E6 GCP (including archiving of essential study documents), the 2013 version of the Declaration of Helsinki, the applicable regulations of the country(ies) in which the study is conducted, and with the Commission Directives 2001/20/EC and 2005/28/EC.

See Appendix B for regulation and guidelines.

## 15.2. Subject Information and Informed Consent

A properly constituted, valid IRB must review and approve the protocol, the investigator's informed consent document, and related subject information and recruitment materials before the start of the study.

It is the responsibility of the investigator to ensure that written informed consent and/or assent is obtained from the subject before any activity or procedure is undertaken that is not part of routine care.

## 15.3. Approval by Institutional Review Board

For Investigational New Drug (IND) studies, the minimum standards of conduct and requirements for informed consent are defined in the FDA regulations.

A valid IRB must review and approve this protocol before study initiation. Written notification of approval is to be provided by the investigator to the sponsor's monitor before shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature. This written approval must consist of a completed IRB approval form, or written documentation from the IRB containing the same information.

Until written approval by the IRB has been received by the investigator, no subject may undergo any procedure not part of routine care for the patient's condition.

Protocol amendments must also be reviewed and approved by the IRB. Written approval from the IRB, or a designee, must be received by Centrexion Therapeutics Corp. before implementation. This written approval will consist of a completed IRB approval form or written documentation from the IRB containing the same information.

## 15.4. Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

## 16. REFERENCES

1. Mamlin L.A., C.A. Melfi, M.L. Parchman, B. Gutierrez, D.I. Allen, B.P. Katz, R.S. Dittus, D.A. Heck and D.A. Freund (1998). "Management of osteoarthritis of the knee by primary care physicians." Arch Fam Med **7**(6): 563-567.

2. Caborn, D., J. Rush, W. Lanzer, D. Parenti, C. Murray and G. Synvisc 901 Study (2004). "A randomized, single-blind comparison of the efficacy and tolerability of hylan G-F 20 and triamcinolone hexacetonide in patients with osteoarthritis of the knee." J Rheumatol **31**(2): 333-343.

3. Centrexion Therapeutics (2015). Investigational Drug Brochure, CNTX-4975 (PEG 300-capsaicin) for Injection. Baltimore, MD 21202, United States, Centrexion Corporation.

4. Caterina, M.J. and D. Julius (2001). "The vanilloid receptor: a molecular gateway to the pain pathway." Annu Rev Neurosci **24**: 487-517.

5. Brederson, J.D., P.R. Kym and A. Szallasi (2013). "Targeting TRP channels for pain relief." Eur J Pharmacol **716**(1-3): 61-76.

6. Simone, D.A., M. Nolano, T. Johnson, G. Wendelschafer-Crabb and W.R. Kennedy (1998). "Intradermal injection of capsaicin in humans produces degeneration and subsequent reinnervation of epidermal nerve fibers: correlation with sensory function." J Neurosci **18**(21): 8947-8959.

7. Baranidharan, G., S. Das and A. Bhaskar (2013). "A review of the high-concentration capsaicin patch and experience in its use in the management of neuropathic pain." Ther Adv Neurol Disord **6**(5): 287-297.

8. Acorda Therapeutics, I. (2009). QUTENZA® (capsaicin) 8% patch Full Prescribing Information. Ardsley, NY 10502, USA, Acorda Therapeutics, Inc.

9. Altman, R.D. and Gold, G.E (2007). “Atlas of individual radiographic features in osteoarthritis, revised.” Osteoarthritis and Cartilage **15**: A1-A56.

10. Hunter, D.J., Altman, R.D., Cicuttini, F., Crema, M.D., Duryea, J. Eckstein, F., Guermazi, A., et al. (2015). “OARSI Clinical Trials Recommendations: Knee imaging in clinical trials in osteoarthritis.” Osteoarthritis and Cartilage **23**: 698-715.

11. Herdman, M., C. Gudex, A. Lloyd, M. Janssen, P. Kind, D. Parkin, G. Bonsel and X. Badia (2011). "Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L)." Qual Life Res **20**(10): 1727-1736.

12. Obradovic, M., A. Lal and H. Liedgens (2013). "Validity and responsiveness of EuroQol-5 dimension (EQ-5D) versus Short Form-6 dimension (SF-6D) questionnaire in chronic pain." Health Qual Life Outcomes **11**: 110.

13. Sampson H.A., Muñoz-Furlong A., Campbell R.L., et al. (2006). "Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium." J Allergy Clin Immunol **117**(2): 391-397.

14. Evans, S. (2007). "When and how can endpoints be changed after initiation of a randomized clinical trial?" PLoS Clin Trials **2**(4): e18.

15. Altman, R., E. Asch, D. Bloch, G. Bole, D. Borenstein, K. Brandt, et al. (1986). "The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the knee." Arthritis Rheum **29**:1039-1049.

# 17. ATTACHMENTS

## 17.1. Schedule of Events

### Table 17-1: Schedule of Events

| **Study 304 Multi-Injection (D1 & WK26); Screening through Week 52** | **Pre-Screening Visit** | **Screening** | **Treat-ment 1** | **Post-Treatment 1 Assessment and Observation** | | | | | **Treat-ment 2*** | **Post-Treatment 2 Assessment and Observation** | | | | **Final Visit/ ET** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day (D) Week (Wk)** | | **D-30 to D1†** | **D1** | **D3*,4,5** | **WK 4*,5** | **WK 8*,5** | **WK 12*,5** | **WK 18*,5** | **WK 26*,5** | **D3*,4,5** | **WK 30*,5** | **WK 38*,5** | **WK 46*,5** | **WK 52*** |
| **Clinic Visit (V) or Telephone Contact (TV)** | | **V1** | **V2** | **TV3** | **V4** | **V5** | **V6** | **V7** | **V8** | **TV9** | **V10** | **V11** | **V12** | **V13** |
| Informed Consent | X | | | | | | | | | | | | | |
| Fixed flexion radiographic imaging (both knees) | X | | | | | | | | | | | | | X |
| Confirmation of OA (K-L grade 2, 3 and 4) of the Knee (Radiographs) by central reader[1] | X[1] | | | | | | | | | | | | | |
| Confirmation of OA of the index knee: American College of Rheumatology (ACR) diagnostic criteria[1] | | X | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | | X | X | | | | | | | | | | | |
| Height and Weight (BMI)[2] | X | | X | | X | | X | | X | | | X | | X |
| Knee Pain (Clinic, NPRS) | X | | | | | | | | | | | | | |
| History of Cancer | X | | | | | | | | | | | | | |
| Demographics, Medical + OA Medication; Treatment History[3] | | X | | | | | | | | | | | | |
| Hospital Anxiety and Depression Scale (HADS) | | X | | | | | | | | | | | | |
| Fibromyalgia Symptom Scale Score (FSS) | | X | | | | | | | | | | | | |
| Knee Circumference | | X | | | | | | | X | | | | | |

