Clinical Trial Protocol

Clinical Trial Protocol Number	LEVI-04-21-02
Title	A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Trial of the Efficacy and Safety of LEVI-04 in Patients with Osteoarthritis of the Knee
Phase	2a
EudraCT Number	2021-006540-28
Coordinating Investigator	Professor Philip Conaghan, MB BS PhD FRACP Leeds Institute of Rheumatic and Musculoskeletal Medicine Woodhouse Lane Leeds, LS2 9JT
Sponsor	Levicept Ltd. Innovation House, Discovery Park Ramsgate Road Sandwich, CT13 9ND, Kent UK Medical Responsible: Dr Colin Michael Perkins MD FRCP(Edin) FFPM Chief Medical Officer, Levicept Ltd
Sponsor Legal Representative in the European Union	NBCD A/S Søborg, Denmark
Clinical Trial Protocol Version	Version 3.0_07FEB2023
Replaces Version	1.0_09MAR2022 and DK version 1.1_24MAY2022

- Confidential –

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1 List of Abbreviations

ACR	American College of Rheumatology
APR	Accurate Pain Reporting
ADA	Anti-Drug Antibody
AE	Adverse Events
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BCTQ	Boston Carpal Tunnel Questionnaire
BMI	Body Mass Index
BT	Body Temperature
BP	Blood Pressure
CRO	Clinical Research Organization
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EOT	End of Trial
FCS	Fully Conditional Specification
FDA	Food and Drug Administration
FIH	First In Human
FU	Follow-up
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HA	Health Authorities
hCG	Human Chorionic Gonadotropin
hsCRP	Highly sensitive C-Reactive Protein
HR	Heart Rate
HV	Healthy Volunteer
IA	Interim Analysis

IB	Investigators Brochure
ICF	Informed Consent Form.
ICH	The International Conference on Harmonization
IEC	Independent Ethics Committees
IMP	Investigational Medicinal Product
IRB	Institutional Review Boards
ITT	The Intention-to-Treat
IWRS	Interactive Web Responding System
JSW	Joint Space Width
KL	Kellgren Lawrence
MedDRA	Medical Dictionary for Regulatory Activities
MG	Milligrams
MI	Multiple Imputations
mITT	Modified Intention-to-Treat
mm	Millimeters
MRI	Magnetic resonance imaging
NGF	Nerve Growth Factor
NOAEL	No Observed Adverse Effect Level
NRS	Numeric Rating Scale
NT3	Neurotrophin-3
NSAID	Non-steroidal Anti-inflammatory Drug
OA	Osteoarthritis
PD	Pharmacodynamics
PDF	Portable Document Form
PGA	Patient Global Assessment
PK	Pharmacokinetics
PP	Per-Protocol
PRR	Placebo Response Reduction
PT	Preferred Term
QTcF	Heart rate corrected QT interval (Fridericia)
RPOA	Rapidly Progressive Osteoarthritis

RSR	Research Subject Responsibility
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIF	Subchondral Insufficiency Fractures
SD	Standard Deviation
SOC	System Organ Classes
SSRI	Selective Serotonin Reuptake Inhibitor
SAS	Survey of Autonomic symptoms
stEPP	Staircase Evoked Pain Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment Emergent Adverse Event
WOMAC	The Western Ontario and McMaster Universities Osteoarthritis Index NRS 3.1 24-hour recall
WOPAIN NRS	WOMAC Pain Subscale NRS 3.1 24-hour recall

Sponsor

Levicept Ltd.

Innovation House, Discovery Park

Ramsgate Road, Sandwich, CT13 9ND, UK

Sponsor Responsibilities

Levicept Ltd. will be responsible for overseeing all aspects of the study.

Clinical Research Organization (CRO)

NBCD A/S

Telefonvej 8D

DK-2680 Søborg,

Denmark

CRO Responsibilities

NBCD A/S will be responsible for clinical operations and monitoring of study.

Investigators and Trial Sites

The trial will be conducted at approximately 15 sites worldwide.

The Coordinating Investigator Professor Philip Conaghan, MB BS PhD FRACP, Leeds Institute of Rheumatic and Musculoskeletal Medicine represents all Investigators for decisions and discussions regarding this trial, consistent with the International Conference on Harmonization (ICH) Topic E6 Good Clinical Practice (GCP); hereafter referred to as ICH GCP. The Coordinating Investigator will provide expert medical input and advice relating to trial design and execution and is responsible for the review and signoff of the clinical trial report.

Signature pages for the Protocol Lead and the Coordinating Investigator as well as a list of Sponsor and CRO responsible persons are provided in Appendix III: Signature Pages and Responsible Persons for the Trial.

The trial will appear in the following clinical trial registries:

http://www.clinicaltrials.gov

https://www.clinicaltrialsregister.eu/

Details of structures and associated procedures will be defined in a separate Clinical Study Management Plan, which will be prepared under the supervision of the Clinical Trial Leader.

2 Protocol Synopsis

Study Title	A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Trial of the Efficacy and Safety of LEVI-04 in Patients with Osteoarthritis of the Knee
Protocol Number	LEVI-04-21-02
Product Name	LEVI-04
Development Phase	2a
Indication	Osteoarthritis (OA) of the knee
Primary Objective	To evaluate the efficacy of LEVI-04 (multiple doses) compared to placebo in reducing pain due to knee OA.
Secondary Objectives	• To evaluate the efficacy of LEVI-04 (multiple doses) compared to placebo in improving physical function. • To evaluate the efficacy of LEVI-04 (multiple doses) compared to placebo in improving joint stiffness. • To evaluate the efficacy of LEVI-04 (multiple doses) compared to placebo in Patient Global Assessment (PGA). • To evaluate the proportion of responders based on various levels of reduced pain in participants receiving LEVI-04 (multiple doses) compared to placebo. • To evaluate rescue medication use in the LEVI-04 group (multiple doses) compared to placebo.
Exploratory Objectives	• To evaluate the efficacy of LEVI-04 compared to placebo in time to onset of pain relief. • To explore associations between imaging biomarkers and pain severity. • To explore associations of biomarkers of the neurotrophin signaling pathway and pain severity.
Safety Objectives	• To evaluate the overall safety of LEVI-04 compared to placebo. • To evaluate the safety of LEVI-04 compared to placebo in relation to the peripheral nervous system. • To evaluate the safety of LEVI-04 compared to placebo in relation to joint safety.

Study Design	This is a randomized, double-blind, placebo-controlled trial of multiple doses and multiple administrations of LEVI-04 for the treatment of pain due to osteoarthritis (OA) of the knee. The study consists of a Screening Period (including a Diary Run-In/analgesic wash-out Period), Randomization, Post-Randomization Period, and a Follow-up Period. Up to 624 participants will be enrolled and randomized to one of four Treatment Arms (see section Treatment Regimen) at the ratio 1:1:1:1. The Investigational Medicinal Product (IMP) will be administered at five visits: Day 1 (Randomization), Week 4, Week 8, Week 12, and Week 16, respectively. A Follow-up/End-of-Trial (FU/EOT) visit will take place at Week 20 and a Follow-Up Safety Phone Visit (Visit 12) will be completed at Week 30. Screening Period The Screening period may take up to 8 weeks (56 days). This period includes at least two visits (Visit 1 and 2), Radiographs of major joints (knees, hips, and shoulders), a Diary Run-In Period of at least 10 days duration and Magnetic Resonance Imaging (MRI) of both knees. The WOMAC Pain subscale Numeric Rating Scale (NRS) 3.1, 24-hour recall (WOPAIN NRS) for both knees (treatment naïve or 48-hour analgesic wash-out from all analgesics required) must be obtained during the Screening period prior to MRI of both knees. Visit assessments and procedures per Schedule of Events (SoE) are recommended completed as below, but one or more elements may be performed in another order as deemed most appropriate by the Investigator. Screening Visit (Visit 1): At this visit, the Informed Consent Form (ICF) will be completed, and initial eligibility determined. • Signed Informed Consent Form • WOPAIN NRS completed for both knees (Treatment-naïve or 48-hour wash-out of analgesics prior required) with a score of ≥20 out of 50 needed for proceeding with Screening. ○ If the participant has taken analgesics in the 48-hours prior, WOPAIN NRS should be completed at Visit 2. • Medical History and Demographics • Concomitant medication including review of contraception for Women of Childbearing Potential (WOCBP) (Appendix I) and use of illicit and recreational substances. • Participants must agree to stop any current analgesic medication when starting the Diary Run-In Period and for the duration of the study (until

	completion of Visit 11 FU/EOT visit), including the remaining Screening period. • Boston Carpal Tunnel Questionnaire (BCTQ) • Survey of Autonomic symptoms (Q1a and Q1b) • Electrocardiography (ECG) • Safety blood tests (including serum pregnancy test) • Physical exam (musculoskeletal exam not required), vital signs, weight, height and Body Mass Index (BMI) • Assessment of eligibility • Ensure the patient is willing and able to tolerate the MRI assessment • Radiographs of both knees, to be read centrally to confirm eligibility on the Kellgren Lawrence (KL) grading (KL grade ≥2), to exclude pathologies other than OA, and to ensure there are no relevant exclusion conditions prior to MRI assessment. • Radiographs of both hips and shoulders, to exclude significant pathology other than OA. <u>Diary Run-In Visit (Visit 2):</u> Assessments as per Table 1: Schedule of Events: • If WOPAIN NRS (48-hour analgesic wash-out required) has not yet been completed for both knees at Visit 1, it is to be collected at Visit 2 prior to issuing of electronic diary (eDiary). • The eDiary will be issued and kept by the participant for the duration of the study (until completion of visit 11 FU/EOT visit). • The participant will undergo eDiary training on Research Subject Responsibilities (RSR), Accurate Pain Reporting (APR) and Placebo Response Reduction (PRR). • Dispensation of analgesic Rescue Medication (RM), paracetamol tablets (maximum 4000 mg/day). Participants will, however, be strongly discouraged from taking the Rescue Medication during the Diary Run-In Period and in the 48-hours prior to scheduled visits. <u>Diary Run-In Period (10-14 days)</u> Participants will be required to stop all analgesic medication (other than the RM provided, to be used if required) • Throughout the Diary Run-In Period, every evening, participants will be asked to 'select the number that best describes their average pain over the past 24 hours' for both knees separately.

	• The Diary Run-In Period is 10-14 days of duration and requires Average Daily NRS Pain scores completed on at least 6 of the last 7 days of the period (not required to be consecutive days). • If, following completion of Day 10 of the Diary Run-In Period, there are not NRS Pain scores on at least 6 of the 7 previous days (i.e. day 4-10 both inclusive, but not required to be consecutive days) or if deemed otherwise reasonable by the Sponsor, it is possible to prolong the Dairy Run-In Period to a maximum of 14 days. • Participants will be required to enter the use of Rescue Medication daily into the eDiary. Diary Eligibility is based on meeting the criteria listed below, which will be calculated automatically from the last 7 days of the Diary Run-In Period and will constitute the Baseline NRS Pain score: • Completion of Average Daily NRS pain score on at least 6 of the last 7 days • Mean Average Daily NRS Pain score ≥4.0 and ≤9.0 • Mean Average Daily NRS Pain variability ≤1.5 After completion of the Diary Run-In Period and eligibility has been confirmed, participants will continue to report their Average Daily NRS Pain scores for each knee in the eDiary until Target Knee has been selected at Visit 3 (Randomization). MRI visit MRI of both knees must be performed and read centrally prior to randomization. It is recommended that its performed once eligibility following the Diary Run-In Period is confirmed. Selection of Target Knee Target Knee will be selected at Visit 3 (Randomization) following completion of the Diary Run-In Period and confirmed eligibility on MRI of both knees. Target Knee must meet following criteria with WOPAIN NRS completed as the last eligibility assessment at Visit 3 (Randomization): • Confirmed OA based on American College of Rheumatology (ACR) clinical diagnostic criteria • Knee pain on most days for at least 3 months prior to Screening • KL grade ≥2 • WOPAIN NRS score of ≥20 out of 50 during Screening (Visit 1 or 2) **and** Randomization (Visit 3) • Baseline NRS Pain score criteria as described above (See MRI Visit)

	• No presence of pathology on radiographs or MRI that would render the participant unsuitable for the study. If both knees are eligible on all above listed criteria, the dominant knee in the opinion of the Investigator will be selected as Target Knee. <u>Randomization (Visit 3, Day 1):</u> Final eligibility assessment (WOPAIN NRS target knee) to be performed prior to randomization and administration of 1st dose IMP. • Review of analgesic use, especially in the 48 hours prior to the visit • RM accountability and re-dispense supply if needed • Selection of Target knee • WOMAC full questionnaire (Target knee only) • Review eligibility including WOPAIN NRS completed at Visit 3 for Target knee • Randomization to Treatment Arm (See Treatment Regimen) • Patient Global Assessment (PGA) • Staircase Evoked Pain Procedure (StEPP) • Physical exam (including musculoskeletal exam) • Weight, BMI, Vital signs and ECG • Repeat eDiary training on APR, PRR, RSR and site will ensure the participant understands how to use eDiary for pain reporting and RM use. • Blood sample for safety labs, pharmokinetics (PK), pharmacodynamic (PD) biomarkers and Anti-Drug Antibodies (ADA) • Urine dipstick (including U-human Chorionic Gonadotropin (hCG) for WOCBP) • Administration of 1st dose IMP Following Randomization the participant will fill out Average Daily NRS Pain in the evening for Target Knee only (i.e from the evening of Visit 3). <u>Visit 4 (Telephone Visit, Week 2)</u> Participants will receive a phone call from site staff. • Ensure the participant understands how to use the eDiary for average daily pain reporting and recording any use of Rescue Medication. • Review of Adverse Events (AE). • Changes in concomitant medication

	Visit 5 (Week 4) Participants return to site for assessments and procedures as per Schedule of Events and 2nd dose of IMP. • Ensure the participant understands how to use the eDiary for average daily pain reporting and recording use of Rescue Medication. • RM accountability and re-dispense supply if needed • Review AEs and concomitant medication • Physical exam (including musculoskeletal exam), vitals and ECG • Urine analysis (including U-hCG for WOCBP) • Blood samples for safety labs, PK, PD biomarkers and ADA • Administration of 2nd dose IMP Visit 6 (Week 5) Participants will return to site for efficacy measures and assessments and procedures as per Schedule of Events. • Review of analgesic use, especially in the 48 hours prior to the visit • WOMAC full questionnaire • StEPP (Staircase Evoked Pain Procedure) • PGA • Review of AEs • Ensure the participant understands how to use the eDiary for average daily pain reporting and recording use of Rescue Medication. Visit 7 (Week 8) Participants will return to site for assessments and procedures as per Schedule of Events and receive their 3rd dose of IMP. • RM accountability and re-dispense supply if needed • Changes in concomitant medication • Review of potential AEs and ongoing AEs • BCTQ • Survey of Autonomic Symptoms (SAS) (Q1a and Q1b) • Physical exam (including musculoskeletal exam), Weight, BMI, Vital signs and ECG • Blood samples for safety labs and PK • Urine analysis (including U-hCG for WOCBP) • Ensure the participant understands how to use the eDiary for average daily pain reporting and recording use of Rescue Medication.

