# PROTOCOL AMENDMENT

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| PRODUCT NAME/NUMBER: | CNTX-4975-05 |
| PROTOCOL NUMBER: | CNTX-4975i-OA-303 |
| IND NUMBER: | # 132,999 |
| EUDRACT NUMBER: | 2018-003094-10 |
| DEVELOPMENT PHASE: | Phase 3 |
| PROTOCOL TITLE: | An Open-label, 8-Week Study to Compare the Comfort and Ease of Use of Five Different Treatment Regimens for CNTX-4975-05 Intra-articular Injection in Subjects with Chronic, Moderate-to-Severe Osteoarthritis Knee Pain |
| PROTOCOL DATE: | Original Protocol Version 1.0, 10 August 2018 |
| AMENDMENT 1 DATE | Version 2.0, 25 April 2019 |
| AMENDMENT 2 DATE | Version 3.0, 13 June 2019 |
| SPONSORED BY: | Centrexion Therapeutics Corp. [redacted] |
| CONTRACT RESEARCH ORGANIZATION: | [redacted] |

This study will be performed in compliance with Good Clinical Practices (GCP) and applicable regulatory requirements, including the archiving of essential documents. Information contained in this protocol is confidential in nature, and may not be used, divulged, published or otherwise disclosed to others except to the extent necessary to obtain approval of the Institutional Review Board or Independent Ethics Committee, or as required by law. Persons to whom this information is disclosed should be informed that this information is confidential and may not be further disclosed without the express permission of Centrexion Therapeutics Corp.

## APPROVAL SIGNATURES

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| VERSION: | Version 3.0, 13 June 2019 |

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]

14-Jun-2019 | 03:59:40 PDT

[redacted]

[redacted]

14-Jun-2019 | 02:34:14 EDT

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Date

# 1 SYNOPSIS

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| PRODUCT NAME/NUMBER | CNTX-4975-05 |
| PROTOCOL NUMBER | CNTX-4975i-OA-303 |
| DEVELOPMENT PHASE | Phase 3 |
| PROTOCOL TITLE | An Open-label, 8-Week Study to Compare the Comfort and Ease of Use of Five Different Treatment Regimens for CNTX 4975-05 Intra-articular Injection 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 knee OA are as follows:<br>**Primary Efficacy Objective:**<br>To determine the optimal procedures for administering CNTX 4975-05 as a single intra-articular (IA) injection into knee(s) with OA, balancing comfort and ease of use of methods of cooling and administration.<br>**Secondary Efficacy Objectives:**<br>• To describe the clinical benefit of CNTX-4975-05 treatment at Week 8 in a single knee with OA<br>• To describe the clinical benefit at Week 8 of treating bilateral knee OA with a single injection to each knee<br>• To describe the clinical benefit at Week 8 of treating a single knee with OA in subjects with partial or total joint replacement (PJR/TJR) in the contralateral knee<br>• To evaluate subject satisfaction (SS) with the overall benefit of CNTX-4975-05<br>• To evaluate SS with IA CNTX-4975-05 relative to SS with contralateral knee PJR or TJR<br>• To evaluate subject and investigator satisfaction (IS) with different treatment regimens<br>• To evaluate the responders to treatment through 8 weeks<br>**Exploratory Efficacy Objectives:**<br>• To explore the likelihood of the need for joint replacement surgery, based on clinical benefit and the subject's assessment of their improvement at Week 8<br>• To explore the effect of subject characteristics (including Kellgren-Lawrence [K-L] grade, sex, body mass index [BMI], age, unilateral versus bilateral knee OA, unilateral versus bilateral injections, and history of contralateral PJR or TJR) on the clinical benefit of IA CNTX-4975-05 at each study visit through Week 8<br>• To explore changes in the frequency of use of background analgesic medication for pain in the injected knee(s) throughout the study period |

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| | **Safety Objective:**<br>• To further evaluate the safety of a single IA injection of [redacted] CNTX-4975-05 to one or both knees in subjects with chronic moderate to severe unilateral or bilateral knee OA pain |
| STUDY DESIGN | This is an open-label, single injection (per knee), 8-week study to evaluate the comfort and ease of use of 5 different treatment regimens, and to evaluate the efficacy and safety of a single IA injection, in one or both knees, of [redacted] CNTX-4975-05 in subjects with chronic, moderate-to-severe knee OA pain. Procedural pain associated with IA injection of the investigational product, CNTX-4975-05, will be controlled primarily through adjunct controlled joint cooling and secondarily by pre-medication with IA lidocaine.<br>**Types of Subjects:**<br>The study population will contain 3 types of subjects, with a targeted minimum of 150 subjects of each type:<br>1. Subjects with unilateral or bilateral OA of the knee, with one knee (the index knee) with moderate to severe pain (K-L grade 1-4) and the other knee (the contralateral knee) with no to mild pain. These subjects will receive an injection of CNTX-4975-05 into the index knee only.<br>2. Subjects with bilateral OA of the knees, with both knees having moderate to severe pain (K-L grade 1-4, with worse pain being the index knee). These subjects will receive an injection of CNTX-4975-05 into each knee (1 week apart, most painful knee [index knee] first, then the following week, the contralateral knee).<br>3. Subjects who have unilateral or bilateral OA of the knee, with one knee with moderate to severe pain (the index knee [K-L grades 1-4]) and previous PJR or TJR in the other knee (the contralateral knee). These subjects will receive an injection of CNTX-4975-05 into the index knee only.<br>All subjects will receive [redacted] CNTX-4975-05 injected into the index knee; subjects with bilateral OA will receive an injection into both knees (injections will be separated by 1 week). Subjects will be followed for 8 weeks.<br>**Pre-Medication:**<br>Prior to the injection procedure, the investigator may, at his or her discretion, pre-medicate subjects with an oral dose of an opioid or non-steroidal anti-inflammatory drug (NSAID). The skin at the point of the anticipated injection(s) may also be infiltrated with 1 to 2 mL of lidocaine and/or a topical analgesic such as ethyl chloride spray. It is recommended not to use more than 2 methods of local analgesia about the knee(s) to be injected.<br>**Injection of CNTX-4975-05:**<br>ALL subjects are required to be administered an IA injection of a full 15 mL of lidocaine (without epinephrine) (1% or 2%, depending on the assigned treatment regimen) to ensure: 1) the local targeted concentration of CNTX-4975 in the joint; 2) distension of the joint capsule to improve access of CNTX-4975 to the joint space; and 3) to provide some analgesia. The full 15 mL of lidocaine (without epinephrine) and the full 2 mL of CNTX-4975-05 must be injected into the knee joint, as directed. The 5 flexion-extension moves of the knee after IA CNTX-4975-05 is injected into the knee also improve access of CNTX-4975 to the entire joint space. The lidocaine may have some modest effect on pain, but the concentration and dispersion of CNTX-4975 into the joint are the primary reasons for lidocaine use. |

The use of ultrasound for IA injections is recommended, but not required. If not using ultrasound guided IA injection, then with a clinical IA injection, joint fluid must be identified within the needle hub before injection of 2% lidocaine (without epinephrine) and CNTX-4975-05. After injection of CNTX-4975, the knee joint will be passively flexed and extended 5 times over 1 minute to facilitate distribution of the CNTX-4975 within the knee. 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.

The duration of cooling and the knee pain upon discontinuation of cooling must be entered into the electronic case report form [eCRF]. If cooling must be reapplied, the time and knee pain level must be recorded in the eCRF, and timing of subsequent pain assessments should be on the standard time lines in the eCRF.

Each site will be randomly assigned 1 of the following 5 treatment regimens to be employed for ALL subjects at that site:

| **Group** | **Cooling Device** | • **Pre-cool**<br>• **Lidocaine %**<br>• **Post-lido cool** | **Needle** | **Post-dose cooling** |
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| 1. Breg Cooling Control Group | Breg ice water pump | • 15 mins<br>• 2% lidocaine<br>• 30 mins | **Separate** needles for lidocaine and CNTX-4975-05 | 30 to 90 mins as needed |
| 2. Gel Pack Cooling Group | Elasto-Gel | • 40 mins<br>• 2% lidocaine<br>• 10 mins | **Separate** needles for lidocaine and CNTX-4975-05 | 10 to 90 mins as needed |
| 3. Shortened Gel Pack Cooling Group | Elasto-Gel | • 30 mins<br>• 2% lidocaine<br>• 5 mins | **Separate** needles for lidocaine and CNTX-4975-05 | up to 90 mins as needed |
| 4. Single Needle Injection Gel Pak Cooling Group-2% Lidocaine | Elasto-Gel | • 45 mins<br>• 2% lidocaine<br>• no cooling | **Single** needle for lidocaine and CNTX-4975-05 | up to 90 mins as needed |
| 5. Single Needle Injection Gel Pack Cooling Group-1% Lidocaine | Elasto-Gel | • 45 mins<br>• 1% lidocaine<br>• no cooling | **Single** needle for lidocaine and CNTX-4975-05 | up to 90 mins as needed |

See study manual for specific instructions on the use of the Breg Cooling Wrap and the Elasto-Gel Cooling Wrap.

1. **Breg Cooling Control Group** (used in protocols CNTX-4975i-OA-301 and CNTX-4975i-OA-304 for comfort and blinding of the protocols)
    a. Controlled joint cooling wrap with an ice water pump system (Breg Cooler) will be applied 15 minutes prior to IA injection of the full 15 mL 2% lidocaine (without epinephrine) into the knee joint using standard aseptic techniques.
    b. Inject IA the full 15 mL of 2% lidocaine (without epinephrine) into the knee joint using appropriate aseptic techniques.
    c. Controlled cooling will be resumed for a further 30 minutes after the IA injection of the full 15 mL 2% lidocaine (without epinephrine) into the knee joint.
    d. The cooling device will be removed, and CNTX-4975-05 IA injection will be administered using standard aseptic techniques.

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| | e. Controlled cooling will be reapplied for a minimum of 30 minutes, and up to 90 minutes, as needed, after CNTX-4975-05 injection, depending on the subject's comfort. The cooling may be discontinued after a minimum of 30 minutes after IA CNTX-4975-05 injection, if the subject has a pain level that is acceptable for the subject and investigator (0-4 scale: none, mild, moderate, moderately severe, and severe).<br>2. **Gel Pack Cooling Group**<br>a. Gel pack cooling applied for 40 minutes to the knee using the gel pack over a stockinette or light-weight pants. This may be outside of the exam room, but at the investigator's discretion, may be done in the exam room. If done outside the exam room, subject may be moved to the exam room ± 5 minutes of the 40-minute cooling (with gel pack remaining on the knee).<br>b. Inject IA the full 15 mL 2% lidocaine (without epinephrine) into the knee joint using appropriate aseptic techniques.<br>c. Gel pack cooling is applied for 10 minutes to the knee using the gel pack over a stockinette or light-weight pants.<br>d. The gel pack will then be removed, and CNTX-4975-05 IA injection will be administered using appropriate aseptic techniques.<br>e. Gel pack cooling will be reapplied for a minimum of 10 minutes, and up to 90 minutes, as needed, after CNTX-4975-05 injection, depending on the subject's comfort. The cooling may be discontinued after a minimum of 10 minutes after IA CNTX-4975-05 injection. If the subject has a pain level that is acceptable for the subject and investigator (0-4 scale: none, mild, moderate, moderately severe and severe).<br>3. **Shortened Gel Pack Cooling Group**<br>a. Gel pack cooling applied for 30 minutes to the knee using the gel pack over a stockinette or light-weight pants. This may be outside of the exam room, but at the investigator's discretion, may be done in the exam room. If done outside the exam room, subject may be moved to the exam room ± 5 minutes of the 30-minute cooling (with gel pack remaining on the knee).<br>b. Inject IA the full 15 mL 2% lidocaine (without epinephrine) into the knee joint using appropriate aseptic techniques.<br>c. Gel pack cooling is applied for 5 minutes to the knee using the gel pack over a stockinette or light-weight pants.<br>d. The gel pack will then be removed, and CNTX-4975-05 IA injection will be administered using appropriate aseptic techniques.<br>e. Gel pack cooling may be reapplied for up to 90 minutes, as needed, after CNTX-4975-05 injection, depending on the subject's comfort. The subject may remain in the exam room, or be moved to a more comfortable area with the gel pack. The gel pack may be discontinued after IA CNTX-4975-05 injection if the subject has a pain level that is acceptable for the subject and investigator (0-4 scale: none, mild, moderate, moderately severe and severe).<br>4. **Single Needle Injection Gel Pack Cooling Group-2% IA Lidocaine**<br>a. Gel pack cooling applied for 45 minutes to the knee using the gel pack over a stockinette or light-weight pants. This may be outside of the exam room, but at the investigator's discretion, may be done in the exam room. If done outside the exam room, subject may be |

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| | moved to the exam room ± 5 minutes of the 45-minute cooling (with gel pack remaining on the knee).<br>b. Inject IA the full 15 mL 2% lidocaine (without epinephrine) into the knee joint using appropriate aseptic techniques.<br>c. After the 2% lidocaine IA injection, CNTX-4975-05 IA injection, using the same needle, will be injected into the knee joint using appropriate aseptic techniques after 3 minutes of the 2% lidocaine (without epinephrine).<br>d. Gel pack cooling may be reapplied for up to 90 minutes, as needed, after CNTX-4975-05 injection, depending on the subject's comfort. The subject may remain in the exam room, or be moved to a more comfortable area with the gel pack. The gel pack may be discontinued after a minimum of 10 minutes after IA CNTX-4975-05 injection if the subject has a pain level that is acceptable for the subject and investigator (0-4 scale: none, mild, moderate, moderately severe and severe).<br>5. **Single Needle Injection Gel Pack Cooling Group-1% IA Lidocaine**<br>a. Gel pack cooling applied for 45 minutes to the knee using the gel pack over a stockinette or light-weight pants. This may be outside of the exam room, but at the investigator's discretion, may be done in the exam room. If done outside the exam room, subject may be moved to the exam room ± 5 minutes of the 40-minute cooling (with gel pack remaining on the knee).<br>b. Inject IA the full 15 mL 1% lidocaine (without epinephrine) into the knee joint using appropriate aseptic techniques.<br>c. After the 1% lidocaine IA injection, CNTX-4975-05 IA injection, using the same needle, will be injected into the knee joint using appropriate aseptic techniques after 3 minutes of the 1% lidocaine (without epinephrine).<br>d. Gel pack cooling may be reapplied for up to 90 minutes, as needed, after CNTX-4975-05 injection, depending on the subject's comfort. The subject may remain in the exam room, or be moved to a more comfortable area with the gel pack. The gel pack may be discontinued after IA CNTX-4975-05 injection if the subject has a pain level that is acceptable for the subject and investigator (0-4 scale: none, mild, moderate, moderately severe and severe).<br>Subjects should not take a hot bath or shower, or expose the injected knee(s) to external heat, within 12 hours after the injection.<br>On Day 3 post-injection, study staff will call subjects to assess adverse events (AEs), subject assessment of procedure pain and satisfaction, knee pain with walking, and the use of rescue medication (for bilateral knee injections, calls will occur 3 days after each injection). Subjects will return to the clinic at Weeks 4 and 8 for study assessments.<br>Efficacy will be assessed on the OA index knee (and contralateral knee in bilateral knee injection subjects) using a numeric pain rating scale (NPRS); the Knee Injury and Osteoarthritis Outcome Score (KOOS), which includes subscales for pain, other symptoms, activities of daily living, sports and recreation, and quality of life; a joint replacement questionnaire; a subject satisfaction questionnaire; an investigator satisfaction questionnaire; and rescue medication use. Pain with walking will also be collected and assessed for the contralateral knee.<br>For subjects with bilateral knee injections, the contralateral knee will be assessed using the same scales as the index knee, and the effect of bilateral knee injections will be |