| **Study 304 Multi-Injection (D1 & WK26); Screening through Week 52** | **Pre-Screening Visit** | **Screening** | **Treat-ment 1** | **Post-Treatment 1 Assessment and Observation** | | | | | **Treat-ment 2*** | **Post-Treatment 2 Assessment and Observation** | | | | **Final Visit/ ET** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day (D) Week (Wk)** | | **D-30 to D1†** | **D1** | **D3*,4,5** | **WK 4*,5** | **WK 8*,5** | **WK 12*,5** | **WK 18*,5** | **WK 26*,5** | **D3*,4,5** | **WK 30*,5** | **WK 38*,5** | **WK 46*,5** | **WK 52*** |
| **Clinic Visit (V) or Telephone Contact (TV)** | | **V1** | **V2** | **TV3** | **V4** | **V5** | **V6** | **V7** | **V8** | **TV9** | **V10** | **V11** | **V12** | **V13** |
| Abdominal Girth | | X | | | | | | | | | | | | X |
| Physical Examination[6] | | X | X | | X | | X | | X | | | X | | X |
| Sensory testing (Likert Scale) | | | X | | | | X | | X | | | | | X |
| 12-Lead Electrocardiogram (ECG) | | X | | | | | | | X | | | | | X |
| Clinical Laboratory Testing[7] | | X[8] | X[8] | | | | X | | X | | | X | | X |
| Urine Drug Screen[9] | | X | X | | | | X | | X | | | | | X |
| Urine Pregnancy Test[10] | | X | X | | | | X | | X | | | | | X |
| Vital Signs (standing & sitting) | | X | X[11] | | X | | X | X | X[11] | | X | | X | X |
| Randomization[12] | | | X | | | | | | | | | | | |
| Training/Retraining on Pain Rating and Entering data on ePRO System[13] | | X | X | X | X | X | X | X | X | X | X | X | X | |
| IP Injection (Dosing)[14] (30-minute post-injection observation required) | | | X | | | | | | X | | | | | |
| Injection Site Assessment (erythema, edema)[15] | | | X | | X | | | | X | | X | | | |
| Subject Assessment of Procedure Pain[16] | | | X | | | | | | X | | | | | |
| Subject Assessment of Satisfaction with Treatment Procedure | | | | X | | | | | | X | | | | |
| Daily Knee Pain diary (NPRS) By ePRO[17] | | X | X | X | X | X | X | X | X | X | X | X | X | X |

| **Study 304 Multi-Injection (D1 & WK26); Screening through Week 52** | **Pre-Screening Visit** | **Screening** | **Treat-ment 1** | **Post-Treatment 1 Assessment and Observation** | | | | | **Treat-ment 2*** | **Post-Treatment 2 Assessment and Observation** | | | | **Final Visit/ ET** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day (D) Week (Wk)** | | **D-30 to D1†** | **D1** | **D3*,4,5** | **WK 4*,5** | **WK 8*,5** | **WK 12*,5** | **WK 18*,5** | **WK 26*,5** | **D3*,4,5** | **WK 30*,5** | **WK 38*,5** | **WK 46*,5** | **WK 52*** |
| **Clinic Visit (V) or Telephone Contact (TV)** | | **V1** | **V2** | **TV3** | **V4** | **V5** | **V6** | **V7** | **V8** | **TV9** | **V10** | **V11** | **V12** | **V13** |
| Review Daily ePRO Knee Pain Score (NPRS) and Rescue Medication Use Recall[17] | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Knee Pain, Stiffness and Physical Function at Clinic Visits: (WOMAC A, B, and C)[18] | | | X | | X | X | X | X | X | | X | X | X | X |
| Patient Global Impression of Change (PGIC)[19] | | | | X | X | X | X | X | X | X | X | X | X | X |
| Joint Replacement Questionnaire[19] | | | X | | | | X | X | X | | X | X | X | X |
| Knee Injury and Osteoarthritis Outcome Score (KOOS)[19] | | | X | | X | | X | X | X | | X | | X | X |
| Medical Outcomes Study (MOS) Sleep Scale[19] | | | X | | | X | | X | X | | | X | | X |
| Health Status Questionnaire (SF-36)[19] | | | X | | | X | | X | X | | | X | | X |
| Quality of Life EQ-5D-5L[19] | | | X | | | | X | X | X | | | X | | X |
| Work Productivity and Activity Impairment Questionnaire (WPAI)[19] | | | X | | | X | | X | X | | | X | | X |
| Assistive Device Questionnaire[20] | | X | | | X | X | X | X | X | | X | X | X | X |
| Adverse Events[21] | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Rescue Medication use [22,23] | | | X | X[17] | X | X | X | X | X | X | X | X | X | X |
| Concomitant Medications and Therapies | | X | X | X | X | X | X | X | X | X | X | X | X | X |

| **Study 304 Multi-Injection (D1 & WK26); Screening through Week 52** | **Pre-Screening Visit** | **Screening** | **Treat-ment 1** | **Post-Treatment 1 Assessment and Observation** | | | | | **Treat-ment 2*** | **Post-Treatment 2 Assessment and Observation** | | | | **Final Visit/ ET** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day (D) Week (Wk)** | | **D-30 to D1†** | **D1** | **D3*,4,5** | **WK 4*,5** | **WK 8*,5** | **WK 12*,5** | **WK 18*,5** | **WK 26*,5** | **D3*,4,5** | **WK 30*,5** | **WK 38*,5** | **WK 46*,5** | **WK 52*** |
| **Clinic Visit (V) or Telephone Contact (TV)** | | **V1** | **V2** | **TV3** | **V4** | **V5** | **V6** | **V7** | **V8** | **TV9** | **V10** | **V11** | **V12** | **V13** |
| Subject Termination Form[24] | | | | | | | | | | | | | | X |

Abbreviations: ACR = American College of Rheumatology; D = day; ECG = electrocardiogram; ePRO = electronic patient reported outcome; ET = early termination; FSS = Fibromyalgia Symptom Scale Score; HADS = Hospital Anxiety and Depression Scale; KOOS = knee injury and osteoarthritis outcome score; MOS = medical outcomes study sleep scale; NPRS = numeric pain rating scale; OA = osteoarthritis; PGIC = patient global impression of change; SF-36 = short form 36; TV = telephone visit; V = visit; Wk = week; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; WPAI = Work Productivity and Activity Impairment Questionnaire

† If subjects are unable to complete the Screening assessments due to technical issues, the site is permitted a +3 business day window to complete the assessments (Screening period of 33 days instead of 30 days).