	• Administration of 3rd dose IMP Visit 8 (Week 12) Participants will return to site for assessments and procedures as per Schedule of Events and receive their 4th dose of IMP. • Ensure the participant understands how to use the eDiary for average daily pain reporting and recording use of Rescue Medication. • RM accountability and re-dispense supply if needed • Changes in concomitant medication • Review of potential AEs and ongoing AEs • Physical exam (including musculoskeletal exam), vitals and ECG • Urine analysis (including U-hCG for WOCBP) • Blood samples for safety labs and PK • Administration of 4th dose IMP Visit 9 (Week 16) Participants will return to site for assessments and procedures as per Schedule of Events and receive their 5th and final dose of IMP. • Ensure the participant understands how to use the eDiary for average daily pain reporting and recording use of Rescue Medication. • RM accountability and re-dispense supply if needed • Changes in concomitant medication • Review of potential AEs and ongoing AEs • Physical exam (including musculoskeletal exam), vitals and ECG • Urine analysis (including hCG -female participants only)) • Blood samples for safety labs and PK • Administration of 5th dose IMP Visit 10 (Week 17) Participants will return to site for efficacy measures and assessments and procedures as per Schedule of Events. • Review of analgesic use, especially in the 48 hours prior to the visit • RM accountability and re-dispense supply if needed • WOMAC full questionnaire • StEPP • PGA • Review of potential AEs and ongoing AEs

	• Ensure the participant understands how to use the eDiary for average daily pain reporting and recording use of Rescue Medication. Visit 11 (Follow-up/End-of-Trial Visit, Week 20) Participants will have their final study visit, with assessments per the Schedule of Events. From completion of Visit 11 procedures and assessments, the participant is no longer required to abstain from study prohibited concomitant medications. • Review of analgesic use, especially in the 48 hours prior to the visit • Review AEs and concomitant medication. • SAS (Q1a and Q1b) • BCTQ • Physical exam (including musculoskeletal exam), Vital signs, Weight and BMI • Blood samples for Safety labs, PK, PD biomarkers and ADA • Urine dipstick hCG for WOCBP • Final accountability of Rescue Medication • Radiographs bilateral knee-, shoulder- and hip joints • MRI Target Knee Visit 12 (Follow-up Safety Phone Visit, Week 30) • Participants will receive a phone call from site staff to review AEs and current use of concomitant medication.
Planned Number of Sites	Approximately 15 Sites Worldwide
Study Population	Inclusion Criteria: 1. Signed ICF 2. Male or female participants between ≥40 and ≤80 years of age 3. BMI ≤40 kg/m2 4. The ability, in the opinion of the investigator, to utilize the eDiary device provided and comply with study requirements 5. History of knee pain on most days for at least 3 months prior to Screening 6. Confirmation of OA of the Target knee a. Radiographs of both knees with a Posterior-Anterior, Fixed-flexion view taken during the Screening Period b. American College of Rheumatology (ACR) clinical and radiographic diagnostic criteria

	7. Evidence of Target knee OA with a KL grade ≥2, determined through central reading 8. Target Knee must have a score of ≥20 out of 50 on the WOMAC NRS 3.1 pain subscale during Screening and at Randomization 9. The Baseline NRS Pain score will be derived from the last seven days of the Diary Run-In Period and must meet following criteria: a. Completion of Average Daily NRS Pain score on at least 6 of the 7 days b. Mean Average Daily NRS Pain score must be ≥4.0 and ≤9.0 c. Mean Average Daily NRS Pain variability must be ≤1.5 10. If female and 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 an agreed upon highly effective method of birth control throughout the study period and at least 3 months after last dosing of IMP 11. If male and sexually active with partner of childbearing potential, willing to agree to practice a highly effective method of contraception from Visit 2 and at least 3 months after Visit 11 (week 20) 12. Willing to withdraw from any medication for OA including, but not limited to, Opioids (including semisynthetic opioids), Non-Steroidal Anti-inflammatories (NSAIDs), COX-2 inhibitors, Topical medication, and Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs e.g Duloxetine) 13. Participant agrees to take only the allowed Rescue Medications from the start of the Diary Run-In Period through study completion (FU/EOT visit 11) (maximum 4000 mg paracetamol per day) Exclusion criteria: 1. Presence of OA of other major joints (including but not limited to nontarget knee) that could interfere with assessment of pain due to OA of the target knee, in the opinion of the investigator. 2. Current comorbid condition, other than OA, affecting target knee or systemic illness known to be significantly associated with arthritis or joint pathology affecting any joint, including but not necessarily limited to endocrinopathies or autoimmune disease with significant joint involvement (e.g., Rheumatoid Arthritis); Seronegative Spondyloarthropathies (e.g. Ankylosing Spondylitis, Psoriasis arthritis, Reactive arthritis) 3. Pathological conditions significantly affecting joint and bone health, in the opinion of the Investigator should be excluded (including but not necessarily limited to following findings on x-rays and/or MRI): • Known presence of Rapidly Progressive Osteoarthritis (RPOA) (any joint) • Osteonecrosis (including avascular necrosis) (any joint) • Subchondral insufficiency fractures (SIF) (any major joint)

	• Fractures or stress reactions with radiographic signs of ongoing healing processes (including but not limited to osteoporotic and pathological fractures) (any major joint) • Excessive malalignment of the knee (anatomical axis angle greater than 10 degrees) (Target knee only) • Complete tear of the posterior meniscal root (partial tears and/or anterior meniscal tears not excluded) (either knee) • Large or extensive subchondral cysts (either knee) • Anserine or patellar bursitis (Target knee only) • Significant articular bone loss (any joint) • Articular bone fragmentation or collapse (any joint) • Primary or metastatic tumor (any joint) • Joint infection (any joint) • Paget's disease (any joint) • Osteochondritis dissecans (any joint) 4. Hip dislocation and congenital hip dysplasia with degenerative joint disease should be excluded. 5. History of gout, or pseudogout, unless on hypouricemic therapy (including allopurinol) and no episodes within the last 12 months. 6. Presence of neuropathic pain deemed likely to interfere with trial endpoints, complex regional pain syndrome, or chronic widespread pain syndromes e.g., fibromyalgia 7. History of significant trauma (e.g., intra-articular fracture) or surgery (excluding injection therapies and arthroscopy) to a knee, hip, or shoulder within the previous 1 year or previous target knee alloplasty 8. Planned major surgery or other major invasive procedures while participating in the study 9. Surgery or stent placement for coronary artery disease in the six months prior to screening 10. Nondiagnostic arthroscopy performed on the target knee joint within 180 days prior to Screening; or diagnostic arthroscopy performed on the target knee joint within 90 days prior to Screening 11. Intraarticular injection therapies to the target knee joint within 12 weeks prior to Screening, or to any non-target major joint within 6 weeks prior to Screening 12. Participants likely to be deemed unfit for joint replacement surgery due to concomitant illness, in the investigator opinion 13. Opioid use, including Tramadol, of 4 or more instances per week over the month prior to Screening 14. Known history of hypersensitivity to monoclonal antibodies 15. Presence of any medical condition or unstable health status that, in the judgment of the investigator, might adversely impact the safety of the participant or efficacy results of the trial

	16. Medical history and/or clinical findings (including ECG) of cardiac disease that in the opinion of the investigator are considered of clinical significance, including but not limited to established ischemic heart disease, peripheral arterial disease and /or cerebrovascular disease (unstable angina, myocardial infarction, cardiovascular thrombotic events, transient ischemic attacks, and stroke are considered clinically significant if time of event occured within six months prior to screening) 17. Active malignancy or history of malignancy within the past 5 years, with exception of resected and cured basal cell carcinoma and squamous cell carcinoma of the skin 18. Clinically significant abnormal laboratory parameter(s) and/or electrocardiogram (ECG) parameter(s) during Screening, that, in the judgment of the Investigator, would preclude the participant from participation in this study 19. Participation in other studies involving investigational drug(s) within 30 days (or 90 days for biologics) prior to screening 20. History of Carpal Tunnel Syndrome with signs or symptoms within one year of Screening or a Boston Carpal Tunnel questionnaire (Symptom Severity Scale mean score ≥3) 21. Total score on Number of Symptoms (Column Q1a) on the SAS >3 22. Pregnant or breast feeding 23. Previously received any form of anti-Nerve Growth Factor (NGF) 24. Requires walker or wheelchair for mobility (walking stick permitted) 25. Active or historic substance abuse within one year of Screening in the opinion of the Investigator 26. Medical history within 5 years of Screening that involves suicidal ideation, suicide attempt, or increased risk of suicide as assessed by the Investigator. 27. Presence of any contraindication to MRI, including partial or total joint replacements that are expected to interfere with the quality of the imaging
Treatment Regimen	Participants will be randomized to one of three active treatment arms and one placebo arm in 1:1:1:1 ratio. Treatment arms • 0.3 mg/kg dose intravenous infusion of LEVI-04 • 1.0 mg/kg dose intravenous infusion of LEVI-04 • 2.0 mg/kg dose intravenous infusion of LEVI-04 • Placebo dose intravenous infusion Rescue Medication • Paracetamol, up to a maximum dose of 4000 mg/ day, will be dispensed by site at Visit 2 (Diary Run-In Visit).

	Prohibited Medications • Opioid medication • Other medications for treatment of pain due to OA of the Target Knee including, but not limited to, NSAIDs, topical medication, and SNRIs (e.g. Duloxetine)
Endpoints	Primary Endpoint • Change in WOMAC Pain subscale from Randomization (Visit 3) to Visit 10 (week 17). Secondary Endpoints • Change in WOMAC Pain subscale from Randomization (Visit 3) to Visit 6 (week 5). • Change in WOMAC Physical function subscale from Randomization (Visit 3) to Visit 6 (week 5) and Visit 10 (week 17). • Change in WOMAC Stiffness subscale from Randomization (Visit 3) to Visit 6 (week 5) and Visit 10 (week 17). • Change in StEPP from Randomization (Visit 3) to Visit 6 (week 5) and Visit 10 (week 17). • Change in PGA from Visit 6 (week 5) to Visit 10 (week 17). • Proportion of participants achieving 30% and 50% reduction in WOMAC Pain subscale at week 5 and week 17 using a cumulative distribution function. • Rescue Medication usage during the trial • Change in average weekly NRS Pain score from Baseline to Visit 6 (week 5) and Visit 10 (week 17). • Area under the curve of Average Daily NRS Pain score from Baseline to Visit 11 (week 20). Exploratory Endpoints • Time from Randomization to a decrease in average weekly NRS pain of 30% from Baseline NRS Pain score. • Associations of imaging biomarkers and pain severity at Randomization (Visit 3) to Visit 11 (week 20). • Correlations between pain variability during Screening and major efficacy endpoints • Change from Baseline in blood biomarkers of the neurotrophin signaling pathway and associations with clinical outcomes

	Safety Endpoints
	
	• AEs between treatment arms (Count and Severity)
	• Peripheral Nervous System AEs between treatment arms (Count and Severity)
	• Incidences of Joint Events and subtypes of Joint Events. Events include:
	  o Osteonecrosis
	  o Destructive Arthropathy, including RPOA type 2
	  o Changes in signs of inflammation on MRI of the Target Knee,
	  o Subchondral insufficiency fracture
	  o Rapid loss of joint space width (JSW) by 2 mm within 12 months or loss of 50% of JSW if less than 2 mm at baseline. This is also called RPOA type 1
	  o Any other incidence of joint events such as acute fracture, bone marrow infiltration, etc.
	• Incidence of surgical interventions including joint replacement.

Statistical Methods	An interim analysis (IA) will be performed for sample size re-estimation when approximately 208 participants have completed study Visit 6 (week 5) and approximately 80 patients have completed Visit 10 (week 17).

2.1 Table 1: Schedule of Events

	Screening (Up to 56 days)				**Day 1**	**Week 2 Day 15** +/- 3 days	**Week 4 Day 29** +/-3 days	**Week 5 Day 36** +/-3 days	**Week 8 Day 57** +/- 3 days	**Week 12 Day 85** /- 3 days	**Week 16 Day 113** +/- 3 days	**Week 17 Day 120** +/-3 days	**Week 20 Day 141** +/-3 days	**Week 30 Day 211** +/-7 days
Procedure	**Visit 1** Screening Visit	**Visit 2** Diary Run-In Visit	**Diary Run-In Period** (10-14 days)	**MRI visit**	**Visit 3 Randomization** Dose 1	**Visit 4** Phone Visit	**Visit 5** Dose 2	**Visit 6**	**Visit 7** Dose 3	**Visit 8** Dose 4	**Visit 9** Dose 5	**Visit 10**	**Visit 11 FU/EOT Visit***	**Visit 12 FU Safety Phone visit****
Informed Consent	X													
Demography	X													
Medical History	X													
Concomitant Medication[1,2,3]	X	X			X	X	X		X	X	X		X	X
Eligibility Criteria[4]	X	X		X	X									
Selection of Target Knee[5]					X									
Randomization					X									
Radiographs[6]	X												X	
MRI[7]				X									X	
eDiary Review/Training[8]		X			X	X	X	X	X	X	X	X		
Adverse Events	X	X			X	X	X	X	X	X	X	X	X	X
Average Daily NRS Pain (both knees)			←	→										
Average Daily NRS Pain (Target Knee only)					←								→	
Administer Study Drug					X		X		X	X	X			
48 h analgesic wash-out[1]	X	(X)			X		X	X	X	X	X	X	X	
WOPAIN NRS (both knees)[9]	X	(X)												

	Screening (Up to 56 days)				Day 1	Week 2 Day 15 +/- 3 days	Week 4 Day 29 +/-3 days	Week 5 Day 36 +/-3 days	Week 8 Day 57 +/- 3 days	Week 12 Day 85 +/- 3 days	Week 16 Day 113 +/- 3 days	Week 17 Day 120 +/-3 days	Week 20 Day 141 +/-3 days	Week 30 Day 211 +/-7 days
Procedure	**Visit 1** Screening Visit	**Visit 2** Diary Run-In Visit	**Diary Run-In Period** (10-14 days)	**MRI visit**	**Visit 3 Randomization** Dose 1	**Visit 4** Telephone Visit	**Visit 5** Dose 2	**Visit 6**	**Visit 7** Dose 3	**Visit 8** Dose 4	**Visit 9** Dose 5	**Visit 10**	**Visit 11 FU/EOT Visit***	**Visit 12 FU Safety Phone visit***
WOMAC questionnaire (Target knee)					X			X				X		
StEPP					X			X				X		
PGA					X			X				X		
BCTQ	X								X				X	
SAS	X								X				X	
Physical Exam	X				X		X		X	X	X		X	
Musculoskeletal Exam					X		X		X	X	X		X	
Vital Signs	X				X		X		X	X	X		X	
ECG	X				X		X		X	X	X			
Rescue Medication[10]		X			X		X	X	X	X	X	X	X	
Weight	X				X				X				X	
Height	X													
BMI[11]	X				X				X				X	
Blood Safety labs	X				X		X		X	X	X		X	
Serum hCG[12]	X													
Blood Test for PK[13]					X		X		X	X	X		X	
Blood Test for PD[14]					X		X						X	
Anti-Drug Antibodies[14]					X		X						X	
Urine Dipstick analysis[15]					X		X		X	X	X			
Urine Dipstick hCG					X		X		X	X	X		X	

*All participants should complete Visit 11 and Visit 12. If a participant has discontinued trial early (prior to completion of Visit 10), the EOT/FU visit should be completed at 4 weeks (+/-3 days) of last IMP dose received and the Follow-up safety visit (phone visit) be scheduled at least 12 weeks following last IMP administration.

[1]Participants are required to stop any analgesic medication at the start of the Diary Run-In Period and until completion of visit 11 FU/EOT visit. Rescue Medication will be provided (Paracetamol, max 4000 mg/day), but participants must be discouraged from taking it, particularly in the 48 hours prior to visits.

[2]Review of contraception use for WOCBP and male participants with female partners of childbearing potential.

[3]Review usage of illicit and recreational substances

[4]Ensure participant is eligible on all inclusion/exclusion criteria

[5]Selection of Target Knee after completion of the Diary Run-In Period and MRI of both knees has been read.

[6]Radiographs of both knee-,shoulder- and hip joints can be performed at any time prior to Visit 2 as long as they have been evaluated for eligibility prior to Visit 2

[7]MRI to be completed for both knees during Screening and reviewed for eligibility prior to selection of Target Knee at Visit 3. MRI of Target Knee only at study completion (FU/EOT visit)

[8]Ensure that the participant understands how to use the eDiary daily for completion of Average Daily NRS Pain score(s) and recording of any use of Rescue Medication. Accurate Pain Reporting (APR), Placebo Response Reduction (PRR) and Research Subject Responsibility (RSR) training to be completed at Visit 2 and Visit 3. Training modules to be repeated if indicated.

[9]WOMAC Pain subscale (WOPAIN NRS) for both knees to be completed during Screening prior to starting the Diary Run-In Period. The participant is required to abstain from taking analgesics in the 48-hours prior to completion or be treatment naïve. If not completed at Visit 1, WOPAIN NRS can be completed at Visit 2.

[10]Rescue Medication (Paracetamol) dispensation, and use of Rescue Medication accounted for.

[11]BMI calculated automatically in EDC

[12]Serum hCG to be collected during Screening for WOCBP. If needed, safety labs can at all later timepoints include a Serum hCG.

[13]At IMP dosing visits PK samples are to be collected pre-dose and post-dose (following completion of IMP infusion, before leaving the clinic). At Visit 11/EOT the PK sample can be taken at any time of visit.

[14] Samples for PD biomarkers and Anti-Drug Antibodies to be taken pre-dose at Visits 3, 5 and 11.