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| | combined as a composite score to examine the overall benefit. The index knee in these subjects is the one with worse pain with walking. Where both knees have equal pain with walking, then the knee on the subject's dominant side will be designated the index knee.<br><br>Safety will be assessed by injection site assessments (erythema and edema), assessment of procedure pain, AEs, physical examination findings, vital sign measurements, 12-lead electrocardiograms (ECGs), clinical laboratory test results, and sensory testing. |
| PLANNED NUMBER OF SUBJECTS | Approximately 850 subjects will be enrolled. |
| STUDY ENTRY CRITERIA | **Inclusion Criteria:**<br><br>1. Male or female subjects between 40 and 95 years of age (inclusive)<br><br>2. Confirmation of OA of the knee: radiography of both knees using standard standing films (scored by the investigator) or using the fixed flexion method, taken during the Screening Visit (prior radiographs of the knees of sufficient quality that have been taken within 2 years of the Screening Visit may be used for K-L grading). The index knee must show evidence of chronic OA with a K-L grade of 1, 2, 3 or 4. Subjects who were screen failures for the United States (US) CNTX-4975i-OA-301 or CNTX-4975i-OA-304 trials may be considered for this trial if the K-L grade of the index knee is 1-4, inclusive.<br><br>3. Confirmation of OA of the index knee: American College of Rheumatology (ACR) diagnostic criteria (ACR confirmation of bilateral knee OA for subjects who will have bilateral knee injections of CNTX-4975-05).<br><br>4. For subjects for monoarticular knee injection, the index knee must have moderate to severe pain (≥5 and ≤9) at screening associated with OA, which must be stable for a minimum of 6 months prior to Screening, as assessed by the investigator. These subjects may have:<br><br>a) unilateral or bilateral OA, with the index knee having moderate to severe pain, and the contralateral knee having none to mild pain, OR<br><br>b) unilateral or bilateral OA, with the index knee having moderate to severe pain and the other knee having had a PJR or TJR within 5 years of the Screening Visit. The knee with the PJR/TJR is not to be injected with CNTX-4975-05.<br><br>For subjects for bilateral knee injection, the index knee must have moderate to severe pain (≥5 and ≤9) at screening associated with OA, and greater pain in the index knee than in the contralateral knee. Their pain must be stable for a minimum of 6 months prior to Screening, as assessed by the investigator. The index knee in these subjects is the one with the worst pain with walking. Where both knees have equal pain with walking, then the knee on the subject's dominant side will be designated the index knee.<br><br>For qualifying knee pain with walking, subjects will use an NPRS (0-10; 0=no pain, 10=worst possible pain) to rate their knee pain with walking (both knees, except knees with PJR/TJR). The PJR/TJR pain should be rated using the NPRS scale, but will not be a qualifying pain score.<br><br>5. Body mass index ≤45 kg/$m^2$.<br><br>6. 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><br>a) unacceptable AEs; |

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| | b) initial failure to achieve clinically adequate pain relief;<br>c) initial pain relief that was not maintained; and/or<br>d) 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: NSAIDs (including topical), opioids, duloxetine, other systemic therapy, IA corticosteroids, IA visco-supplements, physical therapy, bracing, and orthotics.<br>7. 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 CNTX-4975-05 administration<br>• Total abstinence from sexual intercourse since the last menses before CNTX-4975-05 administration<br>• Intrauterine device<br>• Double barrier method (condoms, sponge, diaphragm, with spermicidal jellies or cream).<br>8. Able to speak, read, and understand the language of the study used for the informed consent.<br>9. 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 (i.e., without assistance) record responses on the efficacy scales during clinic visits<br>e) independently communicate meaningfully with the study personnel.<br>10. Signed informed consent form approved by the institutional review board (IRB)/ independent ethics committee (IEC).<br>11. Subjects may come into the study with a single analgesic of their choice for their OA knee pain (prescription or OTC). The current pain medication must be identified as that taken only for pain in the knee OA or pain in the PJR/TJR, and not for another pain indication. The subjects will complete a daily paper diary of their background knee analgesic medications during the screening period and throughout the trial. Other analgesics may be taken for occasional pain but should not be taken within 24 hours of a clinic visit; these are to be recorded as concomitant medications, not as rescue/background medication for knee osteoarthritis.<br>**Exclusion Criteria:**<br>1. Joint replacement surgery of the index knee at any time, or open surgery of the index knee in the past 24 months. Joint replacement of the contralateral knee is permitted for subjects who will not receive an injection in the contralateral (natural) knee. For subjects with bilateral knee OA who will receive an injection into both |

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| | knees, joint replacement surgery of both knees at any time, or open surgery of the index knee in the past 24 months, is excluded.<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 chondromalacia patellae, inflammatory diseases (e.g., rheumatoid arthritis, psoriatic arthritis), 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. Other chronic pain anywhere in the body that requires the use of chronic analgesic medications, including, but not limited to, local painful areas, myofascial pain syndromes, fibromyalgia, genetic, metabolic abnormalities, hematologic, or neuropathic pain.<br>6. Instability of the index or contralateral knee (e.g., cruciate ligament tear or rupture, significant protruding meniscus, substantial ligamentous laxity, unstable PJR or TJR).<br>7. Misalignment (>10 degrees varus or valgus) of the index knee on standing.<br>8. Documented history of neuropathic arthropathy or finding of bony fragmentation in the index knee with imaging (radiographic, computed tomography, or magnetic resonance imaging).<br>9. Physical/occupational/chiropractic therapy for the lower extremities or acupuncture for the lower extremities within 15 days of Screening, or need for such therapy during the study.<br>10. Plans to have surgery, other invasive procedures, or IA injections (other than CNTX-4975-05) for either knee while participating in the study.<br>11. Current use of opioids for any condition other than for OA of the knees injected with CNTX-4975-05) (maximum dose of 15 mg of hydrocodone [or equivalent] per day).<br>12. Corticosteroid injection into the index or contralateral knee within 90 days of Screening.<br>13. Received IA viscosupplementation (e.g., Synvisc®, Hyalgan®) within 90 days of Screening.<br>14. History of allergic reaction to the planned local anesthesia/analgesic regimens, ethylenediaminetetraacetic acid, Kolliphor HS 15, butylated hydroxytoluene, or capsaicin.<br>15. 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>16. Is pregnant or is breast feeding. |

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| | 17. 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><br>18. Regular use of anticoagulant blood thinners (except low-dose aspirin, Dabigatran 150 mg once daily [qd], Enoxaparin 40 mg qd, Rivaroxaban 10 mg qd, or Apixaban 2.5 mg twice daily, or clopidogrel 75 mg qd, which are allowed).<br><br>19. Active cutaneous disease at the anticipated site of CNTX-4975-05 injection that would prevent the safe administration of CNTX-4975-05.<br><br>20. Ulcer or open wound anywhere on the index knee.<br><br>21. Specific laboratory abnormalities:<br>• Hemoglobin <11.0 g/dL<br>• White blood cells $<2.5 \times 10^9$/L<br>• Neutrophils $<1.5 \times 10^9$/L<br>• Platelets $<100 \times 10^9$/L<br>• Aspartate transaminase or alanine transaminase >2 × upper limit of normal<br>• Creatinine >1.6 mg/dL<br>• Glucose (fasting) >250 mg/dL<br>• Hemoglobin A1c (HgbA1c) >9.0%<br><br>22. 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><br>23. 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><br>24. Prior participation in an ALGRX 4975 or CNTX-4975 study.<br><br>25. Has any of the following characteristics:<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 an unacceptable level of depression or anxiety as measured by the Hospital Anxiety and Depression Scale (HADS) (a score of ≥11)<br>• Has unacceptable chronic pain as measured by the Fibromyalgia Symptom Scale Score (FSS) (a score of ≥13)<br>• Has a positive pregnancy test at the Screening or either Treatment Visit<br>• Has ongoing litigation for workers' compensation |

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| | • 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 pre-filled syringe [redacted] |
| TREATMENT REGIMENS | All subjects will receive a single clinical or ultrasound-guided IA injection of either 1% or 2% lidocaine (without epinephrine), followed by CNTX-4975-05 [redacted] on Study Day 1 (Treatment), along with controlled cooling. Subjects with bilateral moderate to severe OA knee pain, who have not had joint replacement and who qualify to have bilateral IA injections of CNTX-4975-05, will receive an injection in both knees (injections will be separated by 1 week). |
| PLANNED STUDY SITES | No more than 45 concurrent study sites in the US, Germany, Spain and the United Kingdom. |
| CRITERIA FOR EVALUATION | **Primary efficacy endpoint:**<br>The primary endpoint is assessment of the CNTX-4975-05 treatment regimens, with the Breg Cooling Control Group as the standard, using a combination of 3 assessments of the index knee: 1) pain 30 minutes after CNTX-4975-05 injection (using the 0-4 scale of none, mild, moderate, moderately severe, and severe); 2) subject satisfaction with the treatment regimen (SS); and 3) investigator satisfaction with the treatment regimen (IS).<br>**Secondary efficacy endpoints:**<br>• Assessment of the primary combined outcome using the contralateral knee for the subjects who received bilateral injections and the index knee for all other subjects<br>• Assessment of the primary combined outcome for each subject type<br>• Assessment of the primary combined outcome, using the contralateral knee for the subjects who received bilateral injections<br>• Percent of Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) responders at Week 8 for subjects with a single CNTX-4975-05 joint injection (index knee, moderate-to-severe pain; index knee, pain not >3 for contralateral knee)<br>• Percent of OMERACT-OARSI responders at Week 8 for subjects with bilateral knee injections of CNTX-4975-05 (index knee, moderate-to-severe pain index knee; both knees meeting OMERACT-OARSI responder criteria)<br>• Percent of OMERACT-OARSI responders at Week 8 for subjects with a single CNTX-4975-05 joint injection (population with index knee, moderate-to-severe pain index knee; non-index knee with PJR/TJR)<br>• For each of the 3 types of subjects, the absolute change; the number of subjects who have ≥30%, ≥50%, ≥70%, or ≥90% improvement area under the curve; and landmark analysis on the 5 subscales of the KOOS through Week 8 using the average of both knees:<br>o Pain<br>o Other symptoms<br>o Activities of daily living<br>o Sports and recreation |

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| | ○ Quality of life<br>• Assess the SS of treatment with CNTX-4975-05 IA injection for each of the 3 types of subjects, and all subjects in the trial<br>• For subjects with a PJR/TJR, assess their satisfaction with the CNTX-4975-05 IA injection versus their satisfaction with their PJR/TJR<br>**Exploratory Efficacy Endpoints:**<br>Exploratory efficacy endpoints include:<br>• Likelihood of the need for joint replacement surgery, based on KOOS subscales and SS outcomes, from Baseline through Week 8<br>• Subject satisfaction with the treatment of the index knee through Week 8 of the trial (7-point Likert Scale where 1=completely dissatisfied and 7=completely satisfied)<br>• The effect of subject characteristics (including K-L grade, sex, BMI, age, unilateral/bilateral knee OA, bilateral knee OA treatment, and history of contralateral PJR/TJR) on the analgesic efficacy of CNTX-4975-05, using the KOOS subscales at each study visit through Week 8<br>• Frequency of use of background analgesic medication for pain in the injected knee(s) throughout the study period.<br>• Assessment of the mean of the individual outcome measures, using the average of both knees for the subjects who received bilateral knee injections<br>Safety endpoints:<br>• Adverse events<br>• Vital signs<br>• Clinical laboratory evaluations (hematology, chemistry, and urinalysis)<br>• 12-lead ECGs<br>• Physical examination (including the presence or absence of an effusion in the index knee, periarticular pain/tenderness)<br>• Concomitant medications and therapies<br>• Degree of procedure pain (not recorded as AEs)<br>• Local physical findings after injection of the index knee<br>• Injection site assessment of erythema and edema<br>• Sensory testing |
| STATISTICAL METHODS | The primary analysis will compare each experimental treatment regimen to the Breg Cooling Control Group using an equally-weighted, combined score calculated from the following 3 measures: 1) pain 30 minutes after CNTX-4975-05 injection (using the 0-4 scale of none, mild, moderate, moderately severe, and severe), 2) SS with the treatment regimen; and 3) IS with the treatment regimen, all assessed on the index knee. Ratios of the mean values of test/control will have 95% confidence intervals constructed for each treatment regimen versus the Breg Cooling Control Group. For a treatment regimen to be considered clinically acceptable, it must be no more than 30% worse than the Breg Cooling Control Group and the lower limit of the 95% confidence interval for the treatment regimen must be greater than 0.7. This analysis will be performed on the ITT population. |

| | |
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| | For analysis, satisfaction scores (SS and IS) and 30 minute pain after CNTX-4975-05 injection will be transformed to equivalent scales, and 30 minute pain after CNTX-4975-05 injection will be reverse-scored so that higher scores represent lower pain, in order to have the 3 components on the same scale before they are combined by summing the 3 scores for a composite score. A sensitivity analysis will be performed that creates a composite score using the original scales (with the pain scores still reverse-scored to ensure the direction of the effect remains the same), using the ITT population.<br><br>All other continuous secondary and exploratory efficacy endpoints will be summarized using descriptive statistics by subject type, experimental injection procedure, and week/visit, as appropriate, and analyzed using a mixed-model repeated measures 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. |
| SAMPLE SIZE DETERMINATION | Approximately 850 subjects will receive CNTX-4975-05 in an open-label manner. This sample size was chosen based on the need to fulfill safety requirements for regulatory review. |
| STUDY AND TREATMENT DURATION | The overall study duration is expected to be 13 months, with 10 months of active enrollment and about 3 months for screening and treatment follow-up. The sequence and maximum duration of the study periods will be as follows:<br>• Screening Period up to 15 days.<br>• Treatment Period (open-label): 1 day per knee treated, maximum 2 days<br>• Post-treatment period: 8 weeks from the first CNTX-4975-05 IA injection<br><br>The maximum CNTX-4975-05 treatment for each subject is 2 days.<br><br>The maximum study duration for each subject is approximately 10 weeks. |

# 2 SCHEDULE OF EVENTS

## Table 2-1: Schedule of Events

| | Screening Visit | Treatment #1 (single knee)* | Phone F/U | Treatment #2 (Bilateral knees only)* | Phone F/U (Bilateral knees only) | Efficacy Safety | Efficacy Safety/ Early Termination Visit |
|---|---|---|---|---|---|---|---|
| **Clinic Visit (V) or Telephone Visit (TV)** | **V1** | **V2** | **TV3**[a] | **V4**[b] | **TV5**[a,b] | **V6** | **V7** |
| **Study Day/Week** | **Day -14 to Day 1**[c] | **Day 1** | **Day 3** ±1d | **Day 7 (Week 2)** (-2/+5 d) | **V4 +3d** ±1d | **Week 4** ±5d | **Week 8** ± 7d[d] |
| Informed consent | X | | | | | | |
| Confirmation of OA of the knee (K-L grade 1- 4) based on radiographs[e] | X | | | | | | |
| Confirmation of OA of the knee based on American College of Rheumatology diagnostic criteria | X | | | | | | |
| Inclusion/exclusion criteria | X | | | | | | |
| Height and weight (including body mass index) | X | | | | | | |
| History of cancer | X | | | | | | |
| Knee pain with walking (last 24 hours; NPRS of 0-10) | X | X[h] | X | X[h] | X | X | X |
| Demographics, medical history, OA medications & treatment history[f] | X | | | | | | |
| Hospital Anxiety and Depression Scale (HADS) | X | | | | | | |
| Fibromyalgia Symptom Scale Score (FSS) | X | | | | | | |
| Knee circumference | X | | | | | | |
| Physical examination[g] | X | X[h] | | X[h] | | | X |
| 12-Lead electrocardiogram | X | X[h] | | | | | X |
| Clinical laboratory testing[i] | X | | | Xi | | | X |
| Urine drug screen[j] | X | X[h] | | | | X | X |
| Urine pregnancy test[k] | X | X[h] | | X[h] | | X | X |
| Vital signs | X | X[l] | | X[l] | | X | X |

| | Screening Visit | Treatment #1 (single knee)* | Phone F/U | Treatment #2 (Bilateral knees only)* | Phone F/U (Bilateral knees only) | Efficacy Safety | Efficacy Safety/ Early Termination Visit |
|---|---|---|---|---|---|---|---|
| **Clinic Visit (V) or Telephone Visit (TV)** | **V1** | **V2** | **TV3**[a] | **V4**[b] | **TV5**[a,b] | **V6** | **V7** |
| **Study Day/Week** | **Day -14 to Day 1**[c] | **Day 1** | **Day 3** ±1d | **Day 7 (Week 2)** (-2/+5 d) | **V4 +3d** ±1d | **Week 4** ±5d | **Week 8** ± 7d[d] |
| Issue/review/collect paper diary | X | X[h] | | X[h] | | X | X |
| Sensory testing | | X[h] | | X[h] | | | X |
| CNTX-4975-05 injection (dosing)[l] (30-minute post-injection observation required) | | X | | X | | | |
| Injection site assessment (erythema, edema)[n] | | X | | X | | X | |
| Subject assessment of procedure pain (scale of 0-4) [o] | | X | X | X | X | | |
| Knee Injury and Osteoarthritis Outcome Score (KOOS) | | X[w] | | | | X | X |
| Subject satisfaction with treatment procedure[p] | | X | X | X | X | X | X |
| Subject satisfaction with PJR/TJR (as applicable)[p] | | | | | | X | X |
| Retreatment question[q] | | | | | | | X |
| Investigator satisfaction questionnaire[r] | | X | | X | | | X |
| Joint replacement questionnaire[s] | | X | | | | | X |
| Adverse events[t] | | X | X | X | X | X | X |
| Review use of background, analgesic, rescue, and other concomitant medications and therapies[u,v] | X | X | X | X | X | X | X |

Abbreviations: AE=adverse event; d=day; eCRF=electronic case report form; ET=early termination; f/u=follow-up; IA=intra-articular; K-L=Kellgren-Lawrence; NPRS=numeric pain rating scale; NSAID=non-steroidal anti-inflammatory drug; OA=osteoarthritis; PI=principal investigator; PJR=partial joint replacement; TJR=total joint replacement; TV=telephone visit; V=clinic visit

* Sites where crash carts and ACLS-certified personnel are not immediately available will have a window of +/- 14 business days to schedule injections. Once a crash cart and ACLS-certified personnel are available at these sites then all standard windows apply.