* Dates for assessments will include these allowed windows: ± 1 business day for the Day 3 call, ± 5 business days for the Week 4 visit, and ± 7 business days for all visits after Week 4. Sites where crash carts and ACLS-certified personnel are not immediately available will have a window of ± 21 business days to schedule Week 26 injections. Once crash carts and ACLS-certified personnel are available at these sites, all standard windows apply (± 7 business days).

1. A pre-Screening fixed flexion radiograph of both knees must show evidence of chronic OA with K-L grade of 2, 3 or 4 of the index knee. The radiographs need to be completed and read by the central reader prior to conducting a full Screening visit. If the subject meets K-L grade criteria, schedule the subject to return for a full Screening visit as soon as is feasible. The K-L grade report from the central reader will be the official assessment used to qualify the OA grading of each knee in this trial. In addition to a K-L score of 2, 3 or 4 to enter the study, a subject must also have qualifying knee pain. A final fixed flexion radiograph of both knees will be done at Week 52.
2. Height and weight performed at Pre-Screening; subsequent to Pre-Screening, weight should be measured at all visits noted in the table above.
3. Medical History and Demographics, as outlined in the CRFs. OA medications should note all therapies, including doses and regimen when known, and all should note if the medications were over the counter or prescriptions. Treatments should include noninvasive treatments (eg, Physical Therapy) or previous invasive treatments (eg, arthrotomy, arthroscopy – with procedure, if known)
4. Treatment Day 3 will be by telephone; no clinic visit is required. Study staff will call subjects to assess OA pain, overall satisfaction with the treatment procedure, adverse events, and the use of rescue medication. Subjects will be reminded to complete the ePRO (NPRS and rescue medication use).
5. If a subject is discontinuing the study on or before Week 52, the assessments listed for an Early Termination visit should be completed.
6. A complete physical examination (excluding a genitourinary examination) will be performed by the investigator at the Screening Visit, Week 12, Week 26, and at the final clinic visit (Week 52/Early Termination). A partial physical examination will be performed by the investigator on Day 1 (pre-randomization), Week 4, and Week 38. The physical examinations will also evaluate the soft tissue of the index knee for periarticular painful sites, which will be entered onto the Case Report Form at each visit.
7. Clinical laboratory tests will include chemistry, hematology, and urinalysis. Additional tests, including fibrinogen and prothrombin time/partial thromboplastin time, will be done at Screening only (only labs listed in exclusion criteria #23 are required for eligibility). HgbA1c will be done at Screening and Week 52/Early Termination.

8. Subjects are to fast for at least 8 hours prior to the laboratory sample collections performed at the Screening Visit. On Day 1, laboratory tests will be performed prior to randomization. However, the results of these tests are not required prior to randomization and dosing if the Screening test results were within the acceptable protocol ranges.
9. Urine drug screen test results must be confirmed as negative for drugs of abuse prior to randomization.
10. Subjects will be tested for pregnancy if they are women of childbearing potential. A serum pregnancy test will be performed if the urine pregnancy test is positive. Subjects with positive urine pregnancy test results will not be randomized or will be discontinued from study participation. These subjects will be followed until the pregnancy is completed, and the health of the fetus is known.
11. On Day 1 and Week 26, standing and sitting vital signs to be measured within approximately 5 minutes before the injection of IP, and sitting-only vital signs within approximately 5, 15, and 30 minutes after the injection of IP.
12. Eligible subjects will be randomized to their treatment assignment using the Centrexion Randomization Algorithm after the results of all Screening and applicable pre-dose assessments have been obtained and all inclusion and exclusion criteria have been met. For treatment 2, subjects will be injected per their randomized treatment assignment for treatment 1.
13. From the Screening Visit to Week 52, subjects will use an ePRO system daily to rate their index knee pain at bedtime (9:00 PM ± 3 h) for average pain with walking over the previous 24 h, using the NPRS question. Subjects will also need to record their rescue medication usage in ePRO at the same time. Ensure the subject is set-up in the system, trained, and understands how to enter their NPRS score and their rescue medication usage. In case of technical issues, paper copies of the PROs will be provided for subject completion and filed at the site.
14. The IP injection procedure will be standardized across all clinical sites. It is recommended that the IP injection be administered using ultrasound-guided needle placement, but is not required. If imaging-guided injection is not used, then confirmation of location of the needle within the index knee joint must be verified by aspirating joint fluid. If no joint fluid is aspirated, the IP should not be injected. If there is a substantial effusion within the knee joint, the effusion should be aspirated, when possible, such that the estimated remaining joint fluid in the knee is approximately 5-10 mL. Record the amount of joint fluid aspirated. It is recommended, but at the investigator's discretion, to pre-medicate subjects with an opioid, NSAID, or local analgesic (such as ethyl chloride, topical lidocaine, and/or subcutaneous lidocaine – but a recommended maximum of 2 pre-medications may be used prior to treatment (excluding injection of 15 mL 2% lidocaine [without epinephrine] into the index knee). Local anesthesia of the index knee will be performed with 15 mL IA of 2% lidocaine (without epinephrine) 30 minutes prior to injection of the IP. Adjunct use of controlled joint cooling will be applied approximately 15 minutes prior to intra-articular injection of 2% lidocaine (without epinephrine); controlled cooling will be removed and then 2% lidocaine (without epinephrine) will be administered into the index knee immediately followed by adjunct controlled cooling for 30 minutes. At 30 minutes after 2% lidocaine (without epinephrine) administration, the cooling device will be removed and IP injection will be administered into the index knee. Immediately after IP injection, the index knee joint will be passively flexed and extended 5 times over a 1 minute interval to facilitate distribution of the IP within the index knee. Then controlled cooling will be reapplied immediately following the passive flexion and extension for a minimum of 30 minutes, for up to 1 hour after study medication injection. The cooling may be discontinued after a minimum of 30 minutes, application after IP IA injection, if the subject has a pain level that is acceptable for the subject and investigator (NPRS 0-4 scale: none, mild, moderate, moderately severe and severe). However, an additional 30 minutes of controlled cooling (total 1.5 hours after IP administration) may be used if there continues to be moderate-to-severe pain in the index knee, at the investigator's discretion.
15. The injection site will be examined and assessed for erythema and edema by blinded site personnel (using a categorical scale of none, mild, moderate, moderately severe, or severe [0-4]) on Treatment Day 1 and Treatment Day 2 (Week 26) before the injection, after the injection at 1 and 2 h, and at the Week 4 and Week 30 study visits. Significant bruising or other clinically significant injection site reactions will be recorded as AEs.
16. Procedure pain will be assessed by asking subjects to rate their index knee for pain (1) at rest prior to pre-medication; (2) prior to intra-articular 2% lidocaine (without epinephrine); (3) at rest 10 minutes (± 2 minutes) after intra-articular 2% lidocaine (without epinephrine); (4) at 30 minutes (± 5 minutes) after intra-articular injection of the IP and (5) at rest at the 1 h and 2 h time points after intra-articular injection of the IP (± 10 minutes).
17. From the Screening Visit forward, the ePRO system will be used daily to collect responses from subjects on index knee pain with walking over the previous 24 hours. From the Treatment Visit though Week 52, subjects will also be asked to record into the ePRO device their daily usage of any rescue medications.