[15] Urine dipstick analysis to be performed locally at site. If any clinically significant out-of-range values or indicated by symptoms, participant will be referred to primary care.

3 Background Information

3.1 Study Rationale

Symptomatic knee OA is a painful chronic joint disease estimated to affect approximately 45% of the population during a lifetime[1]. Clinical manifestations include joint stiffness, swelling, crepitus, and limited mobility, but the hallmark symptom of OA is pain[2]. Pain is the driving symptom leading patients to seek treatment and the symptom that most affects quality of life[3]. OA pain etiology, however, is complex, heterogenic, and yet to be fully understood[4].

Among several available guidelines for management of knee OA pain The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)[5] and Osteoarthritis Research Society International (OARSI)[6], are consistent in the majority of their recommendations: Following core treatments (e.g. patient education and exercise programs), both the OARSI and ESCEO recommend the use of topical Non-Steroidal Anti-inflammatory Drugs (NSAIDs) and short-term use of paracetamol (acetaminophen) as first-line pharmaceutical management of knee OA pain. Patients with persistent pain are recommended oral NSAIDs, however, only to be used intermittently for the shortest period and at the lowest possible dose, due to their known adverse cardiovascular, hepatic, and renal risks. If such treatments are insufficient or not well tolerated, both guidelines recommend intraarticular corticosteroid injection or/and hyaluronic acid injections. Though highly efficient in the short term (2-4 weeks) intraarticular injections with corticosteroids are associated with osteoporosis, decreased efficiency when used long- term (over 6 weeks),[7] and risk of accelerated cartilage loss[8]. As a last option, prior to recommending surgical intervention, guidelines recommend short-term treatment with opioids or treatment with Duloxetine, a serotonin–norepinephrine reuptake inhibitor (SNRI).

In conclusion treatment options for sufficient long-term OA pain management is limited and/or unsustainable, possibly leading clinicians to overprescribe drugs with serious and complicated long-term effects such as NSAIDs and opioids.

Despite numerous attempts in clinical drug development to provide a durable, safe, and effective treatment option, none have currently been successful. Targeted drug development of pain medication and further research on OA pain pathology is therefore warranted.

3.2 Scientific Rationale and Role of Target in the Disease

LEVI-04's primary mode of action is inhibition of the activity of the Neurotrophins; Nerve Growth Factor (NGF) and Neurotrophin-3 (NT3) to reduce pain.

NGF is an important mediator of pain associated with OA[9]. Monoclonal antibodies against NGF showed efficacy in treating chronic pain due to OA in phase III clinical trials[10,11]. However, risk of Rapidly Progressing Osteoarthritis (RPOA)[12] and adverse effects on the sympathetic nervous system[13] raised concerns regarding their safety.

LEVI-04 is a fusion protein and thus has a different antagonist profile to anti-NGF antibodies and differs on several points:

- Unlike anti-NGF antibodies that require plasma concentrations ~1000-fold the primary affinity to demonstrate efficacy in clinical studies[10], LEVI-04 is efficacious in preclinical models of OA at concentrations of its potency for inhibition of NGF activity.
- LEVI-04 exhibits a more gradual inhibition of NGF-induced activity compared with anti-NGF antibody mediated inhibition.
- Multiple preclinical studies, including comparative histopathology and neuropathological evaluation studies of LEVI-04 and anti-NGF antibodies, have been performed specifically to address any safety concerns (See IB for full overview). These studies confirmed the detrimental effects of anti-NGF antibodies, but found no evidence of such effects of LEVI-04 at therapeutic doses.

Together, this indicates LEVI-04 to not be associated with the known risk of RPOA associated with anti-NGF antibodies. Conversely, treatment with LEVI-04 was found to be associated with improvements in the histopathological assessments compared to the control animals, which could indicate a beneficial disease-modifying effect of LEVI-04. These preclinical findings support the investigation of LEVI-04 as a novel drug for the treatment of OA.

For a full description of the modalities of LEVI-04 and study references, see Description of the Investigational Medical Product (Section 6.1.1) and Investigators Brochure (IB).

3.3 Non-Clinical and Clinical Data

3.3.1 Non-Clinical data

The potential for toxicity of LEVI-04 has been evaluated in preliminary studies and formal toxicology studies. In 4-week, repeat-dose toxicity studies (cynomolgus monkeys and Han Wistar rats), LEVI-04 was well tolerated and no overt adverse toxicological effects were observed.

- LEVI-04 was well tolerated in rats at doses of 10, and 15 mg/kg. From this, the maximum tolerated dose is considered to be above 15 mg/kg.
- LEVI-04 was well tolerated in cynomolgus monkeys at all doses tested. From this study the maximum tolerated dose is considered to be above the 100 mg/kg dose.
- There were no adverse histopathological findings reported in the 4-week rat or cynomolgus monkey studies. ´
- In the rat study, non-adverse findings were limited to an increased incidence of wounding in the head and neck area in all doses tested. This effect was reversed during the treatment free period.
- In the cynomolgus monkey study, non-adverse neuropathological findings were described in the 30 and 100 mg/kg dose groups none of which were statistically significant ($p>0.05$) to those observed in corresponding control animals administered placebo.

- The No Observed Adverse Effect Level (NOAEL) for LEVI-04 in the Han Wistar rat and Cynomolgus monkey was 30 and 100 mg/kg weekly, respectively; the highest dose tested in each study. This correlated with C_{max} values of 1230000 and 1150000 ng/mL in male and female rats, respectively: and 3760000 and 4060000 ng/mL in the male and female monkeys, respectively. The human equivalent doses are 4.8 and 32.3 mg/kg for the NOAEL rat and monkey doses, respectively.

In a 26-week biweekly repeat dose (up to 30 mg/kg/dose) toxicology study in cynomolgus monkeys no relevant findings were made. There were no test related effects on organ weight and no gross nor microscopic findings.

3.3.2 Clinical data

A Levicept First-In-Human (FIH), Phase 1, Placebo-controlled, Double-blind, Single Ascending dose study of LEVI-04 (NCT03227796) was conducted 03 Aug 2021 to 31 Mar 2021 with 56 participants enrolled as cohorts of Healthy Volunteers (HV) (dosed with up to 3.0 mg LEVI-04/kg) and cohorts with knee OA patients (dosed with up to 1.0 mg LEVI-04/kg). Inclusion criteria included age 18–65 years (HV) or 30 to 80 years (OA patients), Body Mass Index (BMI) 18-32 kg/m^2 (HV) or 18-40 kg/m^2 (OA patients). For OA patients only there was a requirement of radiographs with tibiofemoral Kellgren Lawrence (KL)-grade ≥ 1 and <4 for Target Knee and ≤3 for Non-Target Knee, a NRS pain score between 5 and 9 and willingness to discontinue all pain medication (except for tablet paracetamol).

While no effect of LEVI-04 on knee pain or other OA symptoms could be concluded from the Phase I data, there was some evidence of efficacy from studying individual patient data. Three participants, on 0.3 and 1.0 mg/kg LEVI-04 and Placebo, respectively, used notably more Rescue Medication than any other participant either before or after dosing, or both. In the two participants on active, a temporary decrease in Rescue Medication usage coincided with a marked reduction in Target Knee pain and other OA symptoms, while in the Placebo participant, a gradual decrease in pain score correlated with an increase in the use of Rescue Medication. A fourth participant displayed a substantial decrease in WOMAC score after 0.03 mg/kg LEVI-04, with a corresponding decrease in Target Knee pain score, without use of Rescue Medication.

3.3.2.1 Safety and tolerability

LEVI-04 was well tolerated. There were no deaths, non-fatal Serious Adverse Events (SAEs), or AEs leading to participant withdrawal from treatment during the study. All Treatment-Emergent Adverse Events (TEAEs) were mild or moderate in severity. There were no findings of clinically significant physical, neurological or local tolerability, nor significant changes in vital signs, safety ECGs or laboratory variables. LEVI-04 did not elicit an immunogenic response in any participant or cohort. Positive Assays for the Detection of Anti-drugs Antibodies (ADA) to LEVI-04 were detected in one HV; however, those ADAs were present already prior to dosing.

3.3.2.1.1 Healthy Volunteer (HV) cohorts

In the HV Cohort (Cohorts 1–3 and 8), 53.6% reported at least 1 TEAE, only 1 of which (mild anxiety after 3.0 mg/kg LEVI-04) was considered by Investigator to be related to treatment. There was no evidence of a dose-related effect of LEVI-04 on the incidence of TEAEs in HV.

- The two must frequently reported System Organ Classes (SOCs) of the TEAEs were 'Infections and infestations', and 'Nervous system disorders' with 8 reported TEAEs in each class (7 and 6 participants, respectively).

- The most frequently reported TEAEs in HV cohorts were Headache, reported in 2 participants after Placebo, n=3 after 0.01 mg/kg LEVI-04, and n=1 after 3.0 mg/kg LEVI-04)

- All other TEAEs were reported by only one or two participants each, with no correlation to dose.

- Symptoms of autonomic dysfunction assessed by the Survey of Autonomic Symptoms (SAS) questionnaire occurred in 25.0% of HV on at least one occasion before or after dosing. There was no evidence of a dose-related effect of LEVI-04. One participant before 0.003 mg/kg LEVI-04, One participant before 3.0 mg/kg LEVI-04, Two participants before and after 0.01 mg/kg LEVI-04, Two participants before and after 0.03 mg/kg LEVI-04, One participant after Placebo.

3.3.2.1.2 OA patient cohorts

In the OA Cohorts (Cohorts 4–7), 85.7% of OA patients reported at least one TEAE and 21.4% were considered by the Investigator to be related to study treatment. The overall occurrence of TEAEs in OA patients appeared to decrease as the dose of LEVI-04 increased: TEAEs were recorded in 5 (100%) participants each after 0.03 mg/kg and 0.1 mg/kg LEVI-04; 4 (80.0%) participants after 0.3 mg/kg; and 3 (60.0%) participants after 1.0 mg/kg, compared with 7 (87.5%) participants after placebo.

- 'Nervous system disorders' was the most frequently reported SOC of TEAE (16 TEAEs in 11 participants). No participants reported a nervous system disorder TEAE after the highest dose of LEVI-04 (1.0 mg/kg). The most frequently reported TEAE were Headache, reported by three participants each after placebo (37.5%) and 0.03 mg/kg LEVI-04 (60.0%); and one participant after 0.1 mg/kg LEVI-04 (20.0%). Only one instance of headache was considered by the investigator to be related to the study drug, reported after placebo.

- All other drug related TEAEs were reported by only one or two participants each, with no correlation to dose.

- One significant AE was reported in one OA patient after 0.03 mg/kg LEVI-04; Paresthesia of moderate severity with onset about 12 days after dosing. Although not serious, this AE was initially considered to be a suspected AE of Special Interest (AESI), and the participant was referred for neurological review: the neurological assessment was normal (including no

symptoms of carpal tunnel syndrome), and the event was determined to be a pre-existing condition. The AE resolved after 2 days and was considered not related to treatment by the investigator. The final assessment was that this was not an AESI.

- Symptoms of autonomic dysfunction assessed by the SAS questionnaire occurred in 32.1% of OA patients on at least one occasion before or after dosing. There was no evidence of a dose-related effect of LEVI-04 on the incidence of symptoms of autonomic dysfunction. Symptoms were recorded in two participants both before and after 0.03 mg/kg LEVI-04; Three participants before and/or after 0.1 mg/kg; and one participant each before 0.3 and 1.0 mg/kg; and two participants before and after placebo.

4 Trial Objectives

The overall objective of this study is to evaluate the efficacy and safety of LEVI-04 compared to placebo in patients with knee OA. The Primary and Secondary objectives with corresponding endpoints and timeframes are included in following table.

4.1 Table 2: Objectives and mapped Endpoints

Objective(s)	Endpoint(s)
Primary	
To evaluate the efficacy of LEVI-04 (multiple doses) compared to placebo in reducing pain due to knee OA.	Change in WOMAC pain subscale from Randomization (Visit 3) to Visit 10 (week 17)
Secondary	
To evaluate the efficacy of LEVI-04 (multiple doses) compared to placebo in improving physical function.	Change in WOMAC Physical function subscale from Randomization (Visit 3) to Visit 6 (week 5) and Visit 10 (week 17).
	Change in Staircase Evoked Pain Procedure (StEPP) from Randomization (Visit 3) to Visit 6 (week 5) and Visit 10 (week 17)
To evaluate the efficacy of LEVI-04 (multiple doses) compared to placebo in improving joint stiffness.	Change in WOMAC Stiffness subscale from Randomization (Visit 3) to Visit 6 (week 5) and Visit 10 (week 17)
To evaluate the efficacy of LEVI-04 (multiple doses) compared to placebo in Patient Global Assessment (PGA)	Change in PGA from Visit 6 (week 5) to Visit 10 (week 17)

Objective(s)	Endpoint(s)
To evaluate the proportion of responders based on various levels of reduced pain in participants receiving LEVI-04 (multiple doses) compared to placebo	Change in WOMAC Pain subscale from Randomization (Visit 3) to Visit 6 (week 5)
	Proportion of participants achieving 30% and 50% reduction in WOMAC Pain subscale at week 5 and week 17 using a cumulative distribution function
	Change in average weekly NRS Pain score from Baseline to Visit 6 (week 5) and Visit 10 (week 17)
	Area under the curve of Average Daily NRS Pain from Baseline to Visit 11 (week 20)
To evaluate rescue medication use in the LEVI-04 group (multiple doses) compared to placebo.	Rescue Medication usage during the trial
Exploratory	
To evaluate the efficacy of LEVI-04 compared to placebo in time to onset of pain relief	Time from Randomization to a decrease in average weekly NRS pain of 30% from Baseline NRS Pain score.
To explore associations between imaging biomarkers and pain severity	Associations of imaging biomarkers and pain severity at Randomization (Visit 3) to Visit 11 (week 20)
	Correlations between pain variability during screening and major efficacy endpoints
To explore associations of biomarkers of the neurotrophin signaling pathway and pain severity	Change from Baseline in blood biomarkers and associations with clinical outcomes
Safety	
To evaluate the overall safety of LEVI-04 compared to placebo	AEs between treatment arms (Count and Severity)

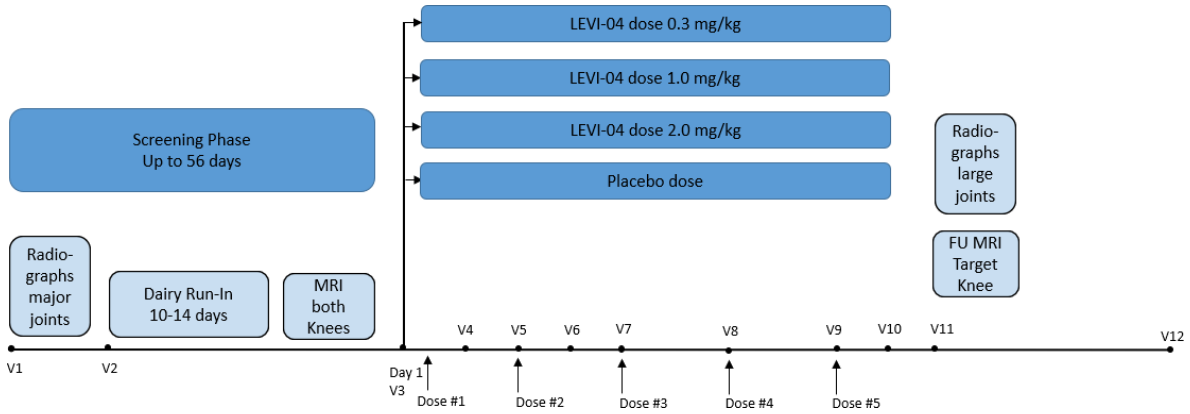
Objective(s)	Endpoint(s)
To evaluate the safety of LEVI-04 compared to placebo in relation to the peripheral nervous system	Peripheral Nervous System AEs between treatment arms (Count and Severity)
To evaluate the safety of LEVI-04 compared to placebo in relation to joint safety.	Incidences of Joint Events and subtypes of Joint Events. Events include: • Osteonecrosis • Destructive Arthropathy, including RPOA type 2 • Changes in signs of inflammation on Magnetic resonance imaging (MRI) of the Target Knee, • Subchondral insufficiency fracture • Rapid loss of JSW by 2 mm within 12 months or loss of 50% of JSW if less than 2 mm at baseline. This is also called RPOA type 1 • Any other incidence of joint events such as acute fracture, bone marrow infiltration, etc.
	Incidence of surgical interventions including joint replacement

5 Investigational Plan

5.1 Overall Trial Design and Plan

This is a Multiple Arm, Multicenter, Prospective, Randomized, Double-blind, Placebo-controlled, Phase 2a study of LEVI-04 intravenous infusion for the treatment of knee osteoarthritis (OA). The purpose of the trial is to evaluate the efficacy, safety, and tolerability of five monthly infusions of LEVI-04 as compared to placebo in participants with radiographic and symptomatic knee OA. Eligible participants will be randomized to one of the four treatment arms: 0.3mg/kg LEVI-04, 1.0 mg/kg LEVI-04, 2.0 mg/kg LEVI-04 or saline vehicle control (placebo) in a 1:1:1:1 ratio (Figure 1). All participants will receive five intravenous IMP infusions 4 weeks apart, i.e. at Randomization (Day 1), Visit 5 (week 4), Visit 7 (week 8), Visit 8 (week 12) and Visit 9 (week 16) with assessments and procedures as per Schedule of Events A Follow-up/End-of-Trial (FU/EOT) visit (Visit 11) and Follow-up Safety Phone Visit (Visit 12) will take place at week 20 and week 30, respectively.