a. On Day 3 post-injection (±1 day), study staff will call subjects to assess OA pain, AEs, subject assessment of procedure pain and satisfaction, knee pain with walking, and the use of rescue medication (for bilateral knee injections, calls will occur 3 days after each injection).
b. Only subjects receiving bilateral knee injections will have Visit 4 and Telephone Visit 5.
c. 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 up to 17 days instead of 14 days).

d. If a subject is discontinuing the study before Week 8, the assessments listed for the Week 8/ET Visit should be completed.
e. A pre-screening radiograph of both knees must show evidence of chronic OA with a K-L grade of 1 to 4 in the index knee as determined by the site PI or radiologist. If the subject has radiographs from Centrexion study CNTX-4975i-OA-301 or CNTX-4975i-OA-304, those radiographs and K-L grading should be used for this study.
f. Medical history and demographics, as outlined in the eCRFs. 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 to be recorded include non-invasive treatments (e.g., physical therapy) and previous invasive treatments (e.g., arthrotomy, arthroscopy – with procedure, if known).
g. A complete physical examination (excluding a genitourinary examination) will be performed by the investigator at the Screening Visit and at the final clinic visit (Week 8/ET). A partial physical examination will be performed by the investigator before each injection). 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.
h. To be performed before injection of CNTX-4975-05.
i. 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. Hemoglobin A1c will be done at the Screening and Week 8/ET Visits. Subjects are to fast prior to the laboratory sample collections performed at the Screening Visit. If the subject is receiving a second knee injection (in the contralateral knee), labs are not required to be repeated if the injection is within 30 days of the screening lab draw (at the investigator's discretion).
j. Urine drug screen must be confirmed as negative for drugs of abuse prior to treatment. For subjects being treated bilaterally, a Urine Drug Screen is not required prior to the second injection.
k. 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 enrolled or will be discontinued from study participation. These subjects will be followed until the pregnancy is completed, and the health of the infant is known.
l. Vital signs are to be performed standing and sitting within approximately 5 minutes before the injection of IP, and sitting-only vital signs within approximately 5, 15, and 30 minutes minutes after the injection of IP.
m. Each site is to follow their assigned, protocol-specified treatment regimen and the protocol-specified CNTX-4975-05 administration procedures.
n. The injection site will be examined and assessed for erythema and edema by site personnel (using a categorical 4-point scale of none, mild, moderate, or severe [0-3]) on Study Day 1 (Treatment) before injection, after the injection at 1 and 2 hours post-dose, and at the Week 4 Visit. For bilateral knee injections, injection site examinations will be performed before and after each injection. Significant bruising or other clinically significant injection site reactions will be recorded as AEs.
o. Procedure pain will be assessed by asking subjects to rate their index knee pain (1) at rest prior to pre-medication; (2) prior to IA lidocaine (without epinephrine); (3) at rest 10 minutes (± 2 minutes) after IA lidocaine (without epinephrine); (4) at 30 minutes (± 5 minutes) after IA injection of CNTX-4975-05; and (5) at rest at the 1-hour and 2-hour time points after IA injection of CNTX-4975-05 (± 10 minutes).
p. Immediately prior to leaving the clinic, the subject will be asked how satisfied they were with the treatment procedure at that visit, using a 7-point Likert Scale where 1=completely dissatisfied and 7=completely satisfied. Subjects with a PJR/TJR will also compare their satisfaction with PJR/TJR versus the CNTX-4975-05 treatment.
q. Subjects will be asked whether they would undergo the study treatment again.
r. The investigator will rate their satisfaction with each subject's study treatment (at V2 and V4 if applicable) and the treatment procedure (at V7).
s. The investigator will judge the likelihood of the need for joint replacement surgery, based on KOOS subscales and subject satisfaction outcomes. The subject will judge the likelihood of the desire for joint replacement surgery, based on their personal response to treatment with CNTX-4975-05.
t. Collection of AEs will begin from the time of signing the informed consent form through the Week 8/ET Visit. On Day 1, the AE assessment must be performed pre-dose. Treatment-emergent AEs will be collected from the time of the injection of CNTX-4975-05 through the Week 8/ET Visit. Potentially

related AEs that are ongoing at the Week 8/ET Visit will be followed until they are stable, resolved, no longer clinically significant (in the opinion of the investigator), or until 4 weeks after the study is completed.

u. Subjects may come into the study with a single analgesic of their choice for their OA knee pain (prescription or OTC). The current pain medication must be identified as that taken only for OA knee pain, not for another pain indication. The subjects will complete a daily paper diary of their background knee analgesic medications during the screening period and throughout the trial.
v. Subjects may take rescue medication for pain of the index knee as needed. Subjects should not take rescue medication within 24 hours 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 their paper diary. Additional rescue medication details will be collected at study visits and follow-up telephone calls and recorded in the source documents and eCRF.
w. For subjects being treated bilaterally, KOOS will be assessed on both knees prior to the first injection but is not required to be completed prior to the second injection.

## 3 TABLE OF CONTENTS

## 3.1 LIST OF TABLES

## REASONS FOR AMENDMENT

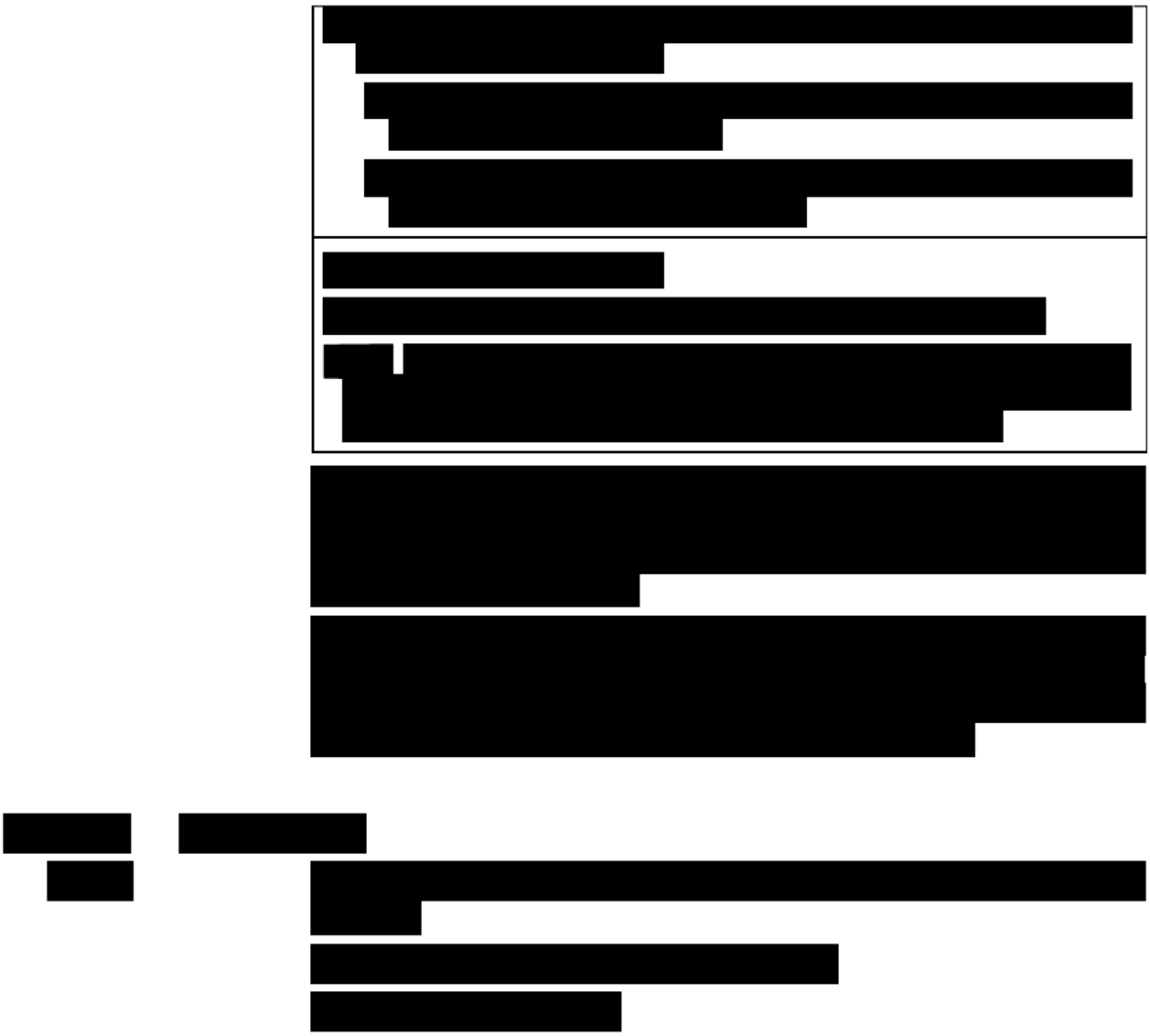
1. The addition of acute allergic/anaphylactic/anaphylactoid reaction as an adverse event of special interest, with new precautions, clinical criteria, assessments, and treatment protocols.
2. The addition of vital sign assessments 15 and 30 minutes after injection of study drug.
3. The addition of a 30-minute post-injection observation period to ensure that subjects do not have a hypersensitivity reaction/anaphylaxis.
4. The addition of crash carts and ACLS-certified personnel to the requirements at each study site.

## SUMMARY OF AMENDED SECTIONS

[redacted]

[redacted]

[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 |
| AE | adverse event |
| ATC | Anatomical Therapeutic Chemical class |
| AUC | area under the curve |
| $AUC_{0\text{-last}}$ | maximum systemic exposure |
| bid | twice daily |
| BMI | body mass index |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| Cmax | maximum plasma concentration |
| CRA | clinical research associate |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| FDA | Food and Drug Administration |
| FSS | Fibromyalgia Symptom Scale Score |
| GCP | Good Clinical Practice |
| HADS | Hospital Anxiety and 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 |
| IEC | Independent Ethics Committee |
| IND | investigational new drug |
| IP | investigational product |
| IRB | Institutional Review Board |
| IS | investigator satisfaction |

| | |
|---|---|
| ITT | intent-to-treat |
| K-L | Kellgren-Lawrence |
| KOOS | Knee Injury and Osteoarthritis Outcome Score |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | mixed-model repeated measures |
| NPRS | numeric pain rating scale |
| NSAID | non-steroidal anti-inflammatory drug |
| OA | osteoarthritis |
| OARSI | Osteoarthritis Research Society International |
| OMERACT | Outcome Measures in Rheumatology |
| OTC | over the counter |
| PJR | partial joint replacement |
| qd | once daily |
| QOL | quality of life |
| QTc | QT interval corrected for heart rate |
| RR | respiratory rate |
| SAE | serious adverse event |
| SD | standard deviation |
| SS | subject satisfaction |
| t½ | half-life |
| TJR | total joint replacement |
| TRPV1 | transient receptor potential vanilloid subfamily member 1 |
| UAE | unexpected adverse event |
| US | United States |
| WOMAC | Western Ontario and McMaster Universities Osteoarthritis Index |

# 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. 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, non-steroidal 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 United States (US) Food and Drug Administration (FDA) and European Medicines Agency 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]

### 5.1.2 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 [redacted] were injected prior to subjects undergoing a total knee joint replacement (TJR). 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] CNTX-4975 to placebo (1:1 randomization, N=12), showed that [redacted] 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] CNTX-4975 via intra-articular (IA) injection [redacted]

In an open-label study (CNTX-4975-114-02P, N=54), subjects received doses ranging from [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 OA 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 of capsaicin into the knee 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 Numeric 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) 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 hours 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.

Two phase 3 pivotal studies will be conducted in the US in approximately 325 subjects with moderate-to-severe OA knee pain. Study CNTX-4975i-OA-301 is a randomized, double-blind, placebo-controlled, single-injection, 52-week study to evaluate the efficacy and safety of a single injection (at Baseline) 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-304, will be conducted in the US using a similar design to CNTX-4975i-OA-301, except there will be both an initial injection (at Baseline) and a second injection [redacted] of [redacted] of CNTX-4975-05, compared to placebo.

### 5.1.3 Pharmacokinetics of Qutenza® Topical 8% Capsaicin Patch versus Intra-articular CNTX-4975-05

Topical capsaicin is approved by the FDA for treatment of post-herpetic neuralgia (Qutenza®; topical 8% capsaicin patch). Each patch contains 179 mg of capsaicin, of which approximately 0.9% (~1.6 mg) is delivered to the skin during a 60-minute application (Center for Drug Evaluation and Research, Application Number: 22-395 Cross Discipline Team Leader Review). A total of 4 Qutenza® patches may be applied at one time, with repeat dosing up to every 3 months (package insert).

Data collected to date suggest that *trans*-capsaicin solutions, formulated with PEG300 or in an aqueous formulation, such as CNTX-4975-05, minimizes long-term systemic exposure, as indicated by the average maximum plasma concentration ($C_{max}$) and the average maximum systemic exposure ($AUC_{0\text{-}last}$) to *trans*-capsaicin being below [redacted], respectively. [redacted] For comparison, these exposure concentrations are similar to those seen with the approved Qutenza® patch in subjects with post-herpetic neuralgia.

For subjects with bilateral knee osteoarthritis IA CNTX-4975-05 treatment, separated by 1 week, each knee receives [redacted], with the total dose delivered systemically is [redacted]. In the case of Qutenza®, a maximum of 4 patches may be applied simultaneously, giving a delivered dose of approximately 6.4 mg. This provides approximately a [redacted]-fold safety margin for the total systemic

dose exposure, relative to the total [redacted] exposure of CNTX-4975-05, and approximately a [redacted]-fold safety margin for the single application, as the capsaicin systemic exposure is less than one day.

## 5.2 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, 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 1% or 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 is provided in the current version of the investigator's brochure (IB).[3] The investigator must become familiar with all sections of the CNTX-4975-05 IB before the start of the study.

# 6 OBJECTIVES

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

## 6.1 Primary Efficacy Objective

The primary objective is to determine the optimal procedures for administering CNTX-4975-05 as a single IA injection into knee(s) with OA, balancing comfort and ease of use of methods of cooling and administration.

## 6.2 Secondary Efficacy Objectives

The secondary efficacy objectives are:

- To describe the clinical benefit of CNTX-4975-05 treatment at Week 8 in a single knee with OA
- To describe the clinical benefit at Week 8 of treating bilateral knee OA with a single injection to each knee
- To describe the clinical benefit at Week 8 of treating a single knee with OA in subjects with partial joint replacement (PJR) or TJR in the contralateral knee
- To evaluate subject satisfaction (SS) with the overall benefit of CNTX-4975-05
- To evaluate SS with CNTX-4975-05 relative to SS with contralateral knee PJR or TJR
- To evaluate SS and investigator satisfaction (IS) with different treatment regimens
- To evaluate the responders to treatment through 8 weeks

## 6.3 Exploratory Efficacy Objectives

The exploratory efficacy objectives are:

- To explore the likelihood of the need for joint replacement surgery, based on clinical benefit and the subject's assessment of their improvement at Week 8
- To explore the effect of subject characteristics (including Kellgren-Lawrence [K-L] grade, sex, body mass index [BMI], age, unilateral versus bilateral knee OA, unilateral versus bilateral injections, and history of contralateral PJR or TJR) on the clinical benefit of CNTX-4975-05 at each study visit through Week 8/Early Termination (ET)
- To explore changes in the frequency of use of background analgesic medication for pain in the injected knee(s) throughout the study period

## 6.4 Safety Objective

The safety objective is:

- To further evaluate the safety of a single IA injection of [redacted] CNTX-4975-05 to one or both knees in subjects with chronic moderate to severe unilateral or bilateral knee OA pain

# 7 STUDY DESIGN

## 7.1 Overall Study Design and Plan

This is an open-label, single injection (per knee), 8-week study to evaluate the comfort and ease of use of 5 different treatment regimens, and to evaluate the efficacy and safety of a single IA injection, in one or both knees, of [redacted] CNTX-4975-05 in subjects with chronic, moderate-to-severe knee OA pain.

The study population will contain 3 types of subjects, with a targeted minimum of 150 subjects of each type:

1. Subjects with unilateral or bilateral OA of the knee, with one knee (the index knee) with moderate to severe pain (K-L grade 1-4) and the other knee (the contralateral knee) with no to mild pain. These subjects will receive an injection of CNTX-4975-05 into the index knee only.
2. Subjects with bilateral OA of the knees, with both knees having moderate to severe pain (K-L grade 1-4, with worse pain being the index knee). These subjects will receive an injection of CNTX-4975-05 into each knee (1 week apart).
3. Subjects who have unilateral OA of the knee, with one knee with moderate to severe pain (the index knee [K-L grades 1-4]) and previous PJR or TJR in the other knee (the contralateral knee). These subjects will receive an injection of CNTX-4975-05 into the index knee only.