Sites should monitor subject compliance of diary entries regularly throughout the 52 weeks. If a subject is not compliant the site should reach out to the subject as soon as noncompliance is observed. In case of technical issues, paper copies of the PROs will be provided for subject completion and filed at the site.

18. Subjects will be asked to complete the WOMAC questionnaire (Parts A, B, and C) on Study Day 1 (Treatment 1) and Week 26 (Treatment 2) prior to receiving pre-medications and at scheduled Study Visits (Weeks 4, 8, 12, 18, 30, 38, 46, and 52).
19. The questionnaires noted in the table above will be collected via an ePRO system at each site visit indicated in the table of assessments.
20. The Assistive Device Usage questionnaire is an instrument to measure any changes in the types of devices used to assist with walking during the study period. Subjects who use assistive devices at the start of the study are asked to identify the type of device used. This question is then asked again at specified visits during the study. The frequency of device use is also captured (Often; Seldom; or Not at All).
21. Collection of AEs will begin from the time of signing the ICF through the Follow-Up Visit or Early Termination Visit, whichever occurs first. On Day 1, the AE assessment must be performed at the pre-dose Baseline. Treatment-emergent AEs will be collected from the time of the injection of IP through the Week 52 Visit. Potentially related AEs that are ongoing at the Week 52 clinic visit will be followed until they are stable, resolved, or no longer clinically significant, in the opinion of the investigator, or until 4 weeks after the study is completed.
22. Subjects may take a single rescue medication for pain of the index knee as needed. These rescue medications may include either acetaminophen/paracetamol, a single NSAID at a time (subjects may switch approved NSAIDs), or tramadol (up to 200 mg daily). Subjects should not take rescue medication within 24 h prior to a clinic visit. Data on the type of rescue medication, and the daily dose of rescue medication, will be collected and will be recorded each day in the ePRO system from Screening up to Week 52 or Early Termination; data on the type of rescue medication, and the daily dose will be reported daily by the subject using ePRO. Additional rescue medication details will be collected at study visits and follow-up telephone calls in the source documents and eCRF.
23. Subjects must stay on their current pain medication as prescribed, or over the counter medication, from the time of Pre-screening through Week 12. The current pain medication must be taken only for pain in the index knee, and not for another pain indication. Their current pain medication must be either one of the allowed rescue medications and dosages, or hydrocodone at a dose up to 15 mg daily (or another opioid equivalent). The rescue medication is not allowed to be in the same drug class as the ongoing medication. For example, subjects will not be allowed to take tramadol as a rescue medication if they are taking an opioid as concomitant medication, or an NSAID as rescue if they are using an NSAID as concomitant medication. Subjects may stay on current pain medication as prescribed or over the counter medication, but this is not required from Week 12 through completion of the study, Week 52.
24. At the final visit, subjects will be asked which treatment they think they received and whether they would undergo the procedure again if their knee pain returned.

## 17.2. Investigator's Agreement

| | |
|---|---|
| PROTOCOL NUMBER: | CNTX-4975i-OA-304 |
| PROTOCOL TITLE: | A Randomized, Double-blind, Placebo-controlled, 2-Injection 52-Week Study to Evaluate the Efficacy and Safety of Intra-articular Injections of CNTX-4975-05 in Subjects with Chronic, Moderate-to-severe Osteoarthritis Knee Pain |
| PROTOCOL DATE: | Version 3.0, 12 October 2020 |

I have read this protocol and agree to conduct this clinical trial as outlined herein. I will ensure that all sub investigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with Centrexion Therapeutics Corp. and [redacted] during the study. I will adhere to all FDA, ICH, and other applicable regulations and guidelines regarding clinical trials on an IP during and after study completion.

Printed Name: _____

Signature: _____

Date: _____

## APPENDICES

A. Study Specific Requirements
B. Regulations and Good Clinical Practice Guidelines
C. Severe Allergic Reaction – Anaphylaxis/ Anaphylactoid Reaction
D. COVID-19 Memo to Study Sites

## A. Study Specific Requirements

Examples of the patient-reported outcome scales that will be used during this study are attached to this appendix. The following is an index:

- American College of Rheumatology (ACR) Diagnostic Criteria
- Hospital Anxiety and Depression Scale (HADS)
- Fibromyalgia Symptom Scale Score (FSS)
- WOMAC Osteoarthritis Index Version NRS3.1
- KOOS Knee Survey
- SF-36 Health Survey
- MOS Sleep Scale
- EQ-5D-5L Health Status Questionnaire
- Joint Replacement Questionnaire
- Patient Global Impression of Change Assessment (PGIC)
- Work Productivity and Activity Impairment Questionnaire (WPAI: SHP)

## B. Regulations and Good Clinical Practice Guidelines

### 1. Regulations

Refer to the following United States Code of Federal Regulations (CFR):

B. FDA Regulations 21 CFR, Parts 50.20 – 50.27
Subpart B – Informed Consent of Human Subjects

C. FDA Regulations 21 CFR, Parts 56.107 – 56.115
Part 56 – Institutional Review Boards
Subpart B – Organization and Personnel
Subpart C – IRB Functions and Operations
Subpart D – Records and Reports

D. FDA Regulations 21 CFR, Parts 312.50 – 312.70
Subpart D – Responsibilities of Sponsors and Investigators

### 1. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URL:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf

## C. Severe Allergic Reaction – Anaphylaxis/ Anaphylactoid Reaction

- [redacted]
- Sampson et al. (2006)

[redacted]

[redacted]

# American College of Rheumatology (ACR) Diagnostic Criteria Idiopathic OA of the Knee

| Clinical and laboratory | Clinical and radiographic | Clinical |
|---|---|---|
| Knee pain | Knee pain | Knee pain |
| + at least 5 of 9: | + at least 1 of 3: | + at least 3 of 6: |
| - Age > 50 years | - Age > 50 years | - Age > 50 years |
| - Stiffness < 30 minutes | - Stiffness < 30 minutes | - Stiffness < 30 minutes |
| - Crepitus | - Crepitus | - Crepitus |
| - Bony Tenderness | + Osteophytes | - Bony Tenderness |
| - Bony enlargement | | - Bony enlargement |
| - No palpable warmth | | - No palpable warmth |
| - ESR <40 mm/hour | | |

| Clinical and laboratory | Clinical and radiographic | Clinical † |
|---|---|---|
| - RF <1:40<br><br>- SF OA | | |
| 92% sensitive | 91% sensitive | 95% sensitive |
| 75% specific | 86% specific | 69% specific |

* ESR = erythrocyte sedimentation rate (Westergren); RF = rheumatoid factor; SF OA = synovial fluid signs of OA (clear, viscous, or white blood cell count <2,000/$mm^3$).