5.1.1 Figure 1: Study Schema



5.2 Discussion of Trial Design

The overall trial design is considered an appropriate study design for Phase 2 drug development and consistent with current regulatory guidance. The primary goal of the study is to establish proof of concept of the biologic activity of LEVI-04 leading to reduction in pain from knee OA compared to placebo. The trial is designed to add to the LEVI-04 safety data collected in the Phase 1 trial (ClinicalTrials.gov: NCT03227796, See IB) and establish the most suitable dose for a Phase 3 trial. The Primary endpoint is change in WOMAC pain subscale score from Randomization (Visit 3) to week 17 (Visit 10). WOMAC pain subscale is a Food and Drug Administration (FDA) recommended clinical trial efficacy endpoint for OA and considered a reliable, validated outcome measure[14,15]. The study duration of 30 weeks which includes 14 weeks to Follow-up Safety Phone Visit 12 from last dose administered, and is considered sufficient to meet study objectives and ensure sufficient oversight of participant safety and follow-up of adverse events. Participants that discontinue trial early will be followed up at least 12 week following last administered dose of IMP. Radiographs of major joints bilaterally (knee-, hip-, and shoulder joints) and MRI of both knees during Screening are included to determine eligibility. Only Target Knee will have MRI completed at FU/EOT visit (week 20). Safety assessments throughout the trial include Physical examination, Vital signs, Clinical laboratory values, ECG, and AEs.

5.2.1 Selection of Trial Population

Only individuals meeting all Inclusion Criteria and no Exclusion Criteria may be enrolled into the trial as participants. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

Prior to performing any trial assessments not part of the participant's routine medical care, the Investigator will ensure that the participant or the participant's legal representative has provided written ICF.

5.2.2 Inclusion Criteria

1. Signed ICF
2. Male or female participants between ≥40 and ≤80 years of age
3. BMI ≤40 kg/m2
4. The ability, in the opinion of the investigator, to utilize the eDiary device provided and comply with study requirements
5. History of knee pain on most days for at least 3 months prior to Screening
6. Confirmation of OA of the Target knee
    a. Radiographs of both knees with a Posterior-Anterior, Fixed-flexion view taken during the Screening Period
    b. American College of Rheumatology (ACR) clinical and radiographic diagnostic criteria
7. Evidence of Target knee OA with a KL grade ≥2, determined through central reading
8. Target Knee must have a score of ≥20 out of 50 on the WOMAC NRS 3.1 pain subscale during Screening and at Randomization
9. The Baseline NRS Pain score will be derived from the last seven days of the Diary Run-In Period and must meet following criteria:
    a. Completion of Average Daily NRS Pain score on at least 6 of the 7 days
    b. Mean Average Daily NRS Pain score must be ≥4.0 and ≤9.0
    c. Mean Average Daily NRS Pain variability must be ≤1.5
10. If female and 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 an agreed upon highly effective method of birth control throughout the study period and at least 3 months after last dosing of IMP
11. If male and sexually active with partner of childbearing potential, willing to agree to practice a highly effective method of contraception from Visit 2 and at least 3 months after Visit 11 (week 20)

12. Willing to withdraw from any medication for OA including, but not limited to, Opioids (including semisynthetic opioids), Non-Steroidal Anti-inflammatories (NSAIDs), COX-2 inhibitors, Topical medication, and Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs e.g Duloxetine)

13. Participant agrees to take only the allowed Rescue Medications from the start of the Diary Run-In Period through study completion (FU/EOT visit 11) (maximum 4000 mg paracetamol per day)

5.2.3 Exclusion Criteria

1. Presence of OA of other major joints (including but not limited to nontarget knee) that could interfere with assessment of pain due to OA of the target knee, in the opinion of the investigator.

2. Current comorbid condition, other than OA, affecting target knee or systemic illness known to be significantly associated with arthritis or joint pathology affecting any joint, including but not necessarily limited to endocrinopathies or autoimmune disease with significant joint involvement (e.g., Rheumatoid Arthritis); Seronegative Spondyloarthropathies (e.g. Ankylosing Spondylitis, Psoriasis arthritis, Reactive arthritis)

3. Pathological conditions significantly affecting joint and bone health, in the opinion of the Investigator should be excluded (including but not necessarily limited to following findings on x-rays and/or MRI):

    - Known presence of Rapidly Progressive Osteoarthritis (RPOA) (any joint)
    - Osteonecrosis (including avascular necrosis) (any joint)
    - Subchondral insufficiency fractures (SIF) (any major joint)
    - Fractures or stress reactions with radiographic signs of ongoing healing processes (including but not limited to osteoporotic and pathological fractures) (any major joint)
    - Excessive malalignment of the knee (anatomical axis angle greater than 10 degrees) (Target knee only)
    - Complete tear of the posterior meniscal root (partial tears and/or anterior meniscal tears not excluded) (either knee)
    - Large or extensive subchondral cysts (either knee)
    - Anserine or patellar bursitis (Target knee only)
    - Significant articular bone loss (any joint)
    - Articular bone fragmentation or collapse (any joint)

- Primary or metastatic tumor (any joint)
- Joint infection (any joint)
- Paget's disease (any joint)
- Osteochondritis dissecans (any joint)

4. Hip dislocation and congenital hip dysplasia with degenerative joint disease should be excluded.
5. History of gout, or pseudogout, unless on hypouricemic therapy (including allopurinol) and no episodes within the last 12 months.
6. Presence of neuropathic pain deemed likely to interfere with trial endpoints, complex regional pain syndrome, or chronic widespread pain syndromes e.g., fibromyalgia
7. History of significant trauma (e.g., intra-articular fracture) or surgery (excluding injection therapies and arthroscopy) to a knee, hip, or shoulder within the previous 1 year or previous target knee alloplasty
8. Planned major surgery or other major invasive procedures while participating in the study
9. Surgery or stent placement for coronary artery disease in the six months prior to screening
10. Nondiagnostic arthroscopy performed on the target knee joint within 180 days prior to Screening; or diagnostic arthroscopy performed on the target knee joint within 90 days prior to Screening
11. Intraarticular injection therapies to the target knee joint within 12 weeks prior to Screening, or to any non-target major joint within 6 weeks prior to Screening
12. Participants likely to be deemed unfit for joint replacement surgery due to concomitant illness, in the investigator opinion
13. Opioid use, including Tramadol, of 4 or more instances per week over the month prior to Screening
14. Known history of hypersensitivity to monoclonal antibodies
15. Presence of any medical condition or unstable health status that, in the judgment of the investigator, might adversely impact the safety of the participant or efficacy results of the trial
16. Medical history and/or clinical findings (including ECG) of cardiac disease that in the opinion of the investigator are considered of clinical significance, including but not limited to established ischemic heart disease, peripheral arterial disease and /or cerebrovascular disease (unstable angina, myocardial infarction, cardiovascular thrombotic events, transient

ischemic attacks, and stroke are considered clinically significant if time of event occured within six months prior to screening)

17. Active malignancy or history of malignancy within the past 5 years, with exception of resected and cured basal cell carcinoma and squamous cell carcinoma of the skin

18. Clinically significant abnormal laboratory parameter(s) and/or electrocardiogram (ECG) parameter(s) during Screening, that, in the judgment of the Investigator, would preclude the participant from participation in this study

19. Participation in other studies involving investigational drug(s) within 30 days (or 90 days for biologics) prior to screening

20. History of Carpal Tunnel Syndrome with signs or symptoms within one year of Screening or a Boston Carpal Tunnel questionnaire (Symptom Severity Scale mean score ≥3)

21. Total score on Number of Symptoms (Column Q1a) on the SAS >3

22. Pregnant or breast feeding

23. Previously received any form of anti-Nerve Growth Factor (NGF)

24. Requires walker or wheelchair for mobility (walking stick permitted)

25. Active or historic substance abuse within one year of Screening in the opinion of the Investigator

26. Medical history within 5 years of Screening that involves suicidal ideation, suicide attempt, or increased risk of suicide as assessed by the Investigator.

27. Presence of any contraindication to MRI, including partial or total joint replacements that are expected to interfere with the quality of the imaging

5.3 Criteria for Initiation of Trial Treatment

- **Pain Assessments**

As an essential part of the eligibility determination process, participants will be evaluated based on following pain instruments: The WOMAC Pain subscale, and Average Daily NRS Pain.

The WOMAC Pain subscale NRS 3.1 (WOPAIN NRS) will be completed for both knees during Screening prior to starting the Diary Run-In Period, with the requirement that the participant is treatment naïve or has not used analgesics during the 48 hours prior to completion and must be ≥20 out of 50. Participants at Visit 1 who have taken analgesics the 48 hours prior to Visit 1 will have WOPAIN NRS completed prior to or at Visit 2 following the 48-hour analgesic washout.

The Baseline NRS Pain score will be derived from the Average Daily NRS Pain score collected on the last seven days of the Diary Run-In Period (Day 10 - Day 14) and at least one knee must meet the criteria as described in inclusion criterion 9.

- **Radiographic Assessments**

For evaluation of relevant Inclusion and Exclusion criteria radiographs of both knees and both shoulders and hips will be taken during the Screening period and at the end of the study. Knee radiographs acquired within three months prior to Screening may be submitted for central reading, provided they meet the study requirements for acquisition and quality. Participants with partial or total joint replacements of any minor and major joints are not excluded from the trial, if the participant is otherwise considered eligible and central radiographic responsible personnel consider the prothesis compatible and safe upon imaging with results at sufficient quality. Conversely, any partial or total knee replacement of the target knee is exclusionary.

Participants with non-target knee joint replacements may however, pending the central radiographic assessment be considered ineligible as the radiographic assessments may provide additional information on joint and bone health related to the joint replacement, which could render the participant unsuitable for the study.

- **MRI Assessments**

Participants will have MRI of both knees conducted prior to Randomization and read centrally for confirmation of eligibility and selection of Target Knee. A follow-up MRI of the Target Knee only will be performed at FU/EOT.

5.4 Withdrawal from Trial Therapy/Early Termination

All participants will be informed that they are free to withdraw from study participation at any time, for any reason, and without prejudice. If a participant withdraws consent to participate or enrolls in another clinical trial (any sub-trial or extension trial in relation to LEVI-04 excluded), it should be adequately reviewed if an adverse event is given as the primary reason for withdrawal.

The Investigator may withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study non-compliance or protocol deviations
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- The study is no longer in the best interest of the participant.

5.4.1 Process for Early Termination

In case a participant discontinues trial prior to completion, the Investigator must make every effort to schedule and complete an EOT visit 4 weeks +/- 3 days following last administration of IMP and a Follow-up Safety Phone Visit (minimum 12 weeks following last dose of IMP). The assessments and procedures to be completed at EOT visit for participants that have withdrawn from study prior to completion and received at least one dose IMP, are as listed for FU/EOT Visit 11 and Safety Follow-up Phone Visit 12. It should be assessed if a TEAE was the primary reason for withdrawal. In this case, the TEAE must be documented, reported, and followed as described in Section 9.1.1.

Reason for participant withdrawal from the study and the date of discontinuation will be recorded on the electronic Case Report Form (eCRF).

A participant will be considered lost to follow-up if he or she fails to return for any scheduled visit and is unable to be contacted by study site staff. Should the participant continue to be unreachable 6 months after IMP administration, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

5.4.2 Participant Replacement and Rescreening Criteria

Participants who have signed ICF and received study ID, but have not yet been randomized, may be replaced. The subject ID number for a withdrawn participant will not be reassigned to another participant.

Participants may be rescreened, with the agreement of the Medical Monitor, if there is reason to believe the initial reason for screen failure has changed substantially since the time of the first screening. Any rescreenings should be clearly documented.

5.5 Premature Termination of the Trial

The clinical trial may be terminated prematurely or suspended at the request of Health Authorities (HA) or if new safety or efficacy information leads to an unfavorable risk benefit judgment for IMP. The Sponsor may discontinue the trial if it becomes unjustifiable for medical or ethical reasons, for poor enrollment, or because of discontinuation of clinical development of IMP. HA, and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

6 Investigational Medical Product and Other Drugs used in the Trial

The term Investigational Medicinal Product (IMP) refers to LEVI-04 or Placebo.

6.1 Description of the Investigational Medical Product

6.1.1 LEVI-04

LEVI-04 (p75NTR-Fc) comprises the extracellular domain of human p75 neurotrophin receptor (p75NTR) coupled to the constant fragment of human immunoglobulin G1 (IgG1).

The active ingredient of LEVI-04 is manufactured by Lonza Group Ltd. According to current Good Manufacturing Practice (GMP) standards and formulated in 25mM histidine, 50mM sodium chloride, 200mM mannitol, pH 6.5.

6.1.2 Placebo

The placebo control, physiological saline (0.9% sodium chloride injection), comparator is an approved, commercially available product sourced and distributed by the Sponsor. IMP packaging and blinding will be performed by preassigned unblinded staff personnel. Administration as an infusion, in the same manner as described for LEVI-04.

6.2 Dosage, Administration and Post-infusion monitoring

Eligible participants will be randomized in the ratio 1:1:1:1 to one of three parallel treatment arms or placebo control arm as following:

- LEVI-04 intravenous infusion dose 0.3 mg/kg
- LEVI-04 intravenous infusion dose 1.0 mg/kg
- LEVI-04 intravenous infusion dose 2.0 mg/kg
- Placebo intravenous infusion

There will be administered five doses during the trial: one at each of the following visits:

- Randomization (Visit 3, Day 1), 1st dose.
- Visit 5 (Week 4), 2nd dose.
- Visit 7 (Week 8), 3rd dose.
- Visit 8 (Week 12), 4th dose.
- Visit 9 (Week 16), 5th and last dose.

Following the completion of the infusion the participant is required to remain at site for a minimum of 30 minutes or longer if indicated based on the opinion of the study staff or at request of the participant, or local authorities.

6.3 Assignment to Treatment Groups

Upon confirmation of eligibility at the Randomization Visit (Visit 3), randomization will be done by means of an Interactive Web-based Randomization System (IWRS) operated through the eCRF. Participants will be randomized centrally at a 1:1:1:1 ratio as described in Section 10.2. Each trial participant will be assigned a unique study identification number (subject ID) to be used throughout the trial for data collection, tracking, and archival purposes. For statistical aspects of randomization, also refer to Section 10.2.

6.4 Non-investigational Medical Products to be used

6.4.1 Rescue Medication

The trial allows Paracetamol to be used as analgesic Rescue Medication in case of intolerable pain beginning at the Diary In-Run Period and for the duration of the Screening period and during the trial. Rescue Medication will be dispensed at The Diary Run-In Visit (Visit 2) and supplemented at following visits as needed. When participants return for a resupply of Rescue Medication, site personnel must perform accountability prior to resupply. During the Diary Run-In Period the use of Rescue Medication is strongly discouraged to facilitate establishment of an accurate baseline pain assessment. The potential consequences concerning eligibility of the participant if they use analgesics during this period will be evaluated on a case-by-case basis. During the treatment phase of the trial (Visit 3 to Visit 11) usage of Rescue Medication is strongly discouraged the 48-hours prior to a study visit (Visit 4 telephone visit exempt). The maximum dose should not exceed 1000 mg per dosing and 4000 mg per 24 hours.