All subjects will receive [redacted] CNTX-4975-05 injected into the index knee; subjects with bilateral OA who qualify will receive an injection into both knees (injections will be separated by 1 week). In addition, all subjects will undergo 1 of 5 treatment regimens consisting of pre- and post-injection cooling with a cold pack (Breg or Elasto-Gel, with varying durations), an IA injection of 15 mL of lidocaine without epinephrine (1% or 2%, depending on the assigned regimen), and either a single injection needle or separate needles, depending on the assigned regimen.

Each site will be randomly assigned 1 of the following 5 treatment regimens to be employed for ALL subjects at that site:

| Group | Cooling Device | • Pre-cool duration<br>• Lidocaine %<br>• Post-lido cool | Needle | Post-dose cooling |
|---|---|---|---|---|
| 1. Breg Cooling Control Group | Breg ice water pump | • 15 mins<br>• 2% lidocaine<br>• 30 mins | separate needles for lidocaine and study drug | 30 to 90 mins as needed |
| 2. Gel Pack Cooling Group | Elasto-Gel | • 40 mins<br>• 2% lidocaine<br>• 10 mins | separate needles for lidocaine and study drug | 10 to 90 mins as needed |
| 3. Shortened Gel Pack Cooling Group | Elasto-Gel | • 30 mins<br>• 2% lidocaine<br>• 5 mins | separate needles for lidocaine and study drug | up to 90 mins as needed |
| 4. Single Needle Injection Gel Pak Cooling Group-2% Lidocaine | Elasto-Gel | • 45 mins<br>• 2% lidocaine<br>• no cooling | single needle for the lidocaine and study drug administrations | up to 90 mins as needed |
| 5. Single Needle Injection Gel Pack Cooling Group-1% Lidocaine | Elasto-Gel | • 45 mins<br>• 1% lidocaine<br>• no cooling | single needle for the lidocaine and study drug administrations | up to 90 mins as needed |

On Day 3 post-injection, study staff will call subjects to assess AEs, subject assessment of procedure pain, knee pain with walking, and the use of rescue medication (for bilateral knee injections, calls will occur 3 days after each injection). Subjects will return to the clinic at Weeks 4 and 8 for study assessments.

Efficacy will be assessed on the OA index knee (and contralateral knee in bilateral knee injection subjects) using a numeric pain rating scale (NPRS); the Knee Injury and Osteoarthritis Outcome Score (KOOS), which includes subscales for pain, other symptoms, activities of daily living, sports and recreation, and quality of life (QOL); a joint replacement questionnaire; a subject satisfaction questionnaire; an investigator satisfaction questionnaire; and rescue medication use. Pain with walking will also be collected and assessed for the contralateral knee.

For subjects with bilateral knee injections, the contralateral knee will be assessed using the same scales as the index knee, and the effect of bilateral knee injections will be combined as a composite score to examine the overall benefit. The index knee in these subjects is the one with worse pain with walking. Where both knees have equal pain with walking, then the knee on the subject's dominant side will be designated the index knee.

Safety will be assessed by injection site assessments (erythema and edema), assessment of procedure pain, AEs, physical examination findings, vital sign measurements, 12-lead electrocardiograms (ECGs), clinical laboratory test results, and sensory testing.

### 7.2 Discussion of Study Design

This open label study, CNTX-4975i-OA-303, is an 8-week study to evaluate the efficacy and safety of a single IA injection (per knee, as applicable) of CNTX-4975-05 in subjects with chronic, moderate-to-severe OA knee pain. Procedural pain associated with IA injection of CNTX-4975-05 will be controlled primarily through adjunct controlled joint cooling and secondarily by pre-medication with IA lidocaine. The planned safety and tolerability and efficacy assessments are standard and appropriate.

### 7.3 Study Site(s)

The study will take place at no more than 45 concurrent sites in the US, Germany, Spain and the United Kingdom. Each site is anticipated to screen a sufficient number of subjects to be able to enroll approximately 18 subjects. A study site with an acceptable recruitment rate and acceptable quality metrics may be allowed to recruit more subjects if other sites have low enrollment.

# 8 SUBJECT POPULATION

## 8.1 Selection of Study Population

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).
2. Confirmation of OA of the knee: radiography of both knees using standard standing films (scored by the investigator) or using the fixed flexion method, taken during the Screening Visit (prior radiographs of the knees of sufficient quality that have been taken within 2 years of the Screening Visit may be used for K-L grading). The index knee must show evidence of chronic OA with a K-L grade of 1, 2, 3 or 4. Subjects who were screen failures for the US CNTX-4975i-OA-301 or CNTX-4975i-OA-304 trials may be considered for this trial if the K-L grade of the index knee is 1-4, inclusive.
3. Confirmation of OA of the index knee: American College of Rheumatology (ACR) diagnostic criteria (ACR confirmation of bilateral knee OA for subjects who will have bilateral knee injections of CNTX-4975-05).
4. For subjects for monoarticular knee injection, the index knee must have moderate to severe pain (≥5 and ≤9) at screening associated with OA, which must be stable for a minimum of 6 months prior to Screening, as assessed by the investigator. These subjects may have:
   a) unilateral or bilateral OA, with the index knee having moderate to severe pain, and the contralateral knee having none to mild pain, OR
   b) unilateral or bilateral OA, with the index knee having moderate to severe pain and the other knee having had a PJR or TJR within 5 years of the Screening Visit. The knee with the PJR/TJR is not to be injected with CNTX-4975-05.

   For subjects for bilateral knee injection, the index knee must have moderate to severe pain (≥5 and ≤9) at screening associated with OA, and greater pain in the index knee than in the contralateral knee. Their pain must be stable for a minimum of 6 months prior to Screening, as assessed by the investigator. The index knee in these subjects is the one with the worst pain with walking. Where both knees have equal pain with walking, then the knee on the subject's dominant side will be designated the index knee.

   For qualifying knee pain with walking, subjects will use an NPRS (0-10; 0=no pain, 10=worst possible pain) to rate their knee pain with walking (both knees, except knees with PJR/TJR). The PJR/TJR pain should be rated using the NPRS scale, but will not be a qualifying pain score.
5. Body mass index ≤45 kg/$m^2$.

6. 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 AEs;
   b) initial failure to achieve clinically adequate pain relief;
   c) initial pain relief that was not maintained; and/or
   d) 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, the following: NSAIDs (including topical), opioids, duloxetine, other systemic therapy, IA corticosteroids, IA viscosupplements, physical therapy, bracing, and orthotics.
7. 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 CNTX-4975-05 administration
   - Total abstinence from sexual intercourse since the last menses before CNTX-4975-05 administration
   - Intrauterine device
   - Double barrier method (condoms, sponge, diaphragm, with spermicidal jellies or cream).
8. Able to speak, read, and understand the language of the study used for the informed consent.
9. 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 (i.e., without assistance) record responses on the efficacy scales during clinic visits
   e) independently communicate meaningfully with the study personnel
10. Signed informed consent form (ICF) approved by the institutional review board (IRB)/independent ethics committee (IEC).
11. Subjects may come into the study with a single analgesic of their choice for their OA knee pain. The current pain medication must be identified as that taken only for pain in the knee OA or pain in the PJR/TJR, and not for another pain indication. The subjects will complete a daily paper diary of their background knee analgesic medications during the screening period and throughout the trial. Other analgesics may be taken for occasional pain but should not be

taken within 24 hours of a clinic visit; these are to be recorded as concomitant medications, not as rescue/background medication for knee osteoarthritis.

### 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, or open surgery of the index knee in the past 24 months. Joint replacement of the contralateral knee is permitted for subjects who will not receive an injection in the contralateral (natural) knee. For subjects with bilateral knee OA who will receive an injection into both knees, joint replacement surgery of both knees at any time, or open surgery of the index knee in the past 24 months, is excluded.
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 chondromalacia patellae, inflammatory diseases (e.g., rheumatoid arthritis, psoriatic arthritis), 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. Other chronic pain anywhere in the body that requires the use of chronic analgesic medications, including, but not limited to, local painful areas, myofascial pain syndromes, fibromyalgia, genetic, metabolic abnormalities, hematologic, or neuropathic pain.
6. Instability of the index or contralateral knee (e.g., cruciate ligament tear or rupture, significant protruding meniscus, substantial ligamentous laxity, unstable PJR or TJR).
7. Misalignment (>10 degrees varus or valgus) of the index knee on standing.
8. Documented history of neuropathic arthropathy or finding of bony fragmentation in the index knee with imaging (radiographic, computed tomography, or magnetic resonance imaging).
9. Physical/occupational/chiropractic therapy for the lower extremities or acupuncture for the lower extremities within 15 days of Screening, or need for such therapy during the study.
10. Plans to have surgery, other invasive procedures, or IA injections (other than CNTX-4975-05) for either knee while participating in the study.
11. Current use of opioids for any condition other than for OA of the knees injected with CNTX-4975-05) (maximum dose of 15 mg of hydrocodone [or equivalent] per day).
12. Corticosteroid injection into the index or contralateral knee within 90 days of Screening.
13. Received IA viscosupplementation (e.g., Synvisc®, Hyalgan®) within 90 days of Screening.
14. History of allergic reaction to the planned local anesthesia/analgesic regimens, ethylenediaminetetraacetic acid, Kolliphor HS 15, butylated hydroxytoluene, or capsaicin.
15. 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.

16. Is pregnant or is breast feeding.
17. 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.
18. Regular use of anticoagulant blood thinners (except low-dose aspirin, Dabigatran 150 mg once daily [qd], Enoxaparin 40 mg qd, Rivaroxaban 10 mg qd, or Apixaban 2.5 mg twice daily [bid], or clopidogrel 75 mg qd, which are allowed).
19. Active cutaneous disease at the anticipated site of CNTX-4975-05 injection that would prevent the safe administration of CNTX-4975-05.
20. Ulcer or open wound anywhere on the index knee.
21. Specific laboratory abnormalities:
    - Hemoglobin <11.0 g/dL
    - White blood cells $<2.5 \times 10^9$/L
    - Neutrophils $<1.5 \times 10^9$/L
    - Platelets $<100 \times 10^9$/L
    - Aspartate transaminase or alanine transaminase >2 × upper limit of normal
    - Creatinine >1.6 mg/dL
    - Glucose (fasting) >250 mg/dL
    - Hemoglobin A1c (HgbA1c) >9.0%
22. 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.
23. 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.
24. Prior participation in an ALGRX 4975 or CNTX-4975 study.
25. Has any of the following characteristics:
    - 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 an unacceptable level of depression or anxiety as measured by the Hospital Anxiety and Depression Scale (HADS) (a score of ≥11)
- Has unacceptable chronic pain as measured by the Fibromyalgia Symptom Scale Score (FSS) (a score of ≥13)
- Has a positive pregnancy test at the Screening or either 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, 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.

Enrolled 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 will be provided [redacted]

## 9.2 Labeling and Packaging

Labeling and packaging of CNTX-4975-05 will be performed [redacted]

## 9.3 Treatments Administered

All subjects will receive [redacted] CNTX-4975-05 injected IA into the index knee; subjects with bilateral OA will receive an IA injection into both knees (injections will be separated by 1 week).

### 9.3.1 Pre-Medication

Prior to the injection procedure, the investigator may, at his or her discretion, pre-medicate subjects with an oral dose of an opioid or NSAID. The skin at the point of the anticipated injection(s) may also be infiltrated with 1 to 2 mL of lidocaine and/or a topical analgesic such as ethyl chloride spray. It is recommended not to use more than 2 methods of local analgesia about the knee(s) to be injected.

### 9.3.2 Joint Treatment Regimens

All subjects are required to be administered an IA injection of a full 15 mL of lidocaine [without epinephrine] (1% or 2%, depending on the assigned treatment regimen) to ensure: 1) the local targeted concentration of CNTX-4975 in the joint; 2) distension of the joint capsule to improve access of CNTX-4975 to the joint space; and 3) to provide some analgesia. The full 15 mL of lidocaine (without epinephrine) and the full [redacted] CNTX-4975-05 must be injected into the knee joint, as directed. The 5 flexion-extension moves of the knee after IA CNTX-4975-05 is injected into the knee also improve access of CNTX-4975 to the entire joint space. The lidocaine may have some modest effect on pain, but the concentration and dispersion of CNTX-4975 into the joint are the primary reasons for lidocaine use.

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.

Each site will be randomly assigned 1 of the following 5 treatment regimens to be employed for ALL subjects at that site:

| Group | Cooling Device | • **Pre-cool**<br>• **Lidocaine %**<br>• **Post-lido cool** | Needle | Post-dose cooling |
|---|---|---|---|---|
| 1. Breg Cooling Control Group | Breg ice water pump | • 15 mins<br>• 2% lidocaine<br>• 30 mins | **Separate** needles for lidocaine and CNTX-4975-05 | 30 to 90 mins as needed |
| 2. Gel Pack Cooling Group | Elasto-Gel | • 40 mins<br>• 2% lidocaine<br>• 10 mins | **Separate** needles for lidocaine and CNTX-4975-05 | 10 to 90 mins as needed |
| 3. Shortened Gel Pack Cooling Group | Elasto-Gel | • 30 mins<br>• 2% lidocaine<br>• 5 mins | **Separate** needles for lidocaine and CNTX-4975-05 | up to 90 mins as needed |
| 4. Single Needle Injection Gel Pak Cooling Group-2% Lidocaine | Elasto-Gel | • 45 mins<br>• 2% lidocaine<br>• no cooling | **Single** needle for lidocaine and CNTX-4975-05 | up to 90 mins as needed |
| 5. Single Needle Injection Gel Pack Cooling Group-1% Lidocaine | Elasto-Gel | • 45 mins<br>• 1% lidocaine<br>• no cooling | **Single** needle for lidocaine and CNTX-4975-05 | up to 90 mins as needed |

See study manual for specific instructions on the use of the Breg Cooling Wrap and the Elasto-Gel Cooling Wrap.

1. **Breg Cooling Control Group** (used in protocols CNTX-4975i-OA-301 and CNTX-4975i-OA-304 for comfort and blinding of the protocols)
    a. Controlled joint cooling wrap with an ice water pump system (Breg Cooler) will be applied 15 minutes prior to IA injection of the full 15 mL 2% lidocaine (without epinephrine) into the knee joint using standard aseptic techniques.
    b. Inject IA the full 15 mL of 2% lidocaine (without epinephrine) into the knee joint using appropriate aseptic techniques.
    c. Controlled cooling will be resumed for a further 30 minutes after the IA injection of the full 15 mL 2% lidocaine (without epinephrine) into the knee joint.
    d. The cooling device will be removed, and CNTX-4975-05 IA injection will be administered using standard aseptic techniques.
    e. Controlled cooling will be reapplied for a minimum of 30 minutes, and up to 90 minutes, as needed, after CNTX-4975-05 injection, depending on the subject's comfort. The cooling may be discontinued after a minimum of 30 minutes after IA CNTX-4975-05 injection, if the subject has a pain level that is acceptable for the subject and investigator (0-4 scale: none, mild, moderate, moderately severe, and severe).

2. **Gel Pack Cooling Group**
    a. Gel pack cooling applied for 40 minutes to the knee using the gel pack over a stockinette or light-weight pants. This may be outside of the exam room, but at the investigator's discretion, may be done in the exam room. If done outside the exam room, subject may be moved to the exam room ± 5 minutes of the 40-minute cooling (with gel pack remaining on the knee).
    b. Inject IA the full 15 mL 2% lidocaine (without epinephrine) into the knee joint using appropriate aseptic techniques.
    c. Gel pack cooling is applied for 10 minutes to the knee using the gel pack over a stockinette or light-weight pants.
    d. The gel pack will then be removed, and CNTX-4975-05 IA injection will be administered using appropriate aseptic techniques.
    e. Gel pack cooling will be reapplied for a minimum of 10 minutes, and up to 90 minutes, as needed, after CNTX-4975-05 injection, depending on the subject's comfort. The cooling may be discontinued after a minimum of 10 minutes after IA CNTX-4975-05 injection. If the subject has a pain level that is acceptable for the subject and investigator (0-4 scale: none, mild, moderate, moderately severe and severe).
3. **Shortened Gel Pack Cooling Group**
    a. Gel pack cooling applied for 30 minutes to the knee using the gel pack over a stockinette or light-weight pants. This may be outside of the exam room, but at the investigator's discretion, may be done in the exam room. If done outside the exam room, subject may be moved to the exam room ± 5 minutes of the 30-minute cooling (with gel pack remaining on the knee).
    b. Inject IA the full 15 mL 2% lidocaine (without epinephrine) into the knee joint using appropriate aseptic techniques.
    c. Gel pack cooling is applied for 5 minutes to the knee using the gel pack over a stockinette or light-weight pants.
    d. The gel pack will then be removed, and CNTX-4975-05 IA injection will be administered using appropriate aseptic techniques.
    e. Gel pack cooling may be reapplied for up to 90 minutes, as needed, after CNTX-4975-05 injection, depending on the subject's comfort. The subject may remain in the exam room, or be moved to a more comfortable area with the gel pack. The gel pack may be discontinued after IA CNTX-4975-05 injection if the subject has a pain level that is acceptable for the subject and investigator (0-4 scale: none, mild, moderate, moderately severe and severe).
4. **Single Needle Injection Gel Pack Cooling Group-2% IA Lidocaine**
    a. Gel pack cooling applied for 45 minutes to the knee using the gel pack over a stockinette or light-weight pants. This may be outside of the exam room, but at the investigator's discretion, may be done in the exam room. If done outside the exam room, subject may be moved to the exam room ± 5 minutes of the 4--minute cooling (with gel pack remaining on the knee).

b. Inject IA the full 15 mL 2% lidocaine (without epinephrine) into the knee joint using appropriate aseptic techniques.
c. After the 2% lidocaine IA injection, CNTX-4975-05 IA injection, using the same needle, will be injected into the knee joint using appropriate aseptic techniques after 3 minutes of the 2% lidocaine (without epinephrine).
d. Gel pack cooling may be reapplied for up to 90 minutes, as needed, after CNTX-4975-05 injection, depending on the subject's comfort. The subject may remain in the exam room, or be moved to a more comfortable area with the gel pack. The gel pack may be discontinued after a minimum of 10 minutes after IA CNTX-4975-05 injection if the subject has a pain level that is acceptable for the subject and investigator (0-4 scale: none, mild, moderate, moderately severe and severe).