† Alternative for the clinical category would be 4 of 6, which is 84% sensitive and 89% specific.

*R. Altman, E. Asch, D. Bloch, G. Bole, D. Borenstein, K. Brandt, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039--1049.*

# Centrexion Therapeutics Protocol CNTX-4975i-OA-304
# Hospital Anxiety & Depression Scale

Subject No: ____ ____ ____ ____ Subject Initials: ____ ____ ____

*Date of Completion:* *Day* ☐☐ *Month* ☐☐☐ *Year* ☐☐☐☐

*Please sign your initials upon completing the questionnaire on the back page*

# Hospital Anxiety and Depression Scale (HADS)

GL Assessment

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings, he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **check the box** which comes closest to how you have been feeling in the past week.

Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long, thought-out response.

---

**I feel tense or "wound up"**
- ☐ Most of the time
- ☐ A lot of the time
- ☐ From time to time, occasionally
- ☐ Never

**I enjoy the things I used to enjoy**
- ☐ Definitely
- ☐ Not quite so much
- ☐ Only a little
- ☐ Hardly at all

**I get a sort of frightened feeling as if something awful is about to happen**
- ☐ Very definitely and fairly badly
- ☐ Yes, but not too badly
- ☐ Sometimes, but it doesn't worry me
- ☐ Never

**I can laugh and see the funny side of things**
- ☐ As much as I always could
- ☐ Not quite so much now
- ☐ Definitely not so much now
- ☐ Never

**Worrying thoughts go through my mind**
- ☐ A great deal of the time
- ☐ A lot of the time
- ☐ Not too often
- ☐ Almost never

**I feel cheerful**
- ☐ Never
- ☐ Not often
- ☐ Sometimes
- ☐ Most of the time

**I can sit at ease and feel relaxed**
- ☐ Always
- ☐ Usually
- ☐ Not often
- ☐ Never

**I feel as if I am slowed down**
- Nearly all the time ☐
- Very often ☐
- Sometimes ☐
- Never ☐

**I get a sort of anxious feeling like "butterflies" in the stomach**
- Never ☐
- Occasionally ☐
- Often ☐
- Very often ☐

**I have lost interest in my appearance**
- Definitely ☐
- Often I don't take as much care as I should ☐
- Sometimes I don't take as much care as I should ☐
- I take just as much care as ever ☐

**I feel restless as if I have to be on the move**
- Definitely ☐
- Quite a lot ☐
- Not very much ☐
- Never ☐

**I look forward with enjoyment to things**
- As much as I ever have ☐
- Somewhat less than I used to ☐
- Much less than I used to ☐
- Rarely ☐

**I get sudden feelings of panic**
- Very often ☐
- Often ☐
- Not very often ☐
- Never ☐

**I can enjoy a good book, radio or television program**
- Often ☐
- Sometimes ☐
- Not often ☐
- Very seldom ☐

# Centrexion Therapeutics Protocol CNTX-4975i-OA-304
# Fibromyalgia Symptoms Scale

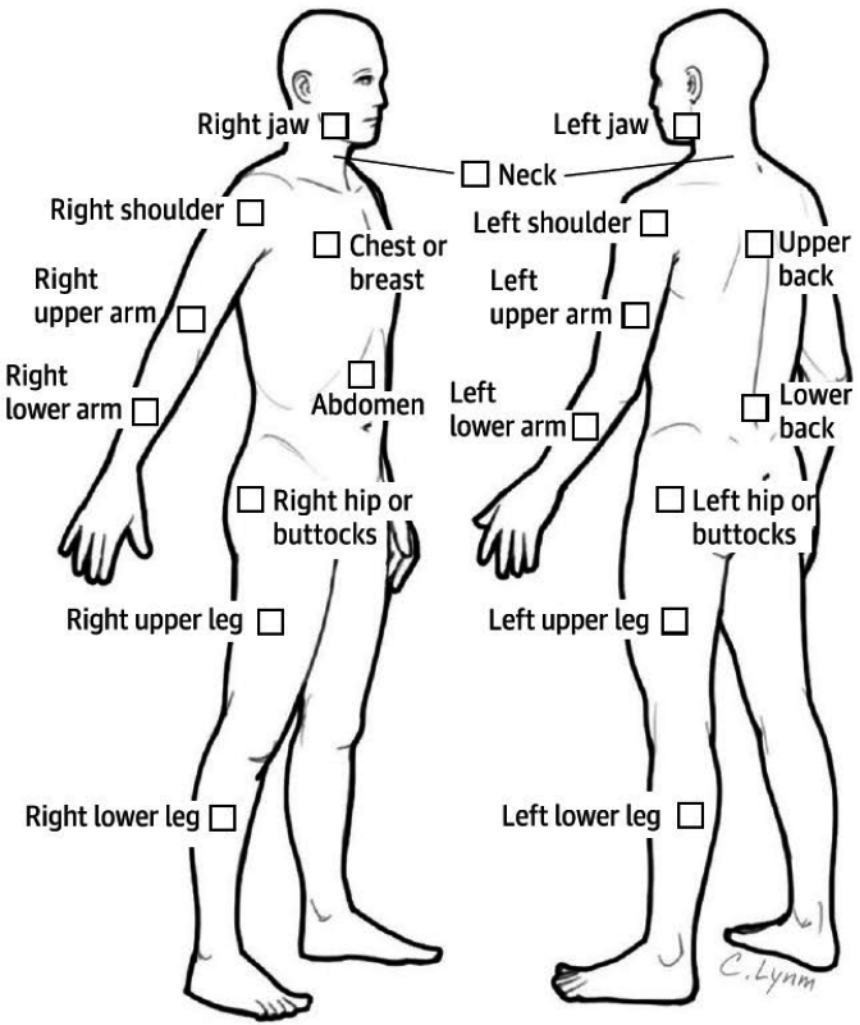
Subject No: ____ ____ ____ ____ Subject Initials: ____ ____ ____

*Date of Completion:* *Day* ☐☐ *Month* ☐☐☐ *Year* ☐☐☐☐

*Please sign your initials upon completing the questionnaire on the back page*

# Patient Self-report Survey for the Assessment of Fibromyalgia

(1) Please indicate if you have had pain or tenderness **during the past 7 days** in the areas shown below.
Check the boxes in the diagram for each area in which you have had pain or tenderness.