The Rescue Medication is intended for treatment of OA pain of the Target Knee only. However, to limit the use of other, non-rescue, prohibited medication, the participant may use the Rescue Medication for other transient, mildly painful events. Site staff will at each visit ensure that the participant uses the eDiary to record Rescue Medication usage.

6.4.2 Permitted Concomitant Medications, Non-Pharmaceutical Supplements, and Therapies

All concomitant medications including non-pharmaceutical supplements taken by the participant during the trial, from the date of signature of ICF, are to be recorded in the appropriate section of the eCRF, noting Name of medication, Dosage, Start Date, and Indication. Use of medications, non-pharmaceuticals and therapies that are considered to not interfere with the trial medication or study outcome measures will be evaluated on a case-to-case basis. The following medications, non-pharmaceutical supplements, and therapies with pain relieving properties are considered permitted:

- Low-dose Aspirin (up to and including 325 mg daily) for prevention of thrombo-embolic events is allowed throughout the trial if the participant has been on a stable dose for at least 4 weeks prior to Screening.
- Heating and cooling pads are allowed throughout the trial

- Physiotherapy is allowed throughout the trial
- Oral Glucosamine is allowed provided the participant has been on a stable dose for least 4 weeks prior to Screening and is kept at a stable dose during trial participation.
- Selective Serotonin Receptor Inhibitors (SSRIs)
- Oral multivitamins

6.4.3 Prohibited Concomitant Medications, Non-Pharmaceutical Supplements and Therapies

The following Concomitant Medication and Non-Pharmaceuticals and Therapies are prohibited from the beginning of the Diary Run-In Period to the Follow-up/End of Trial visit (Visit 11).

Medications, non-pharmaceutical supplements and therapies with analgesic properties expected to potentially interfere significantly with knee pain reporting are prohibited (Oral, topical and intraarticular administration included)

- Includes, but not limited to NSAIDs, Serotonin- Norepinephrine Reuptake Inhibitors (SNRIs, e.g. Dulexetine) and Opiods (including semisynthetic opiods)
- The use of Rescue Medication is strongly discouraged the 48-hours prior to a visit in the treatment period of the trial (Visit 3 to Visit 11)
- Intra-articular injections with Corticosteroids or Hyaluronic acid in a major joint (including Target and non-target knee) during the trial is not permitted.
- Treatment with oral Corticosteroids is not permitted.
- Acupuncture

Following completion of all FU/EOT Visit 11 assessments and procedures, the participants are no longer restricted in their use of concomitant medication, non-pharmaceutical supplements, and therapies.

6.5 Packing and Labeling of the Investigational Medical Product

All IMP will be packaged and labeled in accordance with applicable regulatory requirements and Good Manufacturing Practice (GMP) Guidelines. See IB for more information.

6.5.1 Preparation, Handling and Storage of the Investigational Medical Product

LEVI-04 drug product must be stored between 2 and 8 degrees Celsius (°C), i.e. in the refrigerator. Product batches are conducted with reference to relevant International Council for Harmonization of Technical Requirements for Pharmaceuticals (ICH).

Clinical administration of LEVI-04 involves dilution of drug product with 5% Dextrose in a syringe after which the product is delivered as a 30-minute infusion using an intravenous route with an in-line 0.2 µm filter.

6.5.2 Investigational Medical Product Accountability

The Investigator is responsible for ensuring IMP accountability, including reconciliation of IMP and maintenance of records.

- Upon receipt of IMP, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate documentation and returning it to the location specified. A copy will be archived for the Investigator Site File.
- IMP dispensing will be recorded on the appropriate drug accountability forms, so that accurate records will be available for verification during Monitoring.
- Trial site IMP accountability records will include the following:
  - Confirmation of IMP receipt, in good condition and in the defined temperature range.
  - The inventory of IMP provided for the clinical trial and prepared at the site.
  - Volume of IMP administered.
  - The disposition of any unused IMP.
  - Relevant, Quantities, Batch numbers, Vial numbers, Expiration dates, and participant ID.

The site should maintain records, which adequately document that participants were provided the dose specified in the protocol, and all IMP provided were fully reconciled.

Unused IMP must not be discarded or used for other purposes than the present trial. No IMP that is dispensed to a participant may be re-dispensed to a different participant.

A Monitor will periodically review the IMP accountability forms.

6.5.3 Assessment of IMP Compliance

The IMP is administered as multiple doses or Placebo in the clinic by adequately qualified and trained study staff.

6.5.4 Blinding

This is a double-blinded trial, in which neither participant nor Investigator know the content of the IMP. The Placebo will be indistinguishable from the active IMP once made up for participant administration. Preparation of IMP is performed by unblinded delegate to be identified by site and will not be involved in other aspects of the study. A separate IMP Handling Manual with specific instructions on IMP administration will be provided to sites. All breaks of the trial blind must be adequately documented.

6.5.4.1 Emergency unblinding

The trial blind may be broken by the Investigator for a participant only if knowledge of the IMP is essential for clinical management. If the Investigator unblinds a participant's treatment assignment, they must notify and report the reason hereof to Sponsor and/or delegate within 24-hours of the unblinding. This notification must be done without revealing the unblinded treatment details to Sponsor, except the designated Pharmacovigilance representative.

Under certain circumstances, the Pharmacovigilance representative may be required to unblind the treatment assignment for an individual participant following a SAE. (See Section 9.1.3).

6.6 Treatment of Overdose

An overdose is a dose significantly greater than the highest dose included in the trial protocol (2.0 mg LEVI-04/kg). The potential for toxicity of LEVI-04 has been evaluated in preliminary studies and formal toxicology studies (See Section 3.3). From this, the maximum tolerated dose in cynomolgus monkeys was above 100 mg LEVI-04/kg. In the Good Laboratory Practice (GLP)-compliant, 4-week, repeat-dose toxicity studies (cynomolgus monkeys and Han Wistar rats), LEVI-04 was well tolerated and no adverse toxicological effects were observed.

If the unexpected event of an overdose should occur it must be recorded in the trial medication section of the eCRF and reported to study Pharmacovigilance representative in an expedited manner using the SAE Report Form, even if it does not meet other criteria for an SAE (See Section 9.1.3).

6.7 Medical Care of Participants after last visit

Sponsor will not provide any additional care to participants after the Follow-up Safety Telephone Visit 12 , unless an AE has been reported in which follow-up will take place until resolution/stabilization of the AE (See Section 9.1).

7 Trial Procedures and Assessments

For the timing of assessments and procedures throughout the study, refer to Schedule of Events. Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures listed. If a participant misses a study visit for any reason, the visit should be rescheduled as soon as possible, if considered reasonable in relation to subsequent visits. Protocol waivers or exemptions are not allowed.

7.1 Informed Consent

Prior to performing any study-related procedures, the participant or must sign and date the ICF. The informed consent process must be documented in the participant's records.

7.2 Baseline Demographics

Participant demographic data will be collected at Screening. These include: Date of birth, Sex, and Race.

7.3 Medical History

Each participant's Medical History will be obtained by at Screening, including time of onset of knee OA, defined as the time of emergence of clinically relevant knee pain.

7.4 Concomitant Medications

Relevant medications used at the time of Screening and in the 3-month period preceding Screening should be documented in the eCRF. All medications taken by a participant after the ICF is signed are regarded as concomitant medications and must be documented in the eCRF, including prescribed Medications, Contraceptive, Vaccinations, Over-The-Counter Medication, Herbal Medications, Vitamins and Supplements. See Section 6.4.2 for Permitted Concomitant Medications, Non-Pharmaceutical Supplements, and Therapies.

7.5 Vital Signs

Vital signs include Blood Pressure (BP), Heart Rate (HR) and Body Temperature (BT) and will be collected at Screening, during all dosing visits and at FU/EOT visit (week 20). Vitals to be obtained with the participant in a sitting or lying position.

7.6 Height, Weight, and Body Mass Index (BMI)

Height (centimeters) will only be measured during Screening. Weight (kilograms) to be measured at Screening (Visit 1), Randomization (Visit 3, Day 1), Visit 7 (week 8) and FU/EOT visit 11 (week 20). BMI will be calculated automatically in eCRF based on weight and height.

7.7 Physical Exam

The physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.

7.7.1 Musculoskeletal Exam

The musculoskeletal exam will be completed as part of the physical exam at Visit 3, Visit 5, Visit 7, Visit 8, Visit 9 and Visit 11. The Musculoskeletal Exam includes assessments of shoulder-, hip- and knee joints. Each shoulder will be assessed for range of motion, abduction, internal and external rotation. Both hip joints will be examined for range of motion, internal and external rotation of groin or buttocks. Both knees will be inspected for deformities, varus/valgus alignment and be palpated for effusion, crepitus, and tenderness.

7.8 eDiary Training Modules

Training modules on eDiary Accurate Pain Reporting (APR), Placebo Response Reduction (PRR) and Research Subject Responsibility (RSR) are available through aLearn. If indicated, the participant should be encouraged to repeat the training and re-instructed. Repeated training is recommended every 6 weeks during the study.

7.8.1 Accurate Pain Reporting (APR) training

The APR training is an eDiary training module, available through aLearn, that instructs participants, on how to report pain symptoms accurately and reliably, and on the proper use of measurement instruments, with the aim of increasing the accuracy of participant pain reporting.

7.8.2 Placebo Response Reduction (PRR) training

The PRR training is an eDiary training module, available through aLearn, that teaches the participant about the appropriate expectations of personal benefit while participating in a clinical trial. The purpose is to provide participants with straightforward information that will neutralize the typically excessive expectations that drive high placebo responses in clinical studies.

7.8.3 Research Subject Responsibility (RSR) training

The RSR training is an eDiary training module, available through aLearn, that reviews the daily responsibilities required of the participants in this trial. The training module underlines logistical tasks participants must perform consistently and accurately to effectively participate in the research study.

7.9 Patient-Reported Outcome Instruments

Patient-Reported Outcome Instruments will be completed as outlined in the Schedule of Events. To avoid bias, all questionnaires must be completed by the participant. Prior to completion of the first questionnaires, study staff will instruct the participant in the practical elements of completing the questionnaire. The questionnaires will be completed electronically, but in exceptional cases such as technical issues prohibiting electronic data collection, paper versions may be employed and subsequently entered in the electronic system by the site staff.

7.9.1 WOMAC questionnaire

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a validated patient reported tool designed to detect the degree of symptoms of OA[15], and changes in symptoms, with reference to the past 24-hours. WOMAC is considered a reference standard in the evaluation of change in symptoms in OA clinical trials[16].

The questionnaire consists of 24 questions divided into three subscales; Pain (5 questions), Stiffness (2 questions), and Physical function (17 questions), which will all be graded on the 11-point NRS scale from 0 to 10, where 0 is considered “No symptoms”, and 10 “Worst imaginable pain, stiffness, or impact on physical function, respectively”. The pain subscale of WOMAC is in this protocol

referred to as WOPAIN NRS. WOPAIN NRS to be collected during Screening for both knees. At Randomization (Visit 3) and onwards, WOMAC Pain, Function and Stiffness subscales to be completed for Target Knee only, and should be completed prior to subjects completing the StEPP test. WOPAIN NRS for Target Knee at Visit 3 is the final eligibility assessment and Target Knee must meet inclusion criterion #8.

7.9.2 Boston Carpal Tunnel Questionnaire

The Boston Carpal Tunnel Questionnaire (BCTQ) is a measure of self-reported severity of symptoms and functional status associated with carpal tunnel syndrome. The questionnaire consists of a Symptom Severity scale (11 items) assessing severity of wrist or hand pain, change of sensation, and weakness in hand or wrist the past two weeks and a Functional Status scale (8 items) assessing ability to perform various hand/wrist related tasks[17]. Each item is scored on a 5-point Likert scale from 1 (no symptoms) to 5 (most severe symptoms). The score for the Symptom Severity scale is the mean score of 11 items and the score for the Functional Status scale is the mean score of 8 items. Exclusion criteria is based on Symptom Severity scale only mean score >3.

7.9.3 Survey for Autonomic Symptoms

The Survey of Autonomic Symptoms consists of two columns with two separate scores: A “Number of symptoms score” and a “Total symptom impact score”. The first score refers to the total score from column Q1a where the participant answers Y/N to if he/she has had the specific symptom the last 6 months. Yes counts as 1 point, No as 0 and total score for the Number of symptoms score ranges from 0-11 (males) and 0-12 (females). The “Total symptom impact score“ is the total score from the second column, Q1b and is scored on impact of the symptoms the participant answered yes to having, ranging from 1 (“not bothered by this symptom”) to 5 (“bothered a lot”) (total score range 0-60)[18]. Both column Q1a and Q1b are to be completed. The Number of symptoms (Q1a) score will be used to determine eligibility, with exclusion of participants with a score of > 3 (4 or more).

7.9.4 Patient Global Assessment (PGA)

The PGA is a unidimensional measure of the participant’s overall assessment of disease impact on a given day. A single question is asked the participant and they must select a number on a 11-point scale from 0 (”Very good”) to 10 (“Very bad”)[19]. The question is as following:

“Considering all the ways your osteoarthritis in your knee affects you, how are you doing today?”

7.9.5 Average Daily Numeric Rating Scale (NRS) Pain Score

The Average Daily NRS Pain score measure uses the single 11-point numeric rating scale on which a participant selects a number between 0 (“No pain”) and 10 (“Worst possible pain”) that best reflects their knee pain severity over the past 24-hours [20]:

“Please select the number that best describes your average osteoarthritis pain in your left/right knee in the past 24 hours?”

From the beginning of the Diary Run-In Period, participants will daily in the evenings using the eDiary select their Average Daily NRS Pain score. The participants will continue to collect Average Daily NRS Pain scores for both knees until Visit 3. Following selection of Target Knee, at Visit 3 the Average Daily NRS Pain score only to be completed for Target Knee throughout the trial.

7.9.6 Staircase Evoked Pain Procedure (StEPP)

The StEPP is a stress test and performance-based outcome measure developed to improve the sensitivity to detecting analgesic effect in clinical trials of knee OA. The test consists of stepping fully up onto a 20-cm high platform with one foot, then the other foot and back down (alternating lead leg at each up/down cycle), for a total of 24 times over a 5-minute period[21]. Pain intensity assessments are performed for Target Knee, immediately before and after the exercise on a scale of 0 to 10, with 0 representing “No pain” and 10 representing “Worst possible pain”.

7.10 Laboratory Tests

7.10.1 Blood samples

All efficacy measures should be completed prior to blood draws to limit any potential influence of the procedure on the general perception of pain.

- Laboratory values for an analyte that is outside normal range per the central laboratory will be identified and may be repeated at the Investigator’s discretion.
- Abnormal laboratory value(s) that the Investigator has evaluated as clinically significant and/or leads to participant withdrawal from the study will be recorded as an AE on the eCRF if the respective blood or urine sample was performed after administration of 1st dose IMP (Visit 3) and as Medical History otherwise.
- The Investigator will review all laboratory reports, evaluate the results, and confirm review by signing with date of review.
- All clinical laboratory tests are described in detail in the Laboratory Manual.

7.10.1.1 Safety Hematology and Chemistry

Safety laboratory tests for hematology and chemistry to be completed during Screening (Visit 1), at all dosing visits (Visit 3, Visit 5, Visit 7, Visit 8, Visit 9) and at FU/EOT visit (Visit 11). Serum Human Chorionic Gonadotropin (hCG) to be included at Screening and at other sampling timepoints as needed/indicated. See Table 3 below for Hematology and Chemistry blood samples to be collected.

Table 3: Safety labs

Hematology	Haemoglobin Red cell count (RBC) Total white cell count (WBC) Platelet count Differential blood count (including basophils, eosinophils, neutrophils, lymphocytes and monocytes)
Chemistry	Alanine aminotransferase (ALT) Albumin Alkaline phosphatase (ALP) Aspartate aminotransferase (AST) Bilirubin (Total) Calcium Chloride Cholesterol Creatinine Creatinine Kinase (CK) GGT HDL-Cholesterol LDL-Cholesterol Magnesium Potassium Phosphate (inorganic) Protein (Total) Sodium Urea nitrogen (BUN) C-Reactive Protein, highly sensitive (hsCRP) Serum hCG (only during Screening for WOCBP or if indicated)

7.10.1.2 Pharmacokinetics

Based on the LEVI-04 Phase I study, after dosing by IV infusion for 30 min, serum concentrations of LEVI-04 reached C_{max} within 1.5 h of the end of infusion in most participants, followed by a distribution phase of about 72 h and a slow terminal elimination phase, with a mean $t_{½}$ of 318–419 h (13–17 days) across the 0.01–3.0 mg/kg dose range. There was no notable difference between Heathy Volunteers and OA patients in the serum PK of LEVI-04 after a dose of 0.03 mg/kg. Geometric C_{max} and AUC_{inf} were broadly dose-proportional, and arithmetic mean clearence (CL) and volume of distribution (V_z) were near-constant, over the 0.03–3.0 mg/kg LEVI-04 dose range.