5. **Single Needle Injection Gel Pack Cooling Group-1% IA Lidocaine**
   a. Gel pack cooling applied for 45 minutes to the knee using the gel pack over a stockinette or light-weight pants. This may be outside of the exam room, but at the investigator's discretion, may be done in the exam room. If done outside the exam room, subject may be moved to the exam room ± 5 minutes of the 40-minute cooling (with gel pack remaining on the knee).
   b. Inject IA the full 15 mL 1% lidocaine (without epinephrine) into the knee joint using appropriate aseptic techniques.
   c. After the 1% lidocaine IA injection, CNTX-4975-05 IA injection, using the same needle, will be injected into the knee joint using appropriate aseptic techniques after 3 minutes of the 1% lidocaine (without epinephrine).
   d. Gel pack cooling may be reapplied for up to 90 minutes, as needed, after CNTX-4975-05 injection, depending on the subject's comfort. The subject may remain in the exam room, or be moved to a more comfortable area with the gel pack. The gel pack may be discontinued after IA CNTX-4975-05 injection if the subject has a pain level that is acceptable for the subject and investigator (0-4 scale: none, mild, moderate, moderately severe and severe).

### 9.3.3 Injection of CNTX-4975-05

It is recommended that the CNTX-4975-05 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, CNTX-4975-05 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.

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

### 9.4 Dispensing and Storage

The IP, CNTX-4975-05, is to be used exclusively in the clinical study according to the instructions of this protocol. The investigator is responsible for dispensing CNTX-4975-05 according to the dosage scheme and for ensuring proper storage of the IP.

Until CNTX-4975-05 is administered to the subjects, it must be stored [redacted] 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

All enrolled subjects will be assigned to CNTX-4975-05. Assignment to unilateral or bilateral injections will be determined by the subject's OA pain and previous joint replacement status. The subject's joint treatment regimen will be based on the site at which the subject is enrolled.

Unilateral or Bilateral Injections: The study population will contain 3 types of subjects, with a targeted minimum of 150 subjects of each type:

1. Subjects with unilateral or bilateral OA of the knee, with one knee (the index knee) with moderate to severe pain (K-L grade 1-4) and the other knee (the contralateral knee) with no to mild pain. **These subjects will receive an IA injection in the index knee only.**
2. Subjects with bilateral OA of the knees, with both knees having moderate to severe pain (K-L grade 1-4, with worse pain in the index knee). **These subjects will receive an IA injection into each knee (1 week apart).** The index knee in these subjects is the one with the worst pain with walking. Where both knees have equal pain with walking, then the knee on the subject's dominant side will be designated the index knee.
3. Subjects who have unilateral or bilateral OA of the knee, with one knee with moderate to severe pain (the index knee [K-L grades 1-4]) and previous PJR or TJR in the other knee (the contralateral knee). **These subjects will receive an IA injection into the index knee only.**

Joint Treatment Regimen: Each site will be randomly assigned 1 of the 5 joint treatment regimens to be employed for ALL subjects at that site. The joint treatment regimens are listed in Section 9.3.2.

### 9.6 Blinding and Unblinding Treatment Assignment

This is an open-label study.

### 9.7 Selection of Dose in the Study

The results of a previous OA Phase 2 study, CNTX-4975-OA-502, conducted by the sponsor, demonstrated that [redacted] CNTX-4975 is an effective and well-tolerated treatment for subjects with moderate-to-severe pain from OA in the index knee. A dose [redacted] resulted in a significant decrease in pain with walking relative to placebo as early as [redacted] after CNTX-4975-05 injection, and the pain reduction typically continued beyond [redacted] 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 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 into the index knee (and the contralateral knee, if applicable) at the study site under the surveillance of appropriate study personnel on Study Day 1 (Treatment Day 1). If applicable, injection of the contralateral knee will occur 1 week later.

### 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

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 over the counter [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

Subjects may come into the study with a single analgesic of their choice for their OA knee pain. (prescription or OTC). The current pain medication is to be taken only for OA knee pain, not for another pain indication (such as knee pain in the knee with a PJR/TJR). This medication will be considered the subject's "background" medication; for subjects having both knees injected with CNTX-4975, background medications are those used to treat either knee. From screening through the end of the study, subjects are not to change to a different background pain medication. Subjects are permitted to change their dosage of background medication and/or discontinue their

background medication. Any change in dose, change in dose frequency, or discontinuation of background medication should be entered into the paper diary and the eCRF.

Subjects may take another analgesic as rescue medication for pain of the index knee as needed. The rescue medication is not allowed to be in the same drug class as the ongoing background medication. For example, subjects will not be allowed to take tramadol as a rescue medication if they are already taking an opioid, or an NSAID as rescue if they are already taking an NSAID. Data on the type of rescue and background medication, and the daily dose, will be reported daily by the subjects using a paper diary. Additional rescue medication details will be collected at study visits and follow-up telephone calls in the source documents and eCRF.

Subjects should not take rescue medication for knee osteoarthritis pain, or for other pain, within 24 hours prior to a clinic visit.

Other analgesics may be taken for occasional pain, but should not be taken within 24 hours of a clinic visit; these are to be recorded as concomitant medications, not as rescue or background medication for knee osteoarthritis.

### 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.
- Current use of opioids for any condition other than for OA of the injected knees or PJR/TJR knees (maximum dose of 15 mg of hydrocodone [or equivalent] per day as background medication allowed at entry).
- Regular use of anticoagulant blood thinners (except low-dose aspirin, Dabigatran 150 mg qd, Enoxaparin 40 mg qd, Rivaroxaban 10 mg qd, or Apixaban 2.5 mg bid, which are allowed).
- Use of an investigational medication within 30 days or 5 pharmacokinetic or pharmacodynamic half-lives (whichever is longer) prior to Screening or while participating in the study.
- Physical/occupational/chiropractic therapy for the lower extremities or acupuncture for the lower extremities within 15 days of Screening, or need for such therapy during the course of the study.
- Joint replacement surgery of the index knee at any time, 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. For subjects with bilateral knee OA who will receive an injection into both knees, joint replacement surgery of both knees at any time, or open surgery of the index knee in the past 24 months, is excluded.
- Surgery, or other invasive procedures, or IA injections (other than CNTX-4975-05) while participating in the study.
- Subjects should not take a hot bath or shower, or expose the injected knee(s) to external heat, within 12 hours after the injection.

The subject should be excluded from study participation if they have taken any medication prior to treatment 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 2). 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 Visits

### 10.1.1 Screening Visit, Day -14 to Day 1, Visit 1

The subject must be screened within 14 days before enrollment into the study. The following procedures will be performed at screening.

- Written informed consent
- Confirmation of knee OA K-L grade (1 to 4) of the knee, based on radiographs
- Confirmation of diagnosis of knee OA, based on ACR diagnostic criteria
- Inclusion/exclusion criteria
- Height and weight (BMI)
- History of cancer
- Knee pain with walking (during last 24 hours, assessed in the clinic using NPRS of 0-10)
- Demographics
- Medical history, including current OA medications (prescription and non-prescription medications) and treatment history (including noninvasive or previous invasive treatments)
- HADS
- FSS
- Knee circumference
- Complete physical examination
- ECG
- Clinical laboratory testing (fasting)
- Urine drug screen
- Urine pregnancy test
- Vital signs
- Issue paper diary to the subject with instructions on use and recording of background analgesic and rescue medication for index knee (or bilateral knee for subjects being treated for both knees)

### 10.1.2 Treatment, 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.

- Knee pain with walking (during last 24 hours, assessed in the clinic using NPRS of 0-10)
- Partial physical examination
- ECG
- Urine drug screen
- Urine pregnancy test
- Vital signs (before and after injection of CNTX-4975-05). 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 standing and sitting 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.
- Injection site assessment (erythema, edema) before injection and 1 and 2 hours after the injection
- Review paper diary
- Sensory testing
- Subject assessment of procedure pain (using 0-4 scale)
    - at rest prior to pre-medication;
    - prior to IA lidocaine (without epinephrine);
    - at rest 10 minutes (±2 minutes) after IA lidocaine (without epinephrine);
    - at 30 minutes (±5 minutes) after IA injection of CNTX-4975-05; and
    - at rest at the 1-hour and 2-hour time points after IA injection of CNTX-4975-05 (±10 minutes).
- CNTX-4975-05 injection procedure, including lidocaine and cooling
- KOOS
- IS questionnaire
- Joint replacement questionnaire
- AEs
- Review use of background, analgesic, rescue, and other concomitant medications and therapies
- SS with treatment procedure

### 10.1.3 Day 3, Telephone Visit 3

- Knee pain with walking (during last 24 hours, assessed using NPRS of 0-10)
- Subject assessment of procedure pain (using 0-4 scale)
- AEs
- Review use of background, analgesic, rescue, and other concomitant medications and therapies
- SS with treatment procedure

### 10.1.4 Day 1 of Treatment 2 (Bilaterally Treated Subjects Only), Visit 4

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 should be immediately available. See section 11.2.1 for details.

The following procedures will be performed on Day 1 of Treatment 2 (bilaterally treated subjects only).

- Knee pain with walking (during last 24 hours, assessed in the clinic using NPRS of 0-10)
- Partial physical examination
- Clinical laboratory testing
- Urine pregnancy test
- Vital signs (before and after injection of CNTX-4975-05). 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 standing and sitting 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.
- Assessment of injection site on second knee (erythema, edema) before injection and 1 and 2 hours after the injection
- Review paper diary
- Sensory testing
- Subject assessment of procedure pain (using 0-4 scale)
    - at rest prior to pre-medication;
    - prior to IA lidocaine (without epinephrine);
    - at rest 10 minutes (±2 minutes) after IA lidocaine (without epinephrine);
    - at 30 minutes (±5 minutes) after IA injection of CNTX-4975-05; and
    - at rest at the 1-hour and 2-hour time points after IA injection of CNTX-4975-05 (±10 minutes).
- CNTX-4975-05 injection procedure, including lidocaine and cooling

- IS questionnaire
- AEs
- Review use of background, analgesic, rescue, and other concomitant medications and therapies
- SS with treatment procedure

### 10.1.5 Day 3 of Treatment 2 (Bilaterally Treated Subjects Only), Telephone Visit 5

- Knee pain with walking (during last 24 hours, assessed using NPRS of 0-10)
- Subject assessment of procedure pain (using 0-4 scale)
- AEs
- Review use of background, analgesic, rescue, and other concomitant medications and therapies
- SS with treatment procedure

### 10.1.6 Week 4 Follow-up, Visit 6

- Knee pain with walking (during last 24 hours, assessed in the clinic using NPRS of 0-10)
- Urine drug screen
- Urine pregnancy test
- Vital signs
- Injection site assessment (erythema, edema)
- Review paper diary
- KOOS
- SS with treatment procedure
- SS with PJR/TJR (if applicable)
- AEs
- Review use of background, analgesic, rescue, and other concomitant medications and therapies

### 10.1.7 Week 8, Visit 7 (or Early Termination)

- Knee pain with walking (during last 24 hours, assessed in the clinic using NPRS of 0-10)
- Complete physical examination
- ECG
- Clinical laboratory testing
- Urine drug screen

- Urine pregnancy test
- Vital signs
- Sensory testing
- Review and collect paper diary
- KOOS
- SS with study treatment
- SS with PJR/TJR (if applicable)
- Subject retreatment question
- IS questionnaire
- Joint replacement questionnaire
- AEs
- Review use of background, analgesic, rescue, and other concomitant medications and therapies

## 10.2 Study Duration

### 10.2.1 Overall Study Schedule

The overall study duration is expected to be 13 months, with 10 months of active enrollment and about 3 months for screening and treatment follow-up.

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

1. Screening Period: up to 15 days
2. Treatment Period (open-label): 1 day per knee treated, maximum 2 days
3. Post-treatment Period: 8 weeks from the first CNTX-4975-05 IA injection

The maximum treatment duration for each subject is 2 days. The maximum study duration for each subject is approximately 10 weeks.

## 10.3 Assessments

### 10.3.1 Efficacy

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

At each visit, subjects will assess their average daily index knee pain 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). Subjects will rate each knee separately.

#### 10.3.1.2 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, function in sport and recreation, and knee-related 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.

#### 10.3.1.3 Joint Replacement Questionnaire

The investigator will judge the likelihood of the need for joint replacement surgery, based on KOOS subscales and subject satisfaction outcomes.

The subject will judge the likelihood of the desire for joint replacement surgery, based on their personal response to treatment with CNTX-4975-05.

#### 10.3.1.4 Subject Satisfaction Questionnaire

Subjects will be asked to rate their overall satisfaction with the treatment procedure. Subjects with a PJR/TJR will also compare their satisfaction with their PJR/TJR versus their CNTX-4975-05 treatment. These will be rated using the following 7-point scale:

1 – Completely dissatisfied

2 – Mostly dissatisfied

3 – Somewhat dissatisfied

4 – Neither satisfied or dissatisfied

5 – Somewhat satisfied

6 – Mostly satisfied

7 – Completely satisfied

Subjects will also be asked whether they would undergo the study treatment again.

#### 10.3.1.5 Investigator Satisfaction Questionnaire

The investigator will rate his or her satisfaction with the subject's study treatment.

The investigator will rate his or her satisfaction with the treatment procedure.

#### 10.3.1.6 Rescue Medication Use

Subjects may take rescue medication for pain of the index knee as described in Section 9.12.1, except that they should not use rescue medication within 24 hours before a planned study visit. Data on the type of rescue medication and background analgesics for knee OA, and the daily dose, will be reported daily by the subject on a paper diary from Screening through Week 8/ET. 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 assessments (erythema and edema), assessment of procedure pain, AEs, physical examination findings, vital sign measurements, 12-lead ECG findings, clinical laboratory test results, and sensory testing.

#### 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 2).

| | |
|---|---|
| Hematology | hemoglobin, hematocrit, red blood cell count, red blood cell 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 | Only for women of childbearing potential. A serum pregnancy test will be performed if the urine pregnancy test is positive. |
| Urine Drug Screen | amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and tetrahydrocannabinol |
| Other | HgbA1c |
| Knee Radiographs | Radiographs of both knees using standard standing films or using the fixed flexion method. Scoring will use the Kellgren-Lawrence Grading Scale. |

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.

##### 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 or her assessment of the clinical relevance in the appropriate eCRF.

All laboratory values that, 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 be conducted according to the schedule of events, Section 2 and will include systolic and diastolic blood pressure, heart rate (HR) and respiratory rate (RR), and will be measured with the subject standing and also after the subject has been in a sitting position for 5 minutes. Temperature will also be measured at all office visits.

#### 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, Section 2. The investigator should assess periarticular tenderness and pain in the soft tissue of the injected knee(s) at each physical examination and record the results on the eCRF. At each physical examination, 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.

Height and weight will be measured at the Screening Visit. Knee circumference will be measured at Screening.

The principal investigator or his or 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) before each CNTX-4975-05 injection, after each injection at 1 and 2 hours post-dose, and at the Week 4 study visit. 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 before each CNTX-4975-05 injection and at Week 8/ET. 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, the 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 IA lidocaine (without epinephrine); (3) at rest 10 minutes (±2 minutes) after IA lidocaine (without epinephrine); (4) at 30 minutes (±5 minutes) after IA injection of CNTX-4975-05 and (5) at rest at the 1-hour and 2-hour time points after IA injection of CNTX-4975-05 (±10 minutes).

Categorical scoring will be used: none, mild, moderate, moderately severe, or severe.

# 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 Unexpected Adverse Event

An expected AE is one for which the nature or severity is consistent with the known AE profile of the product. For an investigational product, 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) 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).

### 11.1.3 Serious Adverse Events

An 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.*

### 11.1.4 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.

### 11.1.5 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 Week 8/ET Visit.

### 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 11.1.3.

#### 11.2.3.2 Seriousness

The investigator is to evaluate whether the AE meets serious criteria, as described in Section 11.1.3.

#### 11.2.3.3 Action(s) Taken

Action(s) taken may consist of

| | |
|---|---|
| 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 (e.g., 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 eCRF 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.