(2) For each symptom listed below, use the following scale to indicate the severity of the symptom **during the past 7 days**.

- **No problem**
- **Slight or mild problem:** generally mild or intermittent
- **Moderate problem:** considerable problems; often present and/or at a moderate level
- **Severe problem:** continuous, life-disturbing problems

| | No problem | Slight or mild problem | Moderate problem | Severe problem |
|---|---|---|---|---|
| A. Fatigue | ☐ | ☐ | ☐ | ☐ |
| B. Trouble thinking or remembering | ☐ | ☐ | ☐ | ☐ |
| C. Waking up tired (unrefreshed) | ☐ | ☐ | ☐ | ☐ |

(3) During the **past 6 months** have you had any of the following symptoms?

| | | |
|---|---|---|
| A. Pain or cramps in lower abdomen | ☐ No | ☐ Yes |
| B. Depression | ☐ No | ☐ Yes |
| C. Headache | ☐ No | ☐ Yes |

(4) Have the symptoms in questions 2-3 and pain been present at a similar level for at **least 3 months**?

☐ No ☐ Yes

(5) Do you have a disorder that would otherwise explain the pain?

☐ No ☐ Yes

# WOMAC Osteoarthritis Index NRS3.1

## INSTRUCTIONS TO PATIENTS

In Sections A, B and C, questions will be asked in the following format and you should give your answers by putting an "✗ " in one of the boxes.

**EXAMPLES**:

1. If you put your "✗ "in the box on the far left as shown below, then you are indicating that you have **no** pain.

| No Pain | ✗ | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Pain |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

2. If you put your " ✗ "in the box on the far right as shown below, then you are indicating that you have **extreme** pain.

| No Pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | ✗ | Extreme Pain |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

3. Please note:
   a) that the further to the right you place your " ✗ " the **more** pain you feel.
   b) that the further to the left you place your " ✗ " the **less** pain you feel.
   c) **please do not** place your " ✗ "**outside any of the boxes**.

You will be asked to indicate on this type of scale the amount of pain, stiffness or disability you have felt during the last 48 hours.

Think about your _____ (study joint) when answering the questionnaire. Indicate the severity of your pain and stiffness and the difficulty you have in doing daily activities that you feel are caused by the arthritis in your _____ (study joint).

Your study joint has been identified for you by your health care professional.

If you are unsure which joint is your study joint, please ask before completing the questionnaire.

# WOMAC Osteoarthritis Index NRS3.1

**Section A**

## PAIN

Think about the pain you felt in your _____ (study joint) caused by the arthritis during the last 48 hours.

*(Please mark your answers by putting an "X" in one of the boxes.)*

QUESTION: **How much pain have you had . . .**

1. when walking on a flat surface?

| No Pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Pain |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

2. when going up or down stairs?

| No Pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Pain |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

3. at night while in bed? (that is - pain that disturbs your sleep)

| No Pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Pain |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

4. while sitting or lying down?

| No Pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Pain |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

5. while standing?

| No Pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Pain |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

# WOMAC Osteoarthritis Index NRS3.1

**Section B**

## STIFFNESS

Think about the stiffness (not pain) you felt in your _____ (study joint) caused by the arthritis during the last 48 hours.

Stiffness is a sensation of **decreased** ease in moving your joint.

*(Please mark your answers by putting an "X" in one of the boxes.)*

6. How **severe** has your stiffness been **after you first woke up** in the morning?

| No Stiffness | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Stiffness |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

7. How **severe** has your stiffness been after sitting or lying down or while resting **later in the day**?

| No Stiffness | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Stiffness |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

# WOMAC Osteoarthritis Index NRS3.1

**Section C**

## DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your _____ (study joint) during the last 48 hours. By this we mean **your ability to move around and take care of yourself**.

*(Please mark your answers by putting an "X" in one of the boxes.)*

QUESTION: **How much difficulty have you had . . .**

8. when going down the stairs?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

9. when going up the stairs?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

10. when getting up from a sitting position?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

11. while standing?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

12. when bending to the floor?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

13. when walking on a flat surface?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

# WOMAC Osteoarthritis Index NRS3.1

## DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your _____ (study joint) during the last 48 hours. By this we mean **your ability to move around and take care of yourself**.

*(Please mark your answers by putting an "X" in one of the boxes.)*

QUESTION: **How much difficulty have you had . . .**

14. getting in or out of a car, or getting on or off a bus?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

15. while going shopping?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

16. when putting on your socks or panty hose or stockings?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

17. when getting out of bed?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

18. when taking off your socks or panty hose or stockings?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

19. while lying in bed?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

# WOMAC Osteoarthritis Index NRS3.1

## DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your _____ (study joint) during the last 48 hours. By this we mean **your ability to move around and take care of yourself**.

*(Please mark your answers by putting an "X" in one of the boxes.)*

QUESTION: **How much difficulty have you had . . .**

20. when getting in or out of the bathtub?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

21. while sitting?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

22. when getting on or off the toilet?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

23. while doing heavy household chores?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

24. while doing light household chores?

| No Difficulty | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Extreme Difficulty |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

# 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.***

# Your Health and Well-Being

**This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.** ***Thank you for completing this survey!***

**For each of the following questions, please mark an ☒ in the one box that best describes your answer.**

**1. In general, would you say your health is:**

| Excellent | Very good | Good | Fair | Poor |
|---|---|---|---|---|
| ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

**2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?**

| Much better now than one year ago | Somewhat better now than one year ago | About the same as one year ago | Somewhat worse now than one year ago | Much worse now than one year ago |
|---|---|---|---|---|
| ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

**3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?**

| | | Yes, limited a lot | Yes, limited a little | No, not limited at all |
|---|---|---|---|---|
| a | <u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports | ☐ 1 | ☐ 2 | ☐ 3 |
| b | <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf | ☐ 1 | ☐ 2 | ☐ 3 |
| c | Lifting or carrying groceries | ☐ 1 | ☐ 2 | ☐ 3 |
| d | Climbing <u>several</u> flights of stairs | ☐ 1 | ☐ 2 | ☐ 3 |
| e | Climbing <u>one</u> flight of stairs | ☐ 1 | ☐ 2 | ☐ 3 |
| f | Bending, kneeling, or stooping | ☐ 1 | ☐ 2 | ☐ 3 |
| g | Walking <u>more than a mile</u> | ☐ 1 | ☐ 2 | ☐ 3 |
| h | Walking <u>several hundred yards</u> | ☐ 1 | ☐ 2 | ☐ 3 |
| i | Walking <u>one hundred yards</u> | ☐ 1 | ☐ 2 | ☐ 3 |
| j | Bathing or dressing yourself | ☐ 1 | ☐ 2 | ☐ 3 |