For this protocol, blood samples for measurement of the pharmacokinetics of LEVI-04 to be collected as per Schedule of Events at two timepoints at dosing visits (Visit 3, 5, 7, 8 and 9): Prior to IMP administration (pre-dose PK sample) and following IMP administration (post-dose PK sample). It is recommended that all blood samples are collected following completion of questionnaires, physical exam, and vital signs and ECG.

- The pre-dose PK sample to be taken prior to IMP administration.

- The post-dose PK sample is to be collected, after completion of the IMP infusion, before the subject leaves the clinic
- At the EOT visit, only one PK sample is collected.

7.10.1.3 Blood tests for Pharmacodynamics

In the Phase I study on LEVI-04 (See Section 3.3.2), LEVI-04 did not elicit an immunogenic response in any participants. Immunodepleting positive Anti-Drug antibodies (ADA) to LEVI-04 were detected in one heathy volunteer; however, those ADAs were present already before dosing.

For the current trial, an additional 2ml of blood will be taken at selected timepoints as listed Schedule of Events for testing of biomarkers. Blood samples for Pharmacodynamic (PD) biomarkers to be collected prior to IMP administration at Randomization (Visit 3) and Visit 5 (week 4) and at any time at Visit 11. The PD biomarkers include biomarkers of inflammation and neurotrophin engagement associated with the mode of action of {NGF and Neurotrophin-3 (NT3)}.

7.10.1.4 Anti-Drug Antibodies

Blood samples for ADA to be collected prior to IMP administration at Randomization (Visit 3), Visit 5 (week 4) and at any time at FU/EOT Visit 11.

7.10.2 Urine samples

Urine dipstick analysis will be performed at site including urine leucocytes, erythrocytes, protein, nitrite, pH and hCG (for WOCBP). At FU/EOT Visit 11 only urine dipstick hCG to be taken, unless otherwise indicated. If a urine dipstick analysis is clinically significant out-of-range or otherwise indicated, the participant will be referred to primary care for follow-up.

7.11 Electrocardiogram (ECG)

Standard 12-lead ECG evaluations, reporting Ventricular Rate, PR-, QRS, QT-, and QTcF intervals will be collected as per Schedule of Events. ECGs will be interpreted centrally with a report provided to Investigator of potential findings, that will be noted as ‘abnormal not clinically significant’ or ‘abnormal clinically significant’. The Investigator should include the report ECG findings in their overall assessment of eligibility based on medical history, symptoms and clinical findings on physical exam. ECGs can be repeated at the discretion of the Investigator.

7.12 Radiographic Assessment

Radiographs of bilateral knees using a Fixed-Flexion frame and radiographs of bilateral hip, and shoulders will be obtained during the Screening period to assess eligibility for inclusion in the trial. Radiographs of bilateral knees are obtained for evaluation of relevant inclusion and exclusion criteria. The main consideration in the evaluation of eligibility based on the radiographic reading is to exclude participants for whom study participation is unfavourable, due to joint and/or bone abnormalities that could affect the ability to accurately report their knee pain due to OA, or due to underlying pathology that could potentially result in an adverse event whilst participating in the study.

In the event a potential participant has had a partial or total joint replacement (alloplasty) of a major joint (including non-target knee) at the time of Screening, radiographs should still be obtained as a part of the screening procedures.

Follow-up radiographs of bilateral knee-, hip-, and shoulder-joints (including major joints with partial or total alloplasty) will be collected at the Week 20 visit 11 for evaluation of changes in joint structures. All radiographs will be evaluated by an independent, central reader, unless the participant was screen failed for other reasons following completion of radiographs. Radiographs of joints other than knees, hips or shoulders are not required for assessment of eligibility, in case of known presence of one or more prosthesis in any other joint, unless specifically requested from Sponsor. The central reader will provide a report including potentially relevant findings for eligibility assessment. See Section 5.3 Criteria for Initiation of Trial Treatment.

7.13 MRI Assessment

MRI of both knees to be performed prior to Randomization (Visit 3) in due time to allow for a central read and confirmation of eligibility prior to Randomization. The imaging technical requirements are explained in the Imaging Guidance Overview that will be provided to all sites. MRI images will be evaluated by an independent central reader. Specifics of the exact imaging procedures will be provided in the Imaging Charter. The central reader will provide a report including potentially relevant findings for eligibility assessment. The main consideration in the evaluation of eligibility and selection of Target knee based on the MRI reading is as described for the radiographic reading (see Section 7.12) . It is recommended that data collected from the Diary Run-In period has been evaluated centrally for eligibility prior to MRI of both knees. A Follow-up MRI of Target Knee to be conducted at Visit 11 (Follow-up visit/EOT) +/-3 days. MRIs may be performed at other times during the study if indicated, as agreed with the Independent Adjudication Committee.

7.14 Target knee selection

Target Knee will be selected following completion of Radiographs, Diary Run-In Period and MRI visit and must meet following criteria (See Selection of Trial Population):

- Confirmed OA based on ACR clinical and radiographic diagnostic criteria
- Knee pain on most days for at least 3 months prior to Screening
- KL grade of 2-4 (both inclusive)
- WOMAC Pain subscale score of ≥20 out of 50 at Screening (Visit 1 or 2) **and** Randomization (Visit 3)
- Baseline NRS Pain score derived from the last seven days of the Diary Run-In Period (Day 10-14) which must meet following criteria:
    - Completion of Average Daily NRS Pain score on at least 6 of the 7 days
    - Mean Average Daily NRS Pain score between ≥4.0 and ≤9.0

- Mean Average Daily NRS Pain score variability ≤1.5

- No presence of pathology on Radiographs or MRI that would render the participant unsuitable for the study
- Pain in nontarget knee due to OA, is required as per exclusion criterion #1 to not interfere with assessment of the Target Knee pain
- If both knees meet all criteria, the dominant knee as determined by the Investigator should be selected as Target Knee
- Target Knee will remain unchanged throughout the trial

8 Schedule of Events

The trial will consist of a Screening Period, Diary Run-In Period, Randomization, Post-Randomization Period, and a Follow-up Period. See Table 1: Schedule of Events.

8.1 General Assessments

Participant reported questionnaires and pain assessments should ideally be completed before any other visit procedures (Blood sampling, ECG etc.) are performed. See Schedule of Events for an overview and Study Schema.

8.2 Screening Period (up to 56 days)

The Screening Period consists of two study visits, radiographs of both knees, hips and shoulders and an MRI of both knees up to 56 days before Randomization (Visit 3). The Screening period begins at the signature of the ICF, during which a participant's initial eligibility for the trial will be determined. The below procedures and assessments for completion during the Screening period are recommended to be completed in the order as listed, but one or more elements may be performed in another order as deemed most appropriate by the Investigator. Written informed consent must be obtained prior to progressing the patient into the study.

8.2.1 Visit 1 (Screening visit)

The assessments and procedures include:

- Written Informed Consent for the trial (Section 7.1)
- Concomitant medication (Section 7.4) and specifically analgesic medication use the last 48-hours. Participants must agree to stop any current analgesic medication when starting the Diary Run-In Period and for the duration of the study (until completion of Visit 11 FU/EOT visit), including the remaining Screening period.
- Ensure the participant does not have usage of illicit and recreational substances.

- Review of AEs (See Section Abnormal Laboratory Findings and Other Abnormal Investigational Findings)
- Review if the participant is a Woman of childbearing potential (WOCBP) or partner of a WOCBP (see Appendix I: Contraceptive Guidance and Woman of Childbearing Potential)
- Collection of Demographics (Section 7.2)
- Medical History (Section 7.3)
- WOPAIN NRS completed for both knees (48-hour wash-out of analgesics prior required) with a score of ≥20 out of 50 required in at least one knee to proceed with Screening.
    - If the participant has taken analgesics the 48-hours prior to the visit, the WOPAIN NRS must be completed before or at the Diary Run-In Visit (Visit 2) and the participant can proceed with Screening pending eligibility on remaining inclusion/exclusion criteria.
- Physical examination (not including musculoskeletal examination)
- Vital signs (Section 7.5)
- Height and weight measurements
- BMI to be calculated automatically in the EDC
- Survey of Autonomic symptoms (Section 7.9.3), Q1a (Number of Symptoms) score and Q1b (Total Symptom Impact) score both to be completed. Q1a to use used for eligibility assessment.
- Boston Carpal Tunnel Questionnaire (Section 7.9.2)
- Blood samples for Safety Labs (Section 7.10.1.1 (including serum hCG for WOCBP)
- ECG (Section 7.11)
- Ensure the patient is willing and able to tolerate the MRI assessment
- Radiographs of both knees, to be read centrally to confirm eligibility on the KL grading (KL grade ≥2), to exclude pathologies other than OA, and to ensure there are no relevant exclusion conditions prior to MRI (Section 5.3).
- Radiographs of both hips and shoulders, to be read centrally to exclude significant pathology other than OA (Section 5.3).

8.2.2 Visit 2: Diary Run-In Visit

Assessments and procedures include:

- WOPAIN NRS for both knees if not performed at Visit 1 (participant required to not have taken analgesics 48-hours prior to completion) and it is to be collected at Visit 2 prior to issuing of electronic diary (eDiary).
- Review of AEs and change in concomitant medications

- Review of Eligibility Criteria

- The participant will be dispensed an eDiary device and receive instructions on how to use the device for entering their average knee pain the past 24-hours daily in the evenings and how to report use of RM in the eDiary. The eDiary will be kept for the duration of the study (until completion of visit 11 FU/EOT visit).

- The participant will complete eDiary training modules assessable through aLearn on how to report their pain accurately (APR), how to reduce the placebo response (PRR) and participant trial responsibilities (RSR) (See Section 7.8).

- Dispensation of analgesic Rescue Medication (RM, paracetamol tablets, maximum 4000 mg/day). Participants will, however, be strongly discouraged from taking the Rescue Medication during the Diary Run-In Period and the 48-hours prior to scheduled visits.

8.2.3 Diary Run-In Period

The Diary Run-In Period is considered a wash-out period, where the participant is trained in accurate pain reporting and placebo response reduction and collection of baseline pain data is completed.

Participants are required to stop any analgesic medication they are currently taking from day 1 of starting the Diary Run-In Period. During this period, the use of Rescue Medication is strongly discouraged to facilitate establishment of an accurate Baseline NRS Pain score. The potential consequences concerning eligibility of a participant if they use analgesics during this period will be evaluated on a case-by-case basis. Participants will be required to daily, in the evenings, enter their Average Daily NRS Pain for each knee (Section 7.9.5) and any use of Rescue Medication in the eDiary.

A participant's eligibility will be determined based on the participant's daily pain scores and eDiary compliance on 6 of the last 7 days prior to day 10 (minimum) up to and including day 14 (maximum) of the period. If a participant is eligible on the Baseline NRS Pain score derived for days 10-14 they are considered eligible for the study, and site staff will enter the date that eligibility is confirmed into the EDC for the study. Should a participant initially show as ineligible, site staff may check the report for all 4 of the days from day 10 and up to and including day 14 to avoid screen failing a participant unnecessarily. The Diary Run -in Period can be extended beyond Day 14, if deemed reasonable by the Sponsor. As participants will be entering their pain data at the end of each day, data for day 10 will be available to sites on day 11, and so forth.

Participants may receive a phone call from site staff if they have not been completing their daily eDiary during the Diary Run-In Period.

After completion of the Diary Run-In Period and eligibility has been confirmed, participants will continue to report their Average Daily NRS Pain scores for each knee in the eDiary until the Target Knee has been selected at Visit 3 (Randomization).

8.2.4 MRI visit

It is recommended that data collected from the Diary Run-In Period be evaluated for eligibility prior to MRI of both knees. The participant will continue to report Average Daily NRS Pains scores for both knees until Visit 3. MRI of both knees to be performed prior to Randomization (Visit 3) in due time to allow for central read and confirmation of eligibility.

8.3 Randomization

8.3.1 Visit 3 (Day 1): Randomization Visit, 1st dose IMP

Once eligibility is confirmed based on MRI of the knees, the following should be conducted prior to administration of IMP. The below assessments and procedures as per Schedule of Events are recommended to be performed in the order presented.

- Review of 48-hour washout of Rescue Medication prior to visit.
- Collection of changes in concomitant medication
- Selection of Target Knee
- WOMAC full questionnaire for Target Knee. WOPAIN NRS for Target Knee to meet final eligibility assessment of ≥20 out of 50.
- PGA
- StEPP
- Accountability of Rescue Medication use, and re-supply if needed
- Review of potential new AEs and follow-up on ongoing AEs
- The participant will repeat eDiary training modules assessable through aLearn on how to report their pain accurately (APR), how to reduce the placebo response (PRR) and responsibilities as a research subject (RSR) (eDiary Module Training).
- Ensure that the participant understands how to use the eDiary daily for completion of Average Daily NRS Pain score for Target knee only onwards and record use of Rescue Medication in eDiary.
- Vital signs
- Weight measurement
- BMI calculated automatically in EDC
- Physical exam (including Musculoskeletal Examination)

- Urine dipstick hCG for WOCBP
- Urine dipstick analysis
- ECG
- Final review of eligibility
- Randomization to Treatment Arm
- Blood sample for:
  - Safety Hematology and Chemistry to be collected pre-dosing
  - ADA to be collected pre-dosing
  - PD biomarker sample to be collected pre-dosing.
  - PK blood sample to be collected pre-dosing and post-dosing (following completion of infusion, before the subject leaves the clinic)
- Administration of 1st Dose of IMP.

Following Randomization the participant will fill out Average Daily NRS Pain in the evening for Target Knee only (i.e from the evening of Visit 3).

8.4 Post-Randomization Period

The below assessments and procedures as per Schedule of Events are recommended to be performed in the order presented.

8.4.1 Visit 4 (Week 2, Day 15 ±3 days): Telephone Visit

Site will contact the study participant per phone to,

- Ensure that the participant understands how to use the eDiary daily for completion of Average Daily NRS Pain score for Target knee and record any use of Rescue Medication.
- Review concomitant medication.
- Review of potential new AEs and follow-up on ongoing AEs

8.4.2 Visit 5 (Week 4, Day 29 ±3): 2nd IMP dose

- Review of 48-hour washout of Rescue Medication prior to visit.
- Review concomitant medication
- Review of potential new AEs and follow-up on ongoing AEs

- Ensure that the participant understands how to use the eDiary daily for completion of Average Daily NRS Pain score for Target knee and record any use of Rescue Medication.
    - If needed, repeat of eDiary training in APR, PRR and RSR (eDiary Module Training), accessible through aLearn. Repeated eDiary training is recommended at least every 6 weeks.
- Vital signs
- Physical exam (including Musculoskeletal Examination)
- Perform accountability of Rescue Medication use, and re-supply if needed
- Urine dipsticks
    - hCG for Women of Childbearing Potential (See Appendix I)
    - Urine dipstick analysis
- ECG
- Blood sample for:
    - Safety Hematology and Chemistry to be collected pre-dosing
    - ADA to be collected pre-dosing
    - PD biomarker sample to be collected pre-dosing.
    - PK blood sample to be collected pre-dosing and post-dosing (following completion of IMP infusion, before the subject leaves the clinic.)
- Administration of 2nd Dose of IMP

8.4.3 Visit 6 (Week 5, Day 36 ±3)

- Review of 48-hour washout of Rescue Medication prior to visit.
- WOMAC full questionnaire for Target Knee
- PGA
- Review potential new AEs and ongoing AEs
- StEPP
- Ensure that the participant understands how to use the eDiary daily for completion of Average Daily NRS Pain score for Target knee and record any use of Rescue Medication.

- If needed, repeat of eDiary training in APR, PRR and PSR (eDiary Module Training), accessible through aLearn. Repeated eDiary training is recommended at least every 6 weeks.