### 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) (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. Potentially related AEs that are ongoing at the Week 8 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:

Email: [redacted]

Email: [redacted]

Fax number: [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)
- Subject's study number
- Subject's year of birth
- Subject's gender
- 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?")
- 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 (AE, date of occurrence, subject 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] Pharmacovigilance 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 or her health authorities, IRB/ IEC, 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-303 Safety Management Plan). Each investigator is obligated to learn about the reporting requirements for investigators in his or her country. The study monitor may be able to assist with this.

#### 11.2.7.2 Non-serious Adverse Events

Non-serious AEs will be recorded in the eCRF and reported by [redacted] 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 CNTX-4975-05 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 CNTX-4975-05 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 [redacted] 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 CNTX-4975-05 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 will not be used in this study.

# 13 STATISTICS

The statistical analysis was developed to meet the requirements of the US FDA and the European Medicines Agency.

## 13.1 Study Endpoints

### 13.1.1 Primary Efficacy Endpoint

The primary endpoint is assessment of the CNTX-4975-05 treatment regimens, with the Breg Cooling Control Group as the standard, using a combination of 3 assessments of the index knee: 1) pain 30 minutes after CNTX-4975-05 injection (using the 0-4 scale of none, mild, moderate, moderately severe, and severe); 2) subject satisfaction with the treatment regimen; and 3) investigator satisfaction with the treatment regimen.

### 13.1.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Assessment of the primary combined outcome using the contralateral knee for the subjects who received bilateral injections and the index knee for all other subjects
- Assessment of the primary combined outcome for each subject type
- Assessment of the primary combined outcome, using the contralateral knee for the subjects who received bilateral injections
- Percent of Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) responders at Week 8 for subjects with a single CNTX-4975-05 joint injection (index knee, moderate to severe pain index knee, pain not >3 for contralateral knee)
- Percent of OMERACT-OARSI responders at Week 8 for subjects with bilateral knee injections of CNTX-4975-05 (index knee, moderate to severe pain index knee, both knees meeting OMERACT-OARSI responder criteria)
- Percent of OMERACT-OARSI responders at Week 8 for subjects with a single CNTX-4975-05 joint injection (population with index knee, moderate to severe pain index knee, non-index knee with PJR/TJR)
- For each of the 3 types of subjects, the absolute change; the number of subjects who have ≥30%, ≥50%, ≥70%, or ≥90% improvement area under the curve; and landmark analysis on the 5 subscales of the KOOS through Week 8 using the average of both knees:
    - Pain
    - Other symptoms
    - Activities of daily living
    - Sports and recreation
    - QOL

- Assess the SS of treatment with CNTX-4975-05 IA injection for each of the 3 types of subjects, and all subjects in the trial
- For subjects with a PJR/TJR, assess their satisfaction with the CNTX-4975-05 IA injection versus their satisfaction with their knee with a PJR/TJR

### 13.1.3 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints include:

- Likelihood of the need for joint replacement surgery, based on KOOS subscales and SS outcomes, from Baseline through Week 8
- SS with the treatment of the index knee through Week 8 of the trial (7-point Likert Scale where 1=completely dissatisfied and 7=completely satisfied)
- The effect of subject characteristics (including K-L grade, sex, BMI, age, unilateral/bilateral knee OA, bilateral knee OA treatment, and history of contralateral PJR/TJR) on the analgesic efficacy of CNTX-4975-05, using the KOOS subscales at each study visit through Week 8
- Frequency of use of background analgesic medication for pain in the injected knee(s) throughout the study period.
- Assessment of the mean of the individual outcome measures, using the average of both knees for the subjects who received bilateral knee injections

### 13.1.4 Safety Endpoints

Safety endpoints include:

- AEs
- Vital signs
- Clinical laboratory evaluations (hematology, chemistry, and urinalysis)
- 12-lead ECGs
- Physical examination (including the presence or absence of an effusion in the index knee, periarticular pain/tenderness)
- Concomitant medications and therapies
- Degree of procedure pain (not recorded as AEs)
- Local physical findings after injection of the index knee
- Injection site assessment of erythema and edema
- Sensory testing

## 13.2 Sample Size Determination

Approximately 850 subjects will be treated with CNTX-4975-05. This sample size was chosen based on the need to fulfill safety requirements for regulatory review.

## 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 CNTX-4975-05.
- Intent-to-Treat (ITT): all enrolled subjects.

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

## 13.4 Statistical Analyses

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

Unless otherwise indicated, all testing of statistical significance will be two-sided, and a difference resulting in a $p$ value of $\leq 0.05$ will be considered statistically significant. To control for the overall type I error rate, hierarchical testing based on fixed sequence procedure will be used. If statistical significance is declared for the primary analysis, formal hypothesis testing will be done for the secondary endpoints until a non-significant result is reached. All other $p$ values from secondary and exploratory endpoints, after a non-significant $p$ value is reached, will be considered nominal.

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.

### 13.4.1 Study Subjects and Demographics

#### 13.4.1.1 Disposition and Withdrawals

The numbers of subjects treated, completing, and withdrawing, along with reasons for withdrawal, will be tabulated overall, by subject type, and by injection procedure. The number of subjects in each analysis population will be reported.

#### 13.4.1.2 Protocol Deviations

Protocol deviations will be identified and summarized or listed as appropriate.

#### 13.4.1.3 Demographics and Other Baseline Characteristics

These analyses will be conducted for all analysis populations.

Demographic variables will include age, sex/gender, height, and weight. Information on race and ethnicity will be collected for any eventual analysis of differences in response to CNTX-4975-05, 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 the number and percentage of subjects taking each medication, classified using World Health Organization Drug Dictionary Anatomical Therapeutic Chemical classes and preferred terms.

### 13.4.2 Exposure and Compliance

All subjects will receive up to 1 CNTX-4975-05 injection in each knee, at the study site under the surveillance of appropriate study personnel and, therefore, no compliance will be calculated. Injection procedure details and CNTX-4975-05 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.

#### 13.4.3.1 Primary Analysis

The primary analysis will compare each experimental treatment regimen to the Breg Cooling Control Group using an equally-weighted, combined score calculated from the following 3 measures: 1) pain 30 minutes after CNTX-4975-05 injection (using the 0-4 scale of none, mild, moderate, moderately severe, and severe), 2) SS with the treatment regimen; and 3) IS with the treatment regimen, all assessed on the index knee. Ratios of the mean values of test/control will have 95% confidence intervals constructed for each treatment regimen versus the Breg Cooling Control Group. For a treatment regimen to be considered clinically acceptable, it must be no more than 30% worse than the Breg Cooling Control Group and the lower limit of the 95% confidence interval for the treatment regimen must be greater than 0.7. This analysis will be performed on the ITT population.

For analysis, satisfaction scores (SS and IS) and 30 minute pain after CNTX-4975-05 injection will be transformed to equivalent scales, and 30 minute pain after CNTX-4975-05 injection will be reverse-scored so that higher scores represent lower pain, in order to have the 3 components on the same scale before they are combined by summing the 3 scores for a composite score. A sensitivity analysis will be performed that creates a composite score using the original scales (with the pain scores still reverse-scored to ensure the direction of the effect remains the same), using the ITT population.

All other continuous secondary and exploratory efficacy endpoints will be summarized using descriptive statistics by subject type, experimental treatment regimen, and week/visit, as appropriate, and analyzed using a mixed-model repeated measures (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.

Safety analyses will be conducted using data from the safety population.

#### 13.4.3.2 Secondary and Exploratory Analyses

Secondary and exploratory analyses will include analysis of the combined score by subject type, OMERACT-OARSI responders, KOOS subscale (including AUCs), and SS.

All continuous secondary and exploratory efficacy endpoints will be summarized using descriptive statistics by week/visit, as appropriate, and analyzed using an MMRM analysis or by analysis of covariance, as appropriate. Categorical endpoints will use Pearson's chi-square or Fisher's exact test, as appropriate. *P* values from exploratory 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 assessments (erythema and edema), assessment of procedure pain, AEs, physical examination findings, vital sign measurements, 12-lead ECG findings, clinical laboratory test results, and sensory testing. 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 the Medical Dictionary for Regulatory Activities (MedDRA), Version 16.0 or higher.

Treatment-emergent AEs are defined as:

- AEs with onset at the time of or following the start of treatment with CNTX-4975-05 through the Week 8/ET Visit

The number and percentage of subjects with AEs will be displayed for each injection procedure by system organ class and preferred term. Summaries of AEs by severity and relationship to CNTX-4975-05 will also be provided. Serious AEs and AEs resulting in discontinuation of CNTX-4975-05 will be summarized separately in a similar manner. Subject listings of AEs, SAEs and AEs causing discontinuation of CNTX-4975-05 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 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 Baseline (shift tables) for each clinical laboratory analyte by study visit. Pre- and post-treatment values will also be presented with analysis summary of mean changes from 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 Baseline will be calculated for systolic blood pressure, diastolic blood pressure, HR, and RR.

#### 13.4.4.4 Electrocardiograms

The number and percentage of subjects with normal and abnormal ECG findings will be summarized at each time point. A comparison of QT results will be presented. Summary statistics for Baseline values at Screening and at study visits according to the schedule of events will be displayed for QT and the QT interval corrected for HR (QTc) calculated using Bazett's and Fridericia's QT correction methods. In addition, the number and percent of subjects 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 injection procedure 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.

#### 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 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 a 5-point Likert Scale, where 0=absent sensation and 4=normal sensation, will be summarized at each time point.

#### 13.4.4.8 Procedure Pain

The number and percentage of subjects with each pain assessment categorized as none, mild, moderate, moderately severe, or severe will be summarized at each time point. These pain assessments are also a component of the efficacy endpoints.

### 13.4.5 Interim Analyses

To ensure that the benefit/risk ratio continues to be appropriate for the OA knee indication, interim analyses for a focused review of safety and efficacy may be performed when approximately 20%, 50%, and/or 75% of subjects have completed the trial. The output for the interim analyses will be consistent with the currently planned final analyses.

# 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.

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 17.1), 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 subinvestigators 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., subinvestigators 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/IEC 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 Investigator's Regulatory Documents

The regulatory documents are listed in the Study Manual.

The regulatory 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 CNTX-4975-05 to the study site. Copies of the investigator's regulatory 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 CNTX-4975-05 IB, eCRF completion guidelines, copies of regulatory references, copies of IRB/IEC correspondence, and CNTX-4975-05 accountability records should also be retained as part of the investigator's regulatory documents. It is the investigator's responsibility to ensure that copies of all required regulatory documents are organized, current, and available for inspection.

#### 14.4.2 Case Report Forms

By signing the Investigator's Agreement (Section 17.1), 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 eCRF/EDC system according to the completion guidelines provided by the sponsor or its designee.

The eCRFs must be signed by the investigator or a subinvestigator. 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 eCRF/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 eCRF/EDC system with the source documents
- consenting procedures
- AE procedures
- storage and accountability of CNTX-4975-05 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 17.1), 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 eCRF, 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 (e.g., protocol and/or clinical study report)

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/IEC 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 at 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 subject 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 CNTX-4975 has been approved or the sponsor has discontinued its research with CNTX-4975, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of CNTX-4975

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 his or her 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/IEC 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 CNTX-4975, 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 CNTX-4975 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 CNTX-4975 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/IEC 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 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 studies, the minimum standards of conduct and requirements for informed consent are defined in the FDA regulations.

A valid IRB/IEC 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/IEC approval form or written documentation from the IRB/IEC containing the same information.

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

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

# 17 ATTACHMENTS

## 17.1 Investigator's Agreement

| | |
|---|---|
| PROTOCOL NUMBER: | CNTX-4975i-OA-303 |
| PROTOCOL TITLE: | An Open-label, 8-Week Study to Compare the Comfort and Ease of Use of Five Different Treatment Regimens for CNTX-4975-05 Intra-articular Injection in Subjects with Chronic, Moderate-to-Severe Osteoarthritis Knee Pain |
| VERSION: | Version 3.0, 13 June 2019 |

I have read this protocol and agree to conduct this clinical trial as outlined herein. I will ensure that all subinvestigators 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.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

# 18 APPENDICES

A. Study Specific Requirements

B. Regulations and Good Clinical Practice Guidelines

## 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)
- Knee Injury and Osteoarthritis Outcome Score (KOOS)
- Subject satisfaction questionnaire
- Investigator satisfaction questionnaire
- Joint replacement questionnaire

## B. Regulations and Good Clinical Practice Guidelines

### 1. Regulations

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

- FDA Regulations 21 CFR, Parts 50.20 – 50.27
  Subpart B – Informed Consent of Human Subjects
- 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
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators

### 2. 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

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

**1.** [redacted]

**2.** **Sampson et al. (2006)**

CENTREXION THERAPEUTICS

[redacted]

[redacted]

# Appendix A

**Definitions**:

**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.

**Clinical Criteria for Diagnosing Anaphylaxis**

Criteria for anaphylaxis, Table 1 (Sampson HA, *et al,* J Allergy Clin Immunol 2006;117(2):391-97 is appended to this letter).

**TABLE I.** Clinical criteria for diagnosing anaphylaxis

**Anaphylaxis is highly likely when any one 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

*PEF*, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

**Typical Items Found in Adult Crash Carts**

The list is for demonstration purposes only, as crash carts will differ on medical vs. surgical facilities, or across hospitals, and certainly across countries. The key to an adequate crash cart are solutions and drapes for sterility, methods to deliver IV fluids, vasopressor agents, epinephrine (adrenaline), cardiac arrythmia treatments, vacutainers (for tryptase: e.g. 6 mL dark blue-top [trace element, no additive]), cardiac defibrillator and means of maintaining an airway (oxygen valve bag mask, endotracheal tubes; oxygen available): below is the ACLS partial list

- Alcohol swabs, amiodarone 150 mg/3ml vial, atropine 1mg/10 ml syringe, sodium bicarbonate 50mEq/50 ml syringe, calcium chloride 1gm/10 ml syringe, sodium chloride 0.9% 10 ml vial Inj. 20 ml vial, Dextrose 50% 0.5 mg/ml 50 ml syringe, Dopamine 400 mg/250 ml IV bag, Epinephrine 1 mg/10 ml (1:10,000) syringe, sterile water, lidocaine 100 mg 5ml syringes, lidocaine 2 gm/250 ml IV bag, povidone-iodine swabstick, vasopressin 20 units/ml 1 ml vial
- Endotracheal tubes of various sizes, nasopharyngeal and perhaps oropharyngeal airways, laryngoscope handle and blades of different sizes, a flashlight with extra batteries, a syringe of sufficient size to inflate the cuff on - an endotracheal tube, stylets, bite block, tongue depressors
- V Start Kit (or similar CPR kit), angio-catheters 14 Ga and/or 16 Ga, disinfectants (chloraprep, Betadine, povidone-iodine), Luer lock syringes of various sizes, tourniquet tubing, Insyte autoguards of various sizes, Vacutainers
- ECG electrodes, sterile gloves of various sizes, sutures of various sizes and materials, suction supplies, salem pump (double-lumen nasogastric tube for aspiration of stomach contents), cricothyroidotomy kit, adult cut down pack, Yankauer suction, drapes to create a sterile field, Suction Cath Kit 14 Fr & 18 Fr,
- ECG / cardiac defibrillator

## Guidelines for treatment of Anaphylaxis

As all sites must have ACLS or equivalent training, and appropriate equipment, this overview of treatment is at a high level.

- Rapid assessment and maintenance of airway, breathing and circulation
- Epinephrine (adrenaline) 0.01mg/kg – 0.5 mg maximum dose intramuscularly every 5-15 minutes, as needed.
- High flow oxygen through endotracheal tube or rebreather mask for respiratory symptoms or hypoxia
    - Inhaled beta-2 agonists (e.g. albuterol) for bronchospasm
- With signs of hypoperfusion, position subject in a recumbent position with legs elevated, except for when there is vomiting or shortness of breadth
- Subjects hypotensive despite epinephrine should have fluid resuscitation
- If epinephrine and fluid resuscitation are not adequate for maintaining blood pressure, then vasopressors can be implemented (e.g. noradrenaline [noradrenaline], vasopressin)
- Observation for a period of time must occur as a return of signs and symptoms may recur as epinephrine (adrenaline) blood concentrations decrease, or the subject has a biphasic reaction.