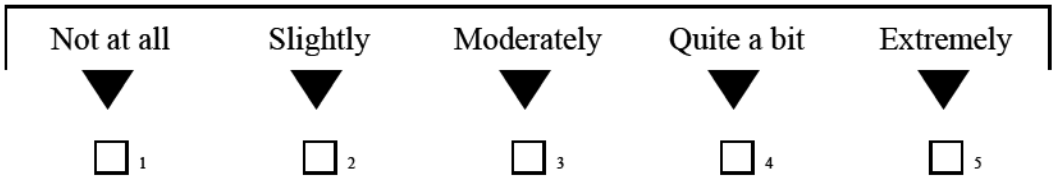
**4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a Cut down on the amount of time you spent on work or other activities | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| b Accomplished less than you would like | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| c Were limited in the kind of work or other activities | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| d Had difficulty performing the work or other activities (for example, it took extra effort) | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

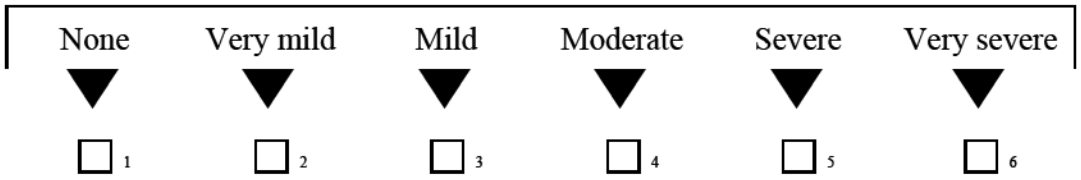
**5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a Cut down on the amount of time you spent on work or other activities | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| b Accomplished less than you would like | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| c Did work or other activities less carefully than usual | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

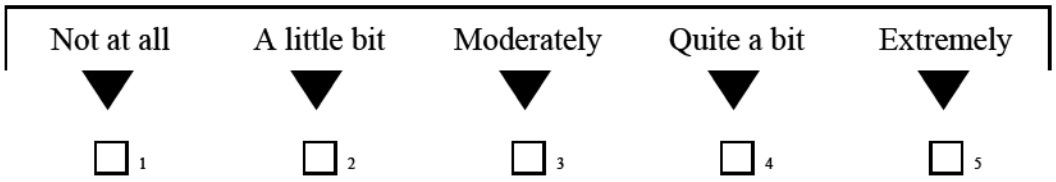
6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**




7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**




8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**



**9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…**

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a Did you feel full of life? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| b Have you been very nervous? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| c Have you felt so down in the dumps that nothing could cheer you up? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| d Have you felt calm and peaceful? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| e Did you have a lot of energy? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| f Have you felt downhearted and depressed? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| g Did you feel worn out? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| h Have you been happy? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| i Did you feel tired? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

**10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?**

| All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|
| ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

**11. How TRUE or FALSE is <u>each</u> of the following statements for you?**

| | Definitely true | Mostly true | Don't know | Mostly false | Definitely false |
|---|---|---|---|---|---|
| a I seem to get sick a little easier than other people | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| b I am as healthy as anybody I know | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| c I expect my health to get worse | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| d My health is excellent | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

***Thank you for completing these questions!***

# Your Sleep

**For each of the following questions, please mark an ☒ in the one box that best describes your answer.**

**1. How long did it usually take for you to <u>fall asleep</u> during the <u>past 4 weeks</u>?**

| 0-15 minutes | 16-30 minutes | 31-45 minutes | 46-60 minutes | More than 60 minutes |
|---|---|---|---|---|
| ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

**2. On the average, how many hours did you sleep <u>each night</u> during the <u>past 4 weeks</u>?**

Write in number of hours per night: ☐☐

**3. How often during the <u>past 4 weeks</u> did you...**

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a | feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc., while sleeping)? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| b | get enough sleep to feel rested upon waking in the morning? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| c | awaken short of breath or with a headache? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| d | feel drowsy or sleepy during the day? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| e | have trouble falling asleep? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

**How often during the <u>past 4 weeks</u> did you...**

| | | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|---|
| f | awaken during your sleep time and have trouble falling asleep again? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| g | have trouble staying awake during the day? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| h | snore during your sleep? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| i | take naps (5 minutes or longer) during the day? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| j | get the amount of sleep you needed? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |




MOS 12-Item Sleep Scale – Revised 2010
United States (English)

# EQ-5D-5L HEALTH QUESTIONNAIRE

Under each heading, please check the ONE box that best describes your health TODAY.

**MOBILITY**

- ☐ I have no problems walking
- ☐ I have slight problems walking
- ☐ I have moderate problems walking
- ☐ I have severe problems walking
- ☐ I am unable to walk

**SELF-CARE**

- ☐ I have no problems washing or dressing myself
- ☐ I have slight problems washing or dressing myself
- ☐ I have moderate problems washing or dressing myself
- ☐ I have severe problems washing or dressing myself
- ☐ I am unable to wash or dress myself

**USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)**

- ☐ I have no problems doing my usual activities
- ☐ I have slight problems doing my usual activities
- ☐ I have moderate problems doing my usual activities
- ☐ I have severe problems doing my usual activities
- ☐ I am unable to do my usual activities

**PAIN / DISCOMFORT**

- ☐ I have no pain or discomfort
- ☐ I have slight pain or discomfort
- ☐ I have moderate pain or discomfort
- ☐ I have severe pain or discomfort
- ☐ I have extreme pain or discomfort