- Accountability of Rescue Medication use, and re-supply if needed

8.4.4 Visit 7 (Week 8, Day 57 ±3 days): 3rd IMP dose

- Review of 48-hour washout of Rescue Medication prior to visit.
- Ensure that the participant understands how to use the eDiary daily for completion of Average Daily NRS Pain score for Target knee and record any use of Rescue Medication.
    - If needed, repeat of eDiary training in APR, PRR and PSR (eDiary Module Training), accessible through aLearn. Repeated eDiary training is recommended at least every 6 weeks.
- Collection of any changes in concomitant medication
- Review of new potential AEs and ongoing AEs
- Accountability of Rescue Medication use, and re-supply if needed
- SAS
- BCTQ
- Vital signs
- Weight measurement
- BMI calculated automatically in EDC
- Physical exam (including Musculoskeletal Examination)
- Urine dipstick hCG for Women of Childbearing Potential
- Urine dipstick analysis
- ECG
- Blood sample for:
    - Safety Hematology and Chemistry to be collected pre-dosing
    - PK of IMP to be collected pre-dosing and post-dosing (following IMP infusion completion, before the subject leaves the clinic.)

- Administration of 3rd Dose of IMP

8.4.5 Visit 8 (Week 12, Day 85 ±3): 4th IMP dose

- Review of 48-hour washout of Rescue Medication prior to visit.
- Ensure that the participant understands how to use the eDiary daily for completion of Average Daily NRS Pain score for Target knee and record any use of Rescue Medication.
    - If needed, repeat of eDiary training in APR, PRR and PSR (eDiary Module Training), accessible through aLearn. Repeated eDiary training is recommended at least every 6 weeks.
- Collection of any changes in concomitant medication
- Review of new potential AEs and ongoing AEs
- Accountability of Rescue Medication use, and re-supply if needed
- Vital signs
- Physical exam (including Musculoskeletal Examination)
- Urine dipstick Pregnancy test for Women of Childbearing Potential
- Urine dipstick analysis
- ECG
- Blood sample for:
    - Safety Hematology and Chemistry to be collected pre-dosing
    - PK of IMP to be collected prior to dosing and post-dosing (following IMP infusion completion, before the subject leaves the clinic.)
- Administration of 4th Dose of IMP

8.4.6 Visit 9 (Week 16, Day 113 ±3 days): 5th dose.

- Review of 48-hour washout of Rescue Medication prior to visit.
- Ensure that the participant understands how to use the eDiary daily for completion of Average Daily NRS Pain score for Target knee and record any use of Rescue Medication.

- If needed, repeat of eDiary training in APR, PRR and PSR (eDiary Module Training), accessible through aLearn. Repeated eDiary training is recommended at least every 6 weeks.

- Collection of any changes in concomitant medication
- Review of new potential AEs and ongoing AEs
- Accountability of Rescue Medication use, and re-supply if needed
- Vital signs
- Physical exam (including Musculoskeletal Examination)
- Urine dipstick hCG for Women of Childbearing Potential
- Urine dipstick analysis
- ECG
- Blood sample for:
  - Safety Hematology and Chemistry to be collected pre-dosing
  - PK blood sample to be collected pre-dosing and post-dosing (following IMP infusion completion, before the subject leaves the clinic)
- Administration of 5th Dose of IMP

8.4.7 Visit 10 (Week 17, Day 120 ±3 days)

- Review of 48-hour washout of Rescue Medication prior to visit.
- Ensure that the participant understands how to use the eDiary daily for completion of Average Daily NRS Pain score for Target knee and record any use of Rescue Medication.
  - If needed, repeat of eDiary training in APR, PRR and PSR (eDiary Module Training), accessible through aLearn. Repeated eDiary training is recommended at least every 6 weeks.
- Review of new potential AEs and ongoing AEs
- WOMAC full questionnaire for Target Knee
- PGA
- StEPP
- Accountability of Rescue Medication use, and re-supply if needed

8.5 Follow-up Period

8.5.1 Visit 11 (Week 20, Day 141 ±3 days): Follow-up Visit/End of Trial Visit

The assessments and procedures as described below apply to Visit 11 and EOT visit for participants that have discontinued trial prior to completion of Visit 10 procedures and assessments. For participants that have discontinued trial early, the EOT visit should be attempted completed within 4 weeks (+/- 3 days) following last received IMP administration.

- Review of 48-hour washout of Rescue Medication prior to visit.
- Assessment of changes in concomitant medication.
- Review of new potential AEs and follow-up on ongoing AEs
- Survey of Autonomic symptoms
- BCTQ
- Vital signs
- Weight measurement
- BMI calculated automatically in EDC
- Physical exam (including Musculoskeletal Examination)
- Blood sample for:
    - Safety Hematology and Chemistry
    - PK blood sample to be collected
    - ADA to be collected
    - PD biomarker sample to be collected
- Urine dipstick hCG for Women of Childbearing Potential
- Final accountability of Rescue Medication
- Radiographs bilateral knee-, shoulder- and hip joints
- MRI Target Knee

8.5.2 Visit 12 (Week 30, Day 212 ±7 days): Follow-up (FU) Safety Phone Visit

Site will contact the study participant per phone to complete following assessments:

- Assessment of changes in concomitant medication
- Review potential new AEs and follow-up on ongoing AEs. See Section 9.4 for description on procedure for AEs ongoing at Visit 12.

9 Assessment of Safety

The safety profile of the IMP will be assessed through the recording, reporting, and analysis of baseline medical conditions, AEs, physical examination findings including vital signs and laboratory tests and procedures, including ECGs in Screening and prior to each dosing. Safety assessments to be performed as per the:

- Interim Analyses Charter
- Independent Adjudication Committee for Adverse Events relating to Joint Safety Charter
- Medical Monitoring Plan
- Pharmacovigilance Plan
- Safety Monitoring Committee Charter

The safety of the participants will be evaluated periodically by an internal Safety Monitoring Committee overseeing the trial safety data. The Independent Adjudication Committee for Adverse Events relating to Joint safety includes the coordinating investigator, a radiologist and rheumatologist, as well as the study Medical Monitor (or delegate). Other specialists will be consulted as appropriate, and actions taken to ensure ongoing participant safety, as determined by the Independent Adjudication Committee.

9.1 Adverse Events

9.1.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product, regardless of causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether considered related to the medicinal product or not. For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself. All AEs observed by the study personnel or reported by the participant during the study (from the time of signing the Informed Consent Form (ICF) to Visit 12 will be documented. Investigators must assess the severity of AEs according to the Qualitative Toxicity Scale, as follows:

Mild: The participant is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate: The participant experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe: Significant impairment of functioning: the participant is unable to carry out his or her usual activities.

Investigators must also systematically assess and reevaluate based on emergence of information, the causal relationship of AEs to IMP as Unrelated or Related. Decisive factors for the assessment of causal relationship of an AE to IMP include, but may not be limited to, temporal relationship between the AE and the IMP administration, known side effects and mode of action of IMP, medical history and comorbidity of the participant, concomitant medication, course of the underlying disease and trial procedures.

Unrelated: Not reasonably related to the IMP. AE could not medically (pharmacologically/clinically) be attributed to the IMP under study in this clinical trial protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the IMP. AE could medically (pharmacologically/clinically) be attributed to the IMP under study in this clinical trial protocol.

9.1.2 Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Safety parameters (including vitals, ECG, body weight and laboratory tests) with absolute value outside the reference range or changed following Screening that are considered by the Investigator as clinically significant must be recorded in the eCRF as AEs. In addition, at the Investigator's discretion, any changes, or trends over time in laboratory parameters can be recorded in the eCRF as AEs if such changes or trends are clinically relevant, even if the absolute values are within the reference range.

Laboratory findings do not need to be reported as AEs in the following cases:

- Laboratory parameters already outside the reference range at Visit 1, unless a further increase/decrease can be considered an exacerbation of a pre-existing condition.
- Abnormal laboratory parameters caused by mechanical or physical influences on the blood sample (e.g., hemolysis) and flagged as such by the laboratory in the laboratory report.

An abnormal laboratory value that cannot be confirmed and after a repeated analysis is considered within normal range should not necessarily be reported as an AE. A repeated analysis should preferably (but not required) to be completed in the same laboratory.

If a laboratory abnormality fulfills these criteria, the identified medical condition (for example, anemia, increased liver parameters) must be reported as the AE rather than the abnormal value itself.

Clinically significant abnormal laboratory values, relevant findings from physical examination, ECG findings, radiograph- and MRI findings from Screening are considered likely to have been present at time of signing of ICF and regarded as Medical History, unless a significant exacerbation of the condition is plausible to have occurred between the time of ICF signature and time of abnormal finding.

9.1.3 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" refers to an event in which the participant is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.)
- Requires inpatient hospitalization or prolongs an existing hospitalization.
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect.
- Is otherwise considered to be medically important. (Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered an SAE.

9.1.4 Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (for example, undesirable effects of any administered treatment) must be documented and reported as SAEs.

9.1.5 Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial are defined as Baseline Medical History and are not to be considered AEs.

9.1.6 Methods of Recording and Assessing Adverse Events

At each trial visit, the participant will be asked about changes in his or her condition. During the reporting period, any unfavorable changes in the participants condition will be recorded as AEs, whether reported by the participant or observed by the investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs and all nonserious AEs of special interest must be additionally documented and reported accordingly.

It is important that each AE report include a description of the event, its duration (onset and resolution dates (and times when it is important to assess the time of AE onset relative to the recorded treatment administration time), its severity, its causal relationship with the trial treatment, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the IMP, and its outcome. In addition, serious cases should be identified, and the appropriate seriousness criteria documented.

9.1.7 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the participant is initially included in the trial (date of signature of ICF) and continues until Visit 12 (Follow-up Safety Phone Visit).

Any SAE assessed as related to LEVI-04 must be reported whenever it occurs, irrespective of the time elapsed since the last administration of LEVI-04.

9.1.8 Definition of SAE Reporting Period

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 hours after becoming aware of the event) inform the Sponsor or its designee in writing. All written reports should be transmitted using the SAE Report Form, which must be completed by the Investigator following specific completion instructions.

Relevant pages from the eCRF may be provided in parallel (for example, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report, autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the eCRF.

The Investigator must respond to any request for follow-up information (for example, additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations. An internal Safety Monitoring Committee (SMC) will review SAEs and other relevant safety data as needed as further described in the Safety Monitoring Committee Charter.

9.1.9 Adverse Events of Special Interest (AESI)

Owing to the action of LEVI-04 on NGF, neurological AEs are of special interest. The following are considered AESIs:

- AE suggestive of new or worsening peripheral neuropathy
- AE of abnormal peripheral sensation (e.g. allodynia, burning sensation, carpal tunnel syndrome, dysesthesia, hyperesthesia, hyperpathia, hypoesthesia, neuralgia, neuritis, neuropathy peripheral, pall anesthesia, paresthesia, peripheral sensory neuropathy, sciatica, sensory disturbance, sensory loss, or tarsal tunnel syndrome) that is reported as an:
    - SAE
    - AE that resulted in the participant being withdrawn from the study.
    - AE ongoing at the end of study participation in the study or,
    - AE of severe intensity.
- Destructive Arthropathy, including RPOA type 2
- SIF
- Rapid loss of joint space width (JSW) of 2 mm within 12 months or less, or loss of 50% of JSW if less than 2 mm at baseline. This is also known as RPOA type 1
- Osteonecrosis
- Any incident acute fracture or bone marrow infiltration.
- Total and partial joint replacement

Suspected events will be monitored by the Safety Monitoring Committee, and any events involving joint safety will be escalated to the Independent Adjudication Committee for Adverse Events relating to Joint Safety, for committee review and appropriate recommendations for the individual participant, and potentially the study. The Adjudication Committee for Adverse Events relating to Joint Safety includes at least one rheumatologist and at least one radiologist who are experts in this field as well as the coordinating Investigator and study Medical Monitor or delegates as further described in the Adjudication Committee for Adverse Events relating to Joint Safety Charter.

9.2 Covid-19 related safety precautions

Sites should take necessary precautions and follow the guidance of their government's public health officials to minimise risk of covid-19 infection to staff and study participants. The European Medicine Agency's most up to date guidance on the "Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic" should be followed where necessary.

9.3 Safety Reporting to Health Authorities (HA), Independent Ethics Committees, and Investigators

The Sponsor or delegate will send appropriate safety notifications to HA in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving trial participants to the IEC that approved the trial.

In accordance with ICH GCP, the Sponsor/designee will inform the Investigator of "findings that could adversely affect the safety of participants, impact the conduct of the trial or alter the IEC's approval/favorable opinion to continue the trial."

In line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and are related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations regarding Safety Report notifications to Investigators will be considered.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For trials covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

9.4 Monitoring of Participants with Adverse Events

AEs are recorded and assessed continuously throughout the trial and are assessed for outcome at Visit 12/Follow-up Safety Phone Visit. All AEs considered related to the IMP and ongoing at Visit 12 must be monitored and followed up by the Investigator until stabilization or until the outcome is known unless the participant is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

9.5 Pregnancy and In Utero Drug Exposure

All pregnancies with an estimated conception date during the period defined and must be recorded by convention in the AE page/section of the eCRF. The same rule applies to pregnancies in female participants and to pregnancies in female partners of male participants. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which

must be transmitted according to the same process as described for SAE. Investigators must actively follow up, document and report on the outcome of all these pregnancies, even if the participants are withdrawn from the trial. The Investigator must notify the Sponsor of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used. Any abnormal outcome must be reported in an expedited manner as described in Section 9.1.3 while normal outcomes must be reported within 45 days after delivery. In the event of a pregnancy in a participant occurring during the trial, the participant must be discontinued from trial medication immediately. The Sponsor must be notified without delay and the participant must be followed as mentioned above.

9.6 Clinical Laboratory Assessments

Blood and urine samples will be collected for the following clinical laboratory tests, following the timing noted in the Schedule of Events, and in accordance with the Laboratory Manual. All samples should be clearly identified.

9.7 Vital Signs, Physical Examinations and Other Assessments

Vital signs including BP, HR, and BT are monitored throughout the study and significant changes reviewed during centralized monitoring and brought to Sponsor attention when necessary.

10 Statistics

10.1 Sample Size

This study is planned to enroll approximately 416 participants, with a possibility of adding an additional 208 participants pending a conditional power analysis done at the interim analysis (IA). It is assumed that there is a minimum effect of 10 out of 100 in change from baseline in WOMAC pain sub-score for at least one of dose groups compared with placebo, and a standard deviation of 19.2 for change from baseline. Dropout rate is assumed to be 15%, distributed evenly over the study duration of the study. An IA will be conducted when approximately 208 participants have completed the Week 5 visit, and approximatey 80 have completed the Week 17 visit. Based on the IA's conditional power analysis, the study will continue as planned with a total of 416 participants randomized, or with an increase of up to 208 participants (an additional 50%) up to a total of 624 participants. The final analysis will be conducted between the three treatment arms and placebo using a simple combination test with weights of 1/2 on the interim Z, and 1/2 on final Z, using a Dunnett's test. Therefore, each comparison will be made at a two-sided 0.0188 level of significance. With this design, the power for a statistically significant difference between at least one active treatment group versus placebo assuming the study will continue to at least the originally planned sample size is:

Effect scenario: treatment mean difference versus placebo			Power with sample size of 416	Increase of sample size to 624 at the IA		
Arm 1	Arm 2	Arm 2	SD=19.2	SD=22	SD=23	SD=24
10	7.5	5	90%	94%	92%	90%
10	5	2.5	88%	92%	89%	86%
10	0	0	86%	91%	88%	85%

10.2 Randomization

The screening/randomization procedure will be centrally managed through an electronic IWRS integrated in the EDC system. To enroll and randomize a new participant, the Investigator/authorized personnel will have to access the EDC system by entering their username and password and filling in the requested data. Randomization will be centrally balanced across the study (not by center).

A total of approximately 416 participants are planned to be randomized in a 1:1:1:1 to the placebo and three active arms. If needed based on the interim conditional power analysis, the sample size will increase up to 624.

10.3 Analysis Sets

10.3.1 Intention-to-Treat Analysis Set (Full Analysis Set)

The Intention-to-Treat (ITT) Analysis Set will include all participants randomly allocated to a treatment, based on the intention to treat "as randomized" principle (i.e., the planned treatment regimen rather than the actual treatment given in case of any difference).