# 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

**Hugh A. Sampson, MD,[a] Anne Muñoz-Furlong, BA,[b] Ronna L. Campbell, MD, PhD,[c] N. Franklin Adkinson, Jr, MD,[d] S. Allan Bock, MD,[e] Amy Branum, MSPH,[f] Simon G. A. Brown, MBBS, PhD,[g] Carlos A. Camargo, Jr, MD,[h] Rita Cydulka, MD, MS,[i] Stephen J. Galli, MD,[j] Jane Gidudu, MD, MPH,[k] Rebecca S. Gruchalla, MD,[l] Allen D. Harlor, Jr, MD,[m] David L. Hepner, MD,[n] Lawrence M. Lewis, MD,[o] Phillip L. Lieberman, MD,[p] Dean D. Metcalfe, MD,[q] Robert O'Connor, MD,[r] Antonella Muraro, MD, PhD,[s] Amanda Rudman, BA,[q] Cara Schmitt, MS,[b] Debra Scherrer, BA,[b] F. Estelle R. Simons, MD,[t] Stephen Thomas, MD, MPH,[u] Joseph P. Wood, MD,[v] and Wyatt W. Decker, MD[c]**

*New York, NY, Fairfax, Va, Rochester, Minn, Baltimore, Hyattsville, and Bethesda, Md, Boulder and Denver, Colo, Fremantle, Australia, Boston, Mass, Cleveland, Ohio, Stanford, Calif, Lilbum, Ga, Dallas, Tex, Eugene, Ore, St Louis, Mo, Cordova, Tenn, Padua, Italy, Winnipeg, Manitoba, Canada, and Scottsdale, Ariz*

**There is no universal agreement on the definition of *anaphylaxis* or the criteria for diagnosis. In July 2005, the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network convened a second meeting on anaphylaxis, which included representatives from 16 different organizations or government bodies, including representatives from North America, Europe, and Australia, to continue working toward a universally accepted definition of anaphylaxis, establish clinical criteria that would accurately identify cases of anaphylaxis with high precision, further review the evidence on the most appropriate management of anaphylaxis, and outline the research needs in this area. (J Allergy Clin Immunol 2006;117:391-7.)**

***Key words:*** *Anaphylaxis, IgE mediated hypersensitivity, anaphylac toid, epinephrine*

Even though anaphylaxis was first described around 100 years ago and is one of the most alarming disorders encountered in medicine, there is no universal agreement on its definition or criteria for diagnosis. Furthermore, this lack of specific criteria for diagnosing anaphylaxis has greatly hampered research into the epidemiology, patho physiology, and management of this disorder; led to confusion on the part of first responders, emergency personnel, primary care physicians, and patients; and resulted in a failure to diagnose and treat anaphylaxis in a consistent manner.[1-3]

In an attempt to resolve these problems, the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) convened a meeting in April 2004 to address these deficiencies.[4] This 2 day symposium brought together experts and representatives from 13 professional, govern mental, and lay organizations to address the issue of defining and managing anaphylaxis. Organizations repre sented included the American Academy of Allergy, Asthma and Immunology; the American Academy of Emergency Physicians; the American Academy of Family Physicians; the American Academy of Pediatrics; the American College of Allergy, Asthma and Immunology; the American College of Emergency Physicians; the

From [a]the Mount Sinai School of Medicine, New York; [b]the Food Allergy & Anaphylaxis Network, Fairfax; [c]the Mayo Clinic, Rochester; [d]the Johns Hopkins University School of Medicine, Baltimore; [e]representing the Food Allergy & Anaphylaxis Network, Boulder; [f]the National Center for Health Statistics, Hyattsville; [g]Fremantle Hospital, Fremantle, WA, Australia; [h]Massachusetts General Hospital, Boston; [i]the Case Western Reserve University School of Medicine, Cleveland; [j]the Stanford University School of Medicine, Stanford; [k]representing the Centers for Disease Control and Prevention, Lilburn; [l]the University of Texas Southwestern Medical Center, Dallas; [m]representing the American Academy of Pediatrics, Eugene; [n]representing the American Society of Anesthesiologists, Boston; [o]representing the Society for Academic Emergency Medicine, St. Louis; [p]representing the American College of Allergy, Asthma and Immunology, Cordova; [q]the National Institute of Allergy and Infectious Diseases, the National Institutes of Health, Bethesda; [r]representing the National Association of EMS Physicians, Baltimore; [s]the University of Padua, Padua, Italy; [t]representing the American Academy of Allergy, Asthma and Immunology, Winnepeg, MB, Canada; [u]representing the American College of Emergency Physicians, Boston; and [v]representing the American Academy of Emergency Medicine, Scottsdale.

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Reprint requests: Hugh A. Sampson, MD, Division of Pediatric Allergy and Immunology, Mount Sinai Hospital, One Gustave L. Levy Pl, Box 1198, New York, NY 10029-6574. E-mail: hugh.sampson@mssm.edu.

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*Abbreviations used*
FAAN: Food Allergy and Anaphylaxis Network
NIAID: National Institute of Allergy and Infectious Disease

American Society of Anesthesiologists; the Centers for Disease Control and Prevention; the Food Allergy Initiative; the International Life Sciences Institute; the National Association of EMS Physicians; the Society for Academic Emergency Medicine; and the US Food and Drug Administration. Clinical criteria were proposed that emphasized the need for heightened suspicion of anaphylaxis in patients with a previous history of allergic reactions to a specific allergen and a known exposure, as well as in patients in whom there is no known history of allergic reactions.

Recently, the Joint Task Force of the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology published an updated practice parameter on the diagnosis and management of anaphylaxis.[5] In this report the Task Force defined anaphylaxis as "as a condition caused by an IgE mediated reaction" and noted that such reactions "are often life threatening and almost always unanticipated." The purpose of the practice parameter was to provide "the practicing physician with an evidence based approach to the diagnosis and management of anaphylactic reactions." In July 2005, the NIAID and FAAN convened a second meeting, which included representatives from the previous organizations and the European Academy of Allergy and Clinical Immunology, the Australasian Society of Clinical Immunology and Allergy, and the Australasian College for Emergency Medicine, to begin the process of facilitating an international agreement. The purpose of this second NIAID/FAAN Symposium was to continue working toward a universally accepted definition of anaphylaxis, establish clinical criteria that would accurately identify cases of anaphylaxis with high precision, further review the evidence on the most appropriate management of anaphylaxis, and outline the research needs in this area.

## DEFINITION OF ANAPHYLAXIS AND CRITERIA FOR DIAGNOSIS

Anaphylaxis is a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy causing substance. Participants at the symposium agreed that a brief, broad definition of anaphylaxis that reflected its course and potential severity would be most useful to both the medical and lay community and recommended the following: "Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death."

To identify individuals experiencing such a reaction, criteria proposed at the first symposium were revised,[4] as outlined in Table I. Participants at the second symposium agreed that the diagnostic criteria must provide the emergency responder or treating physician with a relatively simple and rapid means to make the diagnosis of anaphylaxis. It was acknowledged that no criteria will provide 100% sensitivity and specificity, but it was believed that the criteria proposed are likely to capture more than 95% of cases of anaphylaxis. Because the majority of anaphylactic reactions include skin symptoms,[5-10] which are noted in more than 80% of cases when carefully assessed, it was judged that at least 80% of anaphylactic reactions should be identified by criterion 1, even when the allergic status of the patient and potential cause of the reaction might be unknown. However, cutaneous symptoms might be absent in up to 20% of anaphylactic reactions in children with food allergy or insect sting allergy.[11-13] Consequently, in patients with a known allergic history and possible exposure, criterion 2 would provide ample evidence that an anaphylactic reaction was occurring. Gastrointestinal symptoms were included as a pertinent target response because they have been associated with severe outcomes in various anaphylactic reactions.[9] Finally, criterion 3 should identify the rare patients who experience an acute hypotensive episode after exposure to a known allergen, as described by Pumphrey and Stanworth.[14] Although participants believed that these criteria should accurately identify anaphylactic reactions in more than 95% of cases, it was agreed that these criteria need to be subjected to a prospective multicenter clinical survey to establish their utility and determine whether there is need for further refinement.

## MANAGEMENT OF ANAPHYLAXIS

As with the treatment of any critically ill patient, the treatment of anaphylaxis begins with a rapid assessment and maintenance of airway, breathing, and circulation. When a patient fulfills any of the 3 criteria of anaphylaxis outlined above, the patient should receive epinephrine immediately because epinephrine is the treatment of choice in anaphylaxis. There undoubtedly will be patients who present with symptoms not yet fulfilling the criteria of anaphylaxis yet in whom it would be appropriate to initiate therapy with epinephrine, such as a patient with a history of near fatal anaphylaxis to peanut who ingested peanut and within minutes is experiencing urticaria and generalized flushing. Subsequent interventions are determined on the basis of the clinical course and response to epinephrine. In general, participants at the Second NIAID/FAAN Anaphylaxis Symposium support the therapeutic approach outlined in recently published guidelines.[5] A summary of these guidelines is provided below, along with a more detailed discussion of the recommended route of parenteral epinephrine, positioning during treatment of anaphylaxis, and suggested observation periods after treatment of an anaphylactic episode.

### Epinephrine

Epinephrine is the treatment of choice for anaphylaxis.[5] Aqueous epinephrine, 0.01 mg/kg (maximum dose,

**TABLE I.** Clinical criteria for diagnosing anaphylaxis

**Anaphylaxis is highly likely when any one 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

*PEF*, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

0.5 mg) administered intramuscularly every 5 to 15 minutes as necessary, is the recommended dosage for controlling symptoms and maintaining blood pressure.[15,16] The 5 minute interval between injections can be liberalized to permit more frequent injections if deemed necessary by the clinician.

*Intramuscular versus subcutaneous epinephrine*. A study in children not experiencing anaphylaxis demonstrated more rapid absorption and higher plasma epinephrine levels when epinephrine was administered intramuscularly in the anterior lateral thigh with an autoinjector when compared with values after subcutaneous administration.[17] Similarly, in adults not experiencing anaphylaxis, peak plasma epinephrine concentrations were attained more quickly and were higher after intramuscular epinephrine was injected into the thigh than after epinephrine was injected intramuscularly or subcutaneously into the upper arm (deltoid).[18] Similar results were obtained with both an ampule of epinephrine or a spring loaded (eg, EpiPen [Dey, Napa, Calif]) automatic epinephrine device.[17,18] Epinephrine injected intramuscularly into the deltoid or subcutaneously over the deltoid did not result in a significant increase of plasma epinephrine levels over endogenous epinephrine levels. It should be noted that studies of the route of injection have not been performed in patients experiencing anaphylaxis. On the basis of this evidence, the participants of the NIAID/FAAN Symposium concluded that intramuscular administration of injectable epinephrine in the anterior lateral thigh is preferred over subcutaneous injection. However, as noted below, intravenous epinephrine might be preferred in some cases if an intravenous line is in place (eg, during surgery).

*Intravenous epinephrine*. Intravenous epinephrine is an option for patients with severe hypotension or cardiac arrest unresponsive to intramuscular doses of epinephrine and fluid resuscitation. Although there is no precisely established dosage or regimen for intravenous epinephrine in anaphylaxis, 5 to 10 μg intravenous bolus (0.2 μg/kg) doses for hypotension and 0.1 to 0.5 mg administered intravenously in the presence of cardiovascular collapse have been suggested.[19] A recent single center trial described successful initial management with intravenous epinephrine infusions for anaphylaxis with hypotension, suggesting that this might be a viable strategy.[10,20] Detailed procedures for the preparation and administration of epinephrine infusions have been published.[5] It is important to recognize the potential for lethal arrhythmias when administering intravenous epinephrine, and therefore continuous cardiac monitoring is recommended. Continuous low dose epinephrine infusions might represent the safest and most effective form of intravenous delivery because the dose can be titrated to the desired effect and can avoid the potential for accidental administration of large boluses of epinephrine.

## Oxygen and adrenergic agonists

High flow oxygen (through a nonrebreather mask or endotracheal tube) should be administered to patients experiencing respiratory symptoms or hypoxemia. Those who are hemodynamically unstable might benefit from oxygen as well. Inhaled $\beta_2$ agonists, such as albuterol, might be useful for bronchospasm refractory to epinephrine.[5]

## Positioning of the patient

Patients in anaphylactic shock (ie, those with anaphylaxis and signs of critical organ hypoperfusion) should be placed in a recumbent position with the lower extremities elevated unless precluded by shortness of breath or vomiting. These recommendations are based on evidence that passive leg raise can increase stroke volume and cardiac output by shifting fluid centrally in patients in shock.[21] Furthermore, observations of victims of fatal anaphylactic shock suggest that postural changes, such as moving to a more upright position or being prevented from taking a supine posture, might have contributed to the fatal outcome.[22]

## Fluid resuscitation

Patients who remain hypotensive despite epinephrine should have aggressive fluid resuscitation. Large volumes

**TABLE II.** Biphasic reactions

| Study | Frequency of biphasic reactions | No. of biphasic reactions/total no. of patients in study | Time from initial to biphasic reaction (h) |
|---|---|---|---|
| Brazil and MacNamara[33] | 18% | 6/34 | 4.5 29.5 |
| Douglas et al[31] | 6% | 6/103 | 1 72 |
| Lee and Greenes[34] | 6% | 6/105 | 5.6 47.6 |
| Starks and Sullivan[29] | 20% | 5/25 | 1 8 |
| Brady et al[32] | 3% | 2/67 | 24 28 |
| Smit et al[8] | 5% | 15/282 | 1 23 |

Adapted from Smit et al.[8]

of crystalloid might be needed in the first 5 to 10 minutes; in severe reactions with hypotension, up to 35% of the blood volume might extravasate in the first 10 minutes, and vasodilatation can cause pooling, with even more reduction in the effective blood volume and thus distrib utive shock.[23] The volume given must be tailored to the clinical situation; persistent hypotension requires a more aggressive approach with multiple fluid boluses (10 20 mL/kg under pressure), including colloid, as well as crys talloid, whereas a largely respiratory reaction or one that responds promptly to initial treatment requires less aggres sive fluid management.

## Vasopressors

Potent vasopressors, such as noradrenaline, vasopres sin, or metaraminol, might be required to overcome vasodilatation if epinephrine and fluid resuscitation have failed to maintain a systolic blood pressure of greater than 90 mm Hg.[20] Recent case reports and animal studies have demonstrated that vasopressin is useful when treating hemorrhagic and septic shock. The effect of vasopressin on systemic anaphylaxis has not been investigated, except in clinical case reports. Vasopressin increases blood pres sure because of vasoconstriction through the V1 receptor.[24]

## $H_1$- and $H_2$-antihistamines

Antihistamines ($H_1$ and $H_2$ antagonists) are slower in onset of action than epinephrine, have little effect on blood pressure, and should be considered a second line treat ment for anaphylaxis. Antihistamines are useful for the symptomatic treatment of urticaria angioedema and pru ritus. Diphenhydramine, administered intravenously or intramuscularly (or orally for mild symptoms), can be given at 25 to 50 mg for adults and 1 mg/kg (up to 50 mg) for children. Treatment with a combination of $H_1$ and $H_2$ antagonists has been reported to be more effective in attenuating the cutaneous manifestations of anaphylaxis than treatment with $H_1$ antagonists alone.[25,26] Ranitidine and cimetidine have been most studied, but no controlled studies have demonstrated superiority of one $H_2$ antagonist over another.

## Corticosteroids

The effectiveness of corticosteroids in anaphylaxis has never been determined in placebo controlled trials. However, their usefulness in other allergic diseases has led to their incorporation into anaphylaxis management. Because the onset of action is slow, steroids are not useful in the acute management stage. It has been suggested that their use might prevent a protracted or biphasic reaction, although there is no evidence to prove this.[11,27] If given, the dosing of intravenous corticosteroids should be equiv alent to 1.0 to 2.0 mg/kg per dose of methylprednisolone every 6 hours. Oral administration of prednisone, 1.0 mg/kg, up to 50 mg might be sufficient for milder attacks.

## Glucagon for persistent hypotension in patients taking β-blockers

Although there are no epidemiologic studies that dem onstrate increased frequency of anaphylaxis in patients receiving β blockers, there are multiple reported cases of increased severity or treatment refractory anaphylaxis in these patients.[28] Theoretically, there are multiple mecha nisms by which β blockade could blunt the response to epinephrine. If administration of epinephrine in these patients is ineffective, administration of glucagon can be attempted. Glucagon is thought to reverse refractory hypo tension and bronchospasm by activating adenylate cyclase independent of the β receptor; however, the occurrence and importance of this mechanism of action in anaphy laxis is unproved. The recommended dosage for glucagon is 1 to 5 mg (20 30 μg/kg [maximum dose, 1 mg] in children) administered intravenously over 5 minutes and followed by an infusion (5 15 μg/min) titrated to clinical response. Airway protection must be ensured because glucagon frequently causes emesis.

## Observation

After the treatment of an anaphylactic reaction, an observation period should be considered for all patients because the reaction might recur as the effect of epineph rine wears off (intramuscular epinephrine results in in creased serum levels for an hour or more) and because of the risk of a biphasic reaction. The occurrence of biphasic reactions has been established in the literature and appears to occur in 1% to 20% of anaphylactic reactions (as depicted in Table II).[8,11,27,29-34] In a study evaluating patients with fatal or near fatal food reactions, approxi mately 20% of patients experienced a biphasic reaction, indicating that biphasic reactions might be more likely in patients who present initially with severe symptoms.[11] The reported time intervals between the initial reaction

and the onset of the second phase ranged from 1 to 72 hours.[11,27,30-34] Unfortunately, no reliable clinical predictors have been identified to enable the identification of patients at increased risk of a biphasic reaction, although some studies have suggested that patients requiring higher doses of epinephrine to control initial symptoms or delayed administration of epinephrine might be associated with increased risk of a biphasic reaction.[11,15,33,34] Generally, the same organ systems are involved in the initial and secondary reaction. However, in the study by Smit et al,[8] 3 patients with initially stable vital signs returned with abnormal vital signs (2 with hypotension and 1 with dyspnea and decreased oxygen saturation). On the basis of the evidence to date, the participants attending the NIAID/FAAN Symposium recommended that observation periods be individualized on the basis of the severity of the initial reaction, reliability of the patient, and access to care. A reasonable length of time to consider observing the postanaphylactic patient is 4 to 6 hours in most patients, with prolonged observation times or hospital admission for patients with severe or refractory symptoms. More caution should be used in patients with reactive airway disease because most fatalities associated with anaphylaxis occur in these patients.