# EQ-5D-5L HEALTH QUESTIONNAIRE

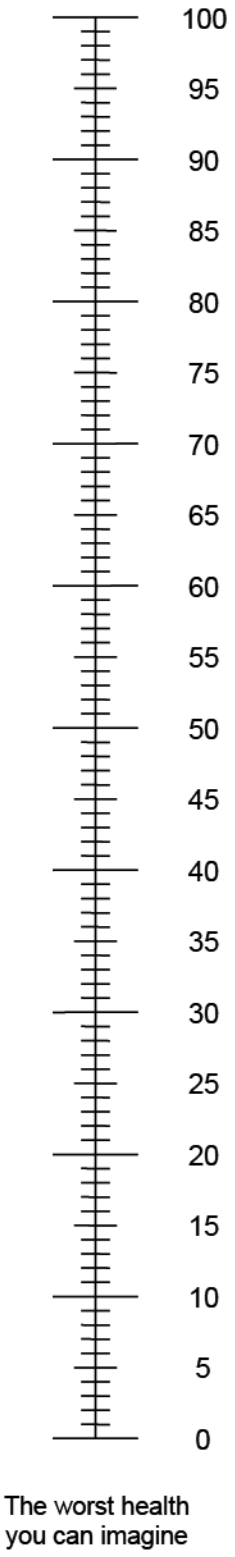
**ANXIETY / DEPRESSION**

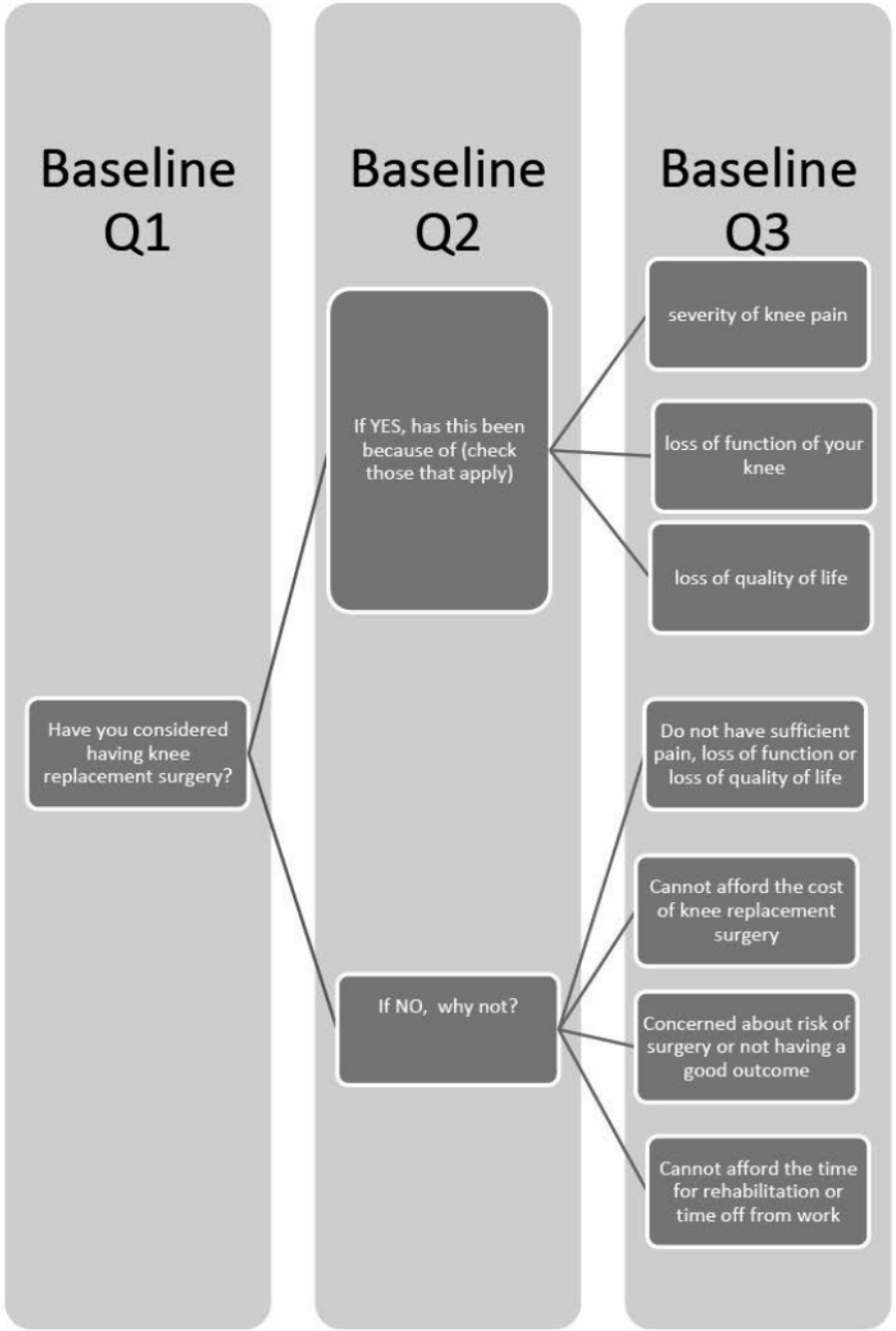
- ☐ I am not anxious or depressed
- ☐ I am slightly anxious or depressed
- ☐ I am moderately anxious or depressed
- ☐ I am severely anxious or depressed
- ☐ I am extremely anxious or depressed

# EQ-5D-5L HEALTH QUESTIONNAIRE

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐






The boxes can have a set of questions with check boxes for those that apply

# JOINT REPLACEMENT QUESTIONNAIRE

## QUESTIONS TO BE ADMINISTERED AT ALL VISITS SUBSEQUENT TO BASELINE VISIT (TREATMENT VISIT 1/ DAY 1)

| | |
|---|---|
| If you considered having a joint replacement at the beginning of the trial, would you still wish to have a total knee replacement? | ○ Yes<br>○ No<br>○ I am undecided<br>○ I did not consider having a joint replacement at the beginning of the trial |
| If yes: | ○ Because my pain is still severe enough<br>○ Because i still have lost too much function<br>○ Because my quality of life is still lower than accpetable |
| If no: | ○ I no longer want a joint replacement<br>○ My pain is not severe enough<br>○ My function has improved and is acceptable<br>○ My quality of life has improved and is acceptable |

# PATIENT GLOBAL IMPRESSION OF CHANGE IN KNEE PAIN

Compared to before study treatment, the pain from my knee osteoarthritis is: (check only one response)

- ☐ very much improved
- ☐ much improved
- ☐ minimally improved
- ☐ no change
- ☐ minimally worse
- ☐ much worse
- ☐ very much worse

**Work Productivity and Activity Impairment Questionnaire: Osteoarthritis of the Knee V2.0 (WPAI:OA)**

The following questions ask about the effect of your osteoarthritis of the knee on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (doing paid work)? _____ NO ___ YES
   *If NO, tick "NO" and go to question 6.*

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your osteoarthritis of the knee? *Include hours you missed on sick days, times you went in late, left early, etc., because of your osteoarthritis of the knee. Do not include time you missed to participate in this study.*

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", go to question 6.)*

5. During the past seven days, how much did your osteoarthritis of the knee affect your productivity while you were working?

*Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If osteoarthritis of the knee affected your work only a little, choose a low number. Choose a high number if osteoarthritis of the knee affected your work a great deal.*

Consider only how much osteoarthritis of the knee affected productivity while you were working.

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Osteoarthritis of the knee had no effect on my work | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Osteoarthritis of the knee completely prevented me from working |

CIRCLE A NUMBER

6. During the past seven days, how much did your osteoarthritis of the knee affect your ability to do your regular daily activities, other than work at a job?

*By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If osteoarthritis of the knee affected your activities only a little, choose a low number. Choose a high number if osteoarthritis of the knee affected your activities a great deal.*

Consider only how much osteoarthritis of the knee affected your ability to do your regular daily activities, other than work at a job.

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Osteoarthritis of the knee had no effect on my daily activities | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Osteoarthritis of the knee completely prevented me from doing my daily activities |

CIRCLE A NUMBER