10.3.2 Modified Intention-to-Treat Analysis Set

The Modified Intention-to-Treat (mITT) Analysis Set will include all participants from the ITT Analysis Set who have a baseline and at least one post-treatment WOMAC pain sub-score assessment available.

10.3.3 Per-Protocol (PP) Analysis Set

The PP Analysis Set will include all participants from the mITT Analysis Set who have been treated according to the trial protocol and fulfill the following criteria:

Absence of major clinical trial protocol deviations with respect to factors likely to affect the efficacy of the treatment, where the nature of such clinical trial deviations will be defined before breaking the blind.

Adequate compliance with trial medication (this will be defined in the Statistical Analysis Plan (SAP)).

10.3.4 Safety Analysis Set

The Safety Analysis Set will include all participants who have been administered at least one dose of trial treatment. Participants will be analyzed according to the actual treatment they receive.

10.3.5 Subgroup Analyses

Subgroup analyses (especially for the analysis of the primary endpoint) will be considered for the categories of OA at baseline (unilateral, bilateral) from the mITT Analysis Set who have a baseline and at least one post-treatment WOMAC pain sub-score assessment available.

10.3.6 Other Analyses

Sensitivity analyses to determine the influence of various degrees of Average Daily NRS pain variability in the screening period on major efficacy endpoints will be performed.

10.4 Description of Statistical Analyses

An outline of the analysis currently planned is presented in the following sections. A detailed SAP will be written and finalized before database lock and unblinding. The SAP will provide full details of all planned data analyses and data display.

10.4.1 Summary Statistics

The summary statistics presented for quantitative variables will be the number of observations (n), the number of missing values (missing), mean, standard deviation (SD), median, first and third quartiles (Q1, Q3), and minimum (min), and maximum values (max).

The summary statistics presented for categorical data will be the number of observations (n), the number of missing values (missing), and the count and percentage of participants in each category

10.4.2 Adjustment for multiplicity

Dunnett's step-down multiple comparison procedure will be used to compare the three active arms to placebo. A two-sided type-1 error of 0.0188 for each comparison will made initially and provide an overall two-sided type-1 error of 0.05. If any of the three comparisons is found to be significant at a two-sided 0.0188 level of significance, the remaining two comparisons will be made at a two-sided 0.0269 level of significance. If either one is significant, the last comparisons will be made at a two-sided 0.05 level of significance. In order to protect the overall type-1 error given the sample size recalculation, a simple combination test will be used to combine the statistics for each treatment comparison from the interim and post-interim data, assigning 1/2 weight to the interim Z-value, and 1/2 to the post-interim Z-value (i.e., the Z-value of the post-interim participants are calculated from the participants not included in the IA). The final Z statistic will be calculated as: $Z= Z_1 (\frac{1}{2})^{0.5} + Z_2 (\frac{1}{2})^{0.5}$ where Z_1 is the interim Z statistic, and Z_2 is the Z statistic calculated on participants not included in the IA.

10.4.3 Missing data

Generally, all data collected and available will be used in the analysis. Missing data for the primary endpoint will be imputed using multiple imputations (MI) methodology. All missing visits data will be imputed using all prior visits data, as well as treatment, and other covariates. Data that is missing at random will be imputed using the randomized treatment assignment, whereas data that is missing due to treatment (adverse event, lack of efficacy, etc.) will be imputed using placebo as the treatment. For the MI model, 100 imputations will be generated using PROC MI of SAS. Fully conditional specification (FCS) model using the regression method will be used with non-missing baseline and post-baseline WOMAC pain sub-score, and other important covariates to impute any missing data including missed visits and missing data due to dropouts. The seed to be used is 20220420. The results from the MI will then be used to derive the value of the change from baseline in the WOMAC pain sub-score at each timepoint, and then analyzed using the analysis of covariance (ANCOVA) model. The results of the 100 analyses will be transformed into a normal statistic and combined into a single analysis using PROC MIANALYZE.

Handling of missing data from questionnaires will depend on whether only single items are missing, or a complete questionnaire is missing. If only single items are missing, the rules defined by the authors of the questionnaires (if any) will be followed. The approach regarding analysis of missing single values,

in absence of rules defined by the authors of a questionnaire, is defined in the SAP. If a complete questionnaire is missing, no imputation will be applied.

10.4.4 Multicenter trials

Study center may have an impact on the study outcomes and therefore will be use as a covariate in the primary and secondary efficacy analyses.

10.4.5 Analysis of Primary Endpoints

The primary population of all efficacy analyses will be the Intent-to-Treat populations defined as all randomized participants. The primary efficacy analyses of continuous data will be analyzed using the ANCOVA model of the change from baseline in score, with treatment, study center, and baseline score as covariates. The primary timepoint for analysis will be week 17. Because of the IA, the final analysis will be conducted between each of the three treatment arms and placebo using a simple combination test (1/2 weight on interim Z, and 1/2 weight on final Z) at a two-sided 0.0188 level of significance (due to Dunnett's adjustment).

The WOMAC pain sub-score will be tabulated per time point (visit) and treatment group, along with the absolute change from baseline where baseline is defined as the latest assessment prior to first treatment administration.

For the treatment effect testing of IMP versus placebo, the null and the alternative hypothesis will be:

H0: Mean (Placebo) = Mean (IMP)

H1: Mean (Placebo) ≠ Mean (IMP)

If the null hypothesis is rejected, the alternative hypothesis will be accepted, and it will be concluded that the treatment effect of IMP differs from placebo.

To assess the robustness of the primary results, sensitivity analysis will be performed with modification of participant population (MITT and PP Analysis Sets). Further investigation of the robustness of the primary results (in particular, the influence of time and covariates) may be performed, if deemed necessary.

10.4.6 Analysis of Secondary Endpoints

The secondary efficacy endpoints will be analyzed using the ITT Analysis Set.

Descriptive statistics for secondary efficacy endpoints will be presented by time point (visit) and treatment group.

The same analysis of variance (ANOVA) model used for the primary endpoint will be used to assess the treatment effect on continuous secondary endpoints.

Logistic regression analysis will be used to assess the treatment effect on the binary efficacy endpoints such as responder rate. Point estimates for the pairwise comparison and corresponding CIs and p-values will be provided.

The amount of rescue medication taken will be analyzed by an ANCOVA with treatment, sex, BMI, baseline Target Knee WOPAIN NRS score, participant characteristic of baseline unilateral/bilateral knee OA as explanatory variables. Dependent variables are the total amount (g) divided by the number of days on study treatment, and in a separate analysis the total number of days with use of Rescue Medication divided by the number of days on study drug.

Strategies for handling of missing eDiary pain data will be described in detail in the statistical analysis plan.

No adjustment for multiplicity in the analyses of the secondary endpoints will be performed

10.4.7 Analysis of Safety and Other Endpoints

Safety data will be summarized descriptively overall and by treatment group, using the Safety Analysis Set. No statistical inference will be applied to safety endpoints.

The incidence rate, severity, and relationship to treatment for all AEs will be summarized by MedDRA SOC, and PT. Descriptive statistics will be presented for clinical laboratory tests, vital signs, and physical examinations. The number and percentage of participants with abnormal or potentially clinically significant clinical laboratory values and vital sign measurements will be summarized by treatment. These thresholds will be pre-defined in the SAP.

10.4.8 Interim and Additional Planned Analyses

An IA will be conducted for the first 208 participants who complete the week 5 visit (Visit 6), and when approximately 80 participants have passed Visit 10 (week 17) Based on the IA's conditional power analysis, the study will continue as planned with a total of 416 participants randomized, or with an increase of 208 participants (an additional 50%) to a total of 624 participants. The final analysis will be conducted between the three treatment arms and placebo using a simple combination test with weights of 1/2 on the interim Z, and 1/2 on final Z, using a Dunnett's test. Therefore, each comparison will be made at a two-sided 0.0188 level of significance.

The IA will be reviewed by a Committee, who will be unblinded, and not be involved in the daily management of the study after this point, and the recommendation from the committee will be to either continue the study to the originally planned sample size or increase the sample size to 624. The details of the IA analysis, including who will be unblinded, will be provided in the Statistical Analysis Plan.

11 Ethical and Regulatory Aspects

11.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at the site and will ensure that the trial is performed in accordance with this protocol, the ethical principles outlined in the Declaration of Helsinki, ICH GCP, and any other applicable regulations. The Investigator must ensure that only participants who have given informed consent are included in the trial.

11.2 Participant Information and Informed Consent

An unconditional prerequisite for each participant prior to participation in the trial is written ICF, which must be given before any trial-related activities are carried out. Adequate information must therefore be given to the participant by the Investigator or an appropriate designee (if local regulations permit) before informed consent is obtained.

A participant information sheet must be prepared in the local language in accordance with ICH GCP and will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential participant, the Investigator or a designate will inform the participant verbally of all pertinent aspects of the trial, using language chosen so that the information can be fully and readily understood by laypersons. The participant will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification.

If permitted by national regulations, a person other than the Investigator may inform the participant about the trial and sign the ICF, as above.

After the information is provided by the Investigator, the ICF must be signed and dated by the participant and the Investigator.

The signed and dated declaration of ICF will remain at the Investigator’s site and must be safely archived so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A signed and dated information and Informed Consent Form should be provided to the participant prior to participation.

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the participant information sheet and any other written information to be provided to the participant and submit them to the IRB for review and opinion. Using the approved revised participant information sheet and other written information, The Investigator will explain the changes to the previous version to each trial participant and obtain new written consent for continued participation in the trial. The participant will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification about the changes.

11.3 Participant Identification and Privacy

A unique number will be assigned to each participant, immediately after informed consent has been obtained. This number will serve as the participant's identifier in the trial as well as in the clinical trial database. All participant data collected in the trial will be stored under the appropriate participant number. Only the Investigator will be able to link trial data to an individual participant via an identification list kept at the site. For each participant, original medical data will be accessible for the purposes of source data verification by the Monitor, audits, and regulatory inspections, but patient confidentiality will be strictly maintained.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing participant data. Participants will be informed accordingly and will be requested to give their consent on data handling procedures in accordance with national regulations.

11.4 Emergency Medical Support and Participant Card

Participants will be provided with Emergency Medical Support cards supplied by the Sponsor for use during trial participation to provide clinical trial participants with a way of identifying themselves as participating in a clinical trial and to give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant.

The first point of contact for all emergencies will be the clinical trial Investigator caring for the affected participant. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (for example, unblinding) will follow the standard process established for Investigators.

11.5 Clinical Trial Insurance and Compensation to Participants

Insurance coverage will be provided for each country participating to the trial. Insurance conditions shall meet good local standards, as applicable.

11.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the trial at a given site, this clinical trial protocol will be submitted together with its associated documents to the responsible IEC or IRB for its favorable opinion or approval, which will be filed in the Investigator Site File. A copy will be filed in the Sponsor Trial Master File at NBCD A/S.

Amendments to this clinical trial protocol will also be submitted to the concerned IEC or IRB before implementation of substantial changes. Relevant safety information will be submitted to the IEC or IRB during the trial in accordance with national regulations and requirements.

11.7 Health Authorities (HA)

Prior to commencement of the trial at a given site, this clinical trial protocol will be submitted together with its associated documents to the responsible HA in accordance with all local and national regulations for each site for its favorable opinion or approval, which will be filed in the Investigator Site File. A copy will be filed in the Sponsor Trial Master File at NBCD A/S.

Amendments to this clinical trial protocol will also be submitted to the concerned HA before implementation of substantial changes. Relevant safety information will be submitted to the HA during the trial in accordance with national regulations and requirements.

12 Trial Management

12.1 Case Report Form Handling

Please view the eCRF Completion Guideline for full details.

The main purpose of the eCRF is to obtain data required by the clinical trial protocol in a complete, accurate, legible, and timely manner. The data in the eCRF should be consistent with the relevant source documents.

The Investigator or designee is responsible for ensuring that the data collected during this trial is accurate and documented. They will then be processed, evaluated, and stored in pseudonymous form in accordance with applicable data protection regulations. The Investigator must ensure that the eCRFs and any other associated documents forwarded to Sponsor, or its designated organization contain no mention of any participant names.

The data will be entered into a validated database. The Sponsor or its designee will be responsible for data processing, in accordance with the Sponsor's data management procedures. Database lock will occur once quality control and quality assurance procedures have been completed. Participant specific PDF files of the eCRFs will be provided to the Investigators at the completion of the trial.

12.2 Source Data and Participant Files

The Investigator must keep a file (medical file, original medical records) on paper or electronically for every participant in the trial. It must be possible to identify each participant by using this participant file. This file will contain the demographic and medical information for the participant listed below and should be as complete as possible. All parties involved adhere to applicable General Data Protection Regulation (GDPR) regulations.

- Participant's full name, age, sex, height, weight, race.
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Trial identification, that is, the Sponsor trial number for this clinical trial, and participant number

- Dates for entry into the trial (ICF) and visits to the site
- Any medical examinations and clinical findings predefined in this clinical trial protocol
- All AEs
- Date that the participant left the trial including any reason for early withdrawal from the trial or IMP (if applicable).

All documents containing source data must be filed, including, but not limited to MRI scan images, ECG recordings, and laboratory results. Such documents must bear the participant number and the date of the procedure. If possible, this information should be printed by the instrument used to perform the assessment or measurement. As necessary, medical evaluation of such records should be performed; all evaluations should be documented, signed, and dated by the Investigator.

12.3 Investigator Site File and Archiving

Upon initiation of the trial, the Investigator will be provided with an Investigator Site File containing all necessary trial documents, which will be completed throughout the trial and updated as necessary. The file must be available for review by the Monitor, during Sponsor audits and for inspection by HA during and after the trial and must be safely archived for at least 15 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the trial. The documents to be archived include the Subject Identification List and the signed participant's Informed Consent Forms. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

All original participant files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

12.4 Monitoring, Quality Assurance, and Inspection by Health Authorities (HA)

This trial will be monitored in accordance with the ICH GCP, and any other applicable regulations. The site Monitor will perform visits to the trial site at regular intervals.

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be participant to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as HA, must be permitted to access all trial documents and other materials at the site, including the Investigator Site File, the completed eCRFs, all IMP and IMP accountability records, and the original medical records or files for each participant.

12.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in writing. Substantive amendments will usually require submission to the HA and to the relevant IEC/ for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC/IRB or to HA only were requested by pertinent regulations. Any amendment that could affect the participant's agreement to participate in the trial requires additional informed consent prior to implementation.

12.6 Clinical Trial Report and Publication Policy

After completion of the trial, a clinical trial report will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3. Posting of data on clinicaltrialsregistrer.eu will occur within 12 months of the formal End of Trial, defined as Last Patient Last Visit.

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14 Appendices

14.1 Appendix I: Contraceptive Guidance and Woman of Childbearing Potential

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

1. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

2. Premenarchal

3. Postmenopausal female
   - Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and/or increased follicle-stimulating hormone [FSH] > 40 mIU/mL), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of <1% per year when used consistently and correctly[a].

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[b]
  - oral
  - injectable

Highly Effective Methods That Are User Independent

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner (A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used).
- Sexual abstinence (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participating in clinical studies.

b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and for at least 90 days after the last dose of study treatment

14.2 Appendix II: Protocol Amendments and List of Changes

Protocol and Amendment Versioning

DOCUMENT HISTORY

Document	**Date**
Version 3.0	07FEB2023
Version 2.0 (not submitted)	05OCT2022
Version DK1.1	24MAY2022
Original Protocol (v.1.0)	09MAR2022

Version 3.0 (07FEB2023)

Overall rationale for the Amendment: Prior to submission of version 2.0 of the protocol, further central inclarities in the protocol arised and the decision to discard submission of protocol version 2.0 and prepare a version 3.0 was made.

Tabulated List of Changes – Version 3.0 (03FEB2023)

Section # and Name	**Description of Change**	**Brief Rationale**
Title Page Document headers **Section 2**: Synopsis Appendix III: Signature Pages and Responsible Persons for the Trial	Updated protocol date/version. Updated contact information.	To incorporate new protocol date and version number and contact information for CRO.
Section 5.4.1: Inclusion Criteria **Section 2:** Synopsis	Inclusion criterion #12 to specify the probihited use of SNRIs as drug class.	It was unclear if the reference to the generic name for the SNRI, Duloxetine included óther medications within the same drug class.

Section 5.4.2: Exclusion Criteria **Section 2:** Synopsis