### Outpatient follow-up and management

Patients who have experienced anaphylaxis from exposures that might be encountered in nonmedical settings should carry self injectable epinephrine for use if anaphylaxis develops.[5,11] As noted above, there has been no universally accepted definition of anaphylaxis. Therefore the clinical criteria suggested above might be helpful in determining who should be prescribed self injectable epinephrine. Until there are universally accepted criteria for the diagnosis of anaphylaxis, the indications for the prescription of self injectable epinephrine will continue to be problematic. Currently, there is a consensus that patients experiencing respiratory or cardiovascular symptoms after exposure to a known allergen in the community should receive self injectable epinephrine. Beyond this consensus, it is unclear who should be given a prescription for self injectable epinephrine. However, limiting prescriptions of self injectable epinephrine to this criteria in patients with peanut and other nut allergy, for example, would fail to cover up to 80% of patients experiencing a fatal anaphylactic reaction.[35] Patients who are prescribed self injectable epinephrine should also have an emergency action plan detailing its use and the follow up management. The complexities of prescribing self injectable epinephrine and providing an accompanying emergency action plan have been described recently by Sicherer and Simons,[36] and the ethical dilemmas have been discussed by Hu et al.[37]

Before discharge from an emergency facility, all patients experiencing an anaphylactic reaction should receive information about how to avoid the precipitating allergen (if known). Other issues to consider include alerting patients about national organizations providing important information and educational materials (eg, the Food Allergy and Anaphylaxis Network, www.foodallergy.org), as well as being advised to obtain prompt follow up with an allergist and notify their primary care physician. At present, these 3 steps (ie, self injectable epinephrine prescription, patient education, and follow up evaluation) are infrequently performed in North American emergency departments.[38,39] Because emergency departments are the treatment setting for most anaphylaxis visits,[1] this represents an important and as yet untapped opportunity to improve patient care.

## RESEARCH NEEDS

The investigation of anaphylaxis has been impeded by the lack of universally accepted diagnostic criteria and the absence of reliable laboratory biomarkers to confirm the clinical impression. This in turn has thwarted efforts to ascertain the incidence and outcome of anaphylaxis in various populations, to determine the most effective forms of therapy, to identify patients at risk for life threatening anaphylaxis, and to elucidate the basic immunologic and pathogenic mechanisms responsible for the variable course of anaphylaxis in different individuals. A multicenter prospective study of the diagnostic criteria proposed herein is needed to determine whether they allow the clinician and investigator to identify accurately patients with anaphylaxis regardless of cause. Assuming that these criteria prove to be adequately sensitive and specific for diagnosing anaphylaxis, studies determining the incidence, cause, clinical features, natural course, and outcome of anaphylaxis are needed to provide the clinician with evidence based features of this disorder that will enable more effective prevention and therapeutic interventions. Clinical trials can be facilitated by the formation of an anaphylaxis consortium.

It was believed that the measurement of certain mast cell derived mediators, such as histamine and tryptase, would provide confirmatory evidence of an anaphylactic reaction. However, in a series of 97 patients presenting to an emergency department and given diagnoses of anaphylaxis, only 42% were found to have increased plasma histamine levels, and 21% were determined to have increased plasma tryptase levels.[26] One small study demonstrated that serial estimations of plasma tryptase levels might improve sensitivity (36% to 73%).[40] Sensitive and specific biomarkers of anaphylaxis and evolving anaphylaxis are needed that will establish the presence of the disorder when sufficient historical information is not available or symptoms are atypical. New proteomic approaches, metabolomic approaches, or both might prove useful in identifying relevant biomarkers. Biomarker assays could be useful to confirm the diagnosis when in doubt, which can have important follow up implications. If available at the bedside, they could even assist in the identification of patients at risk of persistent or delayed phase reactions. However, given the emergency and fulminant nature of this disease, such approaches are unlikely to be useful for guiding immediate resuscitative

interventions. Laboratory trials can be facilitated by the formation of an anaphylaxis registry with close collaboration between different centers and across specialties.

As outlined in the previous symposium,[4] most anaphylactic reactions are due to IgE mediated hypersensitivity reactions resulting from cross linking of allergen specific IgE molecules on the surface of tissue mast cells and possibly basophils. However, this mechanism alone does not explain the severity of the allergic manifestations, the variability in target organ responses among individuals or within the same individual, the differences in threshold doses of allergen necessary to provoke anaphylactic responses, the variable responses to therapy, the induction of biphasic or protracted anaphylactic reactions, or the eventual outcome of the reaction. A recent study suggested that the diversity of IgE allergenic epitope recognition might play a role in the severity of allergic responses,[41] but this represents a fraction of the potential variables occurring between the time an allergen enters the body and the end result of an anaphylactic reaction. For example, it might be informative to perform genomic and functional studies of polymorphisms or gain of function mutations in various mediator, cytokine, and chemokine receptors; the Kit receptor; elements of intracellular signaling pathways; or other factors that might influence either the activation or function of the effector cells of anaphylaxis or the responses of the structural cells in the target organs affected in this disorder.

In addition, investigation is required into the pathophysiologic mechanisms and appropriate treatment of reactions fulfilling the diagnostic criteria listed for anaphylaxis but that do not involve an IgE mediated mechanism, commonly referred to as *anaphylactoid* or *pseudoallergic reactions*. Furthermore, studies have suggested a role for the nervous system in eliciting the full symptom complex of anaphylaxis,[42] and this is an area that warrants further investigation. Well characterized animal models would clearly facilitate efforts to understand the basic pathophysiology occurring during anaphylaxis; to determine the interactions between various cell types; to elucidate effects of mediators, cytokines, and chemokines released during an anaphylactic response; and to delineate better therapeutic strategies. Recently, animal models that appear reflective of anaphylaxis in human subjects have been established in mice,[43] dogs,[44] and pigs,[45] but better models are needed.

During the NIAID/FAAN Symposium and in the recently published practice parameter on anaphylaxis,[5] therapeutic strategies for the management of anaphylaxis were suggested largely on the basis of ''clinical experience.'' In fact, there is a major need to evaluate the most appropriate therapeutic measures and medications for the treatment of anaphylaxis. Although virtually all authorities agree that epinephrine is the drug of choice for the treatment of acute anaphylaxis, there are limited data on the appropriate dose, timing, route, or frequency of administration. $H_1$ and $H_2$ antihistamines, corticosteroids, or both are commonly used in the treatment of anaphylaxis, but there are virtually no data demonstrating their functional role or effectiveness. Prospective controlled trials to establish the appropriate dosing of these medications and the role of other therapeutic interventions, such as the optimal type and rate of fluid replacement, and the use of vasopressors, glucagon, nebulized albuterol or epinephrine, leukotriene inhibitors, and cytokine antagonists (eg, anti TNF) also are warranted. Ideally, therapeutic measures could be studied in appropriate animal models before initiating clinical trials. Before any clinical studies, clinically useful severity scoring and outcome measurement tools need to be validated.

There is also a need for outcomes research in well characterized patients. Little information is available on the benefits and risks of providing epinephrine autoinjectors, antihistamines, corticosteroids, and written medical instructions to patients with food and insect venom allergy and their caregivers (eg, parents and school, day care, and restaurant personnel) and first line emergency personnel. Studies of long term sequelae, adherence to follow up referral, subsequent reactions, and quality of life in patients experiencing anaphylactic reactions also are lacking. As outcome data are becoming available, evaluation of the most effective means of disseminating information about the prevention and management of anaphylaxis to patients, primary care physicians, first responders, and emergency department personnel should help alleviate the tremendous disparities in therapeutic approaches seen in the United States and around the world.

A number of studies from around the world suggest that anaphylactic reactions commonly occur both inside and out of the hospital environment.[46,47] In light of the general increase in IgE dependent allergic disorders in the developed world over the past several decades, there is an urgent need to understand better the basic immunology and pathophysiology of anaphylaxis and to optimize therapy on the basis of well controlled clinical trials. In addition, the characterization of clinical features and discovery of biomarkers that would identify patients at risk for anaphylaxis or for biphasic or prolonged severe reactions would greatly enhance the care of these patients, decrease patient and family anxieties, and reduce the risk of unfavorable outcomes. The universal acceptance of specific clinical criteria to identify anaphylaxis, as proposed here, will facilitate and expedite research in this critical area.



## REFERENCES

1. Bohlke K, Davis RL, DeStefano F, Marcy SM, Braun MM, Thospson RS. Epidemiology of anaphylaxis among children and adolescents enrolled in a health maintenance organization. J Allergy Clin Immunol 2004;113:536-42.
2. Klein JS, Yocum MW. Underreporting of anaphylaxis in a community emergency room. J Allergy Clin Immunol 1995;95:637-8.
3. Sorensen H, Nielsen B, Nielsen J. Anaphylactic shock occurring outside hospitals. Allergy 1989;44:288-90.
4. Sampson HA, Munoz-Furlong A, Bock SA, Schmidt C, Bass R, Chowdhury BA, et al. Symposium on the definition and management of anaphylaxis: summary report. J Allergy Clin Immunol 2005;115:571-4.
5. Lieberman P, Kemp SF, Oppenheimer JJ, Land I, Bernstein IL, Nicklas RA, et al. The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol 2005;115(suppl):S485-523.

6. Kemp SF, Lockey RF, Wolf BL, Lieberman P. Anaphylaxis: a review of 266 cases. Arch Intern Med 1995;155:1749-54.
7. Brown AF, McKinnon D, Chu K. Emergency department anaphylaxis: a review of 142 patients in a single year. J Allergy Clin Immunol 2001;108:861-6.
8. Smit DV, Cameron PA, Rainer TH. Anaphylaxis presentations to an emergency department in Hong Kong: incidence and predictors of biphasic reactions. J Emerg Med 2005;28:381-8.
9. Brown SGA. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol 2004;114:371-6.
10. Brown SGA, Blackmean KE, Stenlake V, Heddle RJ. Insect sting anaphylaxis; prospective evaluation of treatment with intravenous adrenaline and volume resuscitation. Emerg Med J 2004;21:149-54.
11. Sampson HA, Mendelson LM, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. N Engl J Med 1992;327: 380-4.
12. Braganza SC. Acworth JP. McKinnon DR. Peake JE, Brown AF. Paediatric emergency department anaphylaxis: different patterns from adults. Arch Dis Child 2005 Nov 24; [Epub ahead of print].
13. Golden DB. Patterns of anaphylaxis: acute and late phase features of allergic reactions. In: Novartis Foundation, editor. Anaphylaxis. London: John Wiley & Sons, Ltd; 2004. p. 101-15.
14. Pumphrey RSH, Stanworth SJ. The clinical spectrum of anaphylaxis in north-west England. Clin Exp Allergy 1996;26:1364-70.
15. Project Team of The Resuscitation Council (UK). Consensus guidelines: emergency medical treatment of anaphylactic reactions. Resuscitation 1999;41:93-9.
16. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. Guidelines 2000 for cardiorespiratory resuscitation and emergency cardiovascular care. Part 8. Advanced challenges in resuscitation: section 3: special challenges in ECC. Circulation 2000;102(suppl 1):I241-3.
17. Simons FE, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. J Allergy Clin Immunol 1998; 101:33-7.
18. Simons FE, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. J Allergy Clin Immunol 2001; 108:871-3.
19. Hepner DL, Castells MC. Anaphylaxis during the perioperative period. Anesth Analg 2003;97:1381-95.
20. Brown SGA. Cardiovascular aspects of anaphylaxis: implications for treatment and diagnosis. Curr Opin Allergy Clin Immunol 2005;5:359-64.
21. Boulain T, Achard JM, Teboul JL, Richard C, Perotin C, Ginies G. Changes in BP induced by passive leg raising predict response to fluid loading in critically ill patients. Chest 2002;121:1245-52.
22. Pumphrey RSH. Fatal posture in anaphylactic shock. J Allergy Clin Immunol 2003;112:451-2.
23. Fisher M. Clinical observations on the pathophysiology and treatment of anaphylactic cardiovascular collapse. Anaesth Intensive Care 1986;14: 17-21.
24. Kill C, Wranze E, Wulf H. Successful treatment of severe anaphylactic shock with vasopressin. Two case reports. Int Arch Allergy Immunol 2004;134:260-1.
25. Simons FE. Advances in H1-antihistamines. N Engl J Med 2004;351: 2203-17.
26. Lin RY, Schwartz LB, Curry A, Pesola GR, Knight RJ, Lee HS, et al. Histamine and tryptase levels in patients with acute allergic reactions: an emergency department-based study. J Allergy Clin Immunol 2000; 106:65-71.
27. Lieberman P. Biphasic anaphylactic reactions. Ann Allergy Asthma Immunol 2005;95:217-26.
28. Thomas M, Crawford I. Best evidence topic report. Glucagon infusion in refractory anaphylactic shock in patients on beta-blockers. Emerg Med J 2005;22:272-3.
29. Starks BJ, Sullivan TJ. Biphasic and protracted anaphylaxis. J Allergy Clin Immunol 1986;78:76-83.
30. Flood JM, Perry DJ. Role of food allergy in eczematoid dermatitis. Arch Dermatol Syph 1947;55:493-506.
31. Douglas DM, Sukenick E, Andrade WP, Brown JS. Biphasic systemic-anaphylaxis—an inpatient and outpatient study. J Allergy Clin Immunol 1994;93:977-85.
32. Brady WJ, Luber S, Carter CT, Guertler A, Lindbeck G. Multiphasic anaphylaxis: an uncommon event in the emergency department. Acad Emerg Med 1997;4:193-7.
33. Brazil E, MacNamara AF. "Not so immediate" hypersensitivity—the danger of biphasic anaphylactic reactions. J Accid Emerg Med 1998; 15:252-3.
34. Lee JM, Greenes DS. Biphasic anaphylactic reactions in pediatrics. Pediatrics 2000;106:762-6.
35. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol 2001;107:191-3.
36. Sicherer SH, Simons FER. Quandaries in prescribing an emergency action plan and self-injectable epinephrine for first-aid management of anaphylaxis in the community. J Allergy Clin Immunol 2005;115: 575-83.
37. Hu W, Kemp AS, Kerridge I. Making clinical decisions when the stakes are high and the evidence unclear. BMJ 2004;329:852-4.
38. Clark S, Bock SA, Gaeta TJ, Brenner BE, Cydulka RK, Camargo CA. Multicenter study of emergency department visits for food allergies. J Allergy Clin Immunol 2004;113:347-52.
39. Clark S, Long AA, Gaeta TJ, Camargo CA. Multicenter study of emergency department visits for insect sting allergies. J Allergy Clin Immunol 2005;116:643-9.
40. Brown SGA, Blackmean KE, Heddle RJ. Can serum mast cell tryptase help diagnose anaphylaxis? Emerg Med Australasia 2004;16:120-4.
41. Shreffler WG, Beyer K, Burks AW, Sampson HA. Microarray immunoassay: association of clinical history, in vitro IgE function, and heterogeneity of allergenic peanut epitopes. J Allergy Clin Immunol 2004;113: 776-82.
42. Macqueen G, Marshall J, Perdue M, Siegel S, Bienenstock J. Pavlovian conditioning of rat mucosal mast-cells to secrete rat mast-cell protease-Ii. Science 1989;243:83-5.
43. Li XM, Serebrisky D, Lee SY, Huang CK, Bardina L, Schofield BH, et al. A murine model of peanut anaphylaxis: T- and B-cell responses to a major peanut allergen mimic human responses. J Allergy Clin Immunol 2000;106:150-8.
44. Teuber SS, del Val G, Morigasaki S, Jung HR, Eisele PH, Frick OL, et al. The atopic dog as a model of peanut and tree nut food allergy. J Allergy Clin Immunol 2002;110:921-7.
45. Helm R, Furuta GT, Stanley J, Ye J, Cockrell G, Connaughton C, et al. A neonatal swine model for peanut allergy. J Allergy Clin Immunol 2002; 109:136-42.
46. Yocum MW, Butterfield JH, Klein JS, Volcheck GW, Schroeder DR, Silverstein MD. Epidemiology of anaphylaxis in Olmsted County: a population-based study. J Allergy Clin Immunol 1999;104:452-6.
47. Fuchs S, Jaffe DM, Christoffel KK. Pediatric emergencies in office practices: prevalence and office preparedness. Pediatrics 1989;83: 931-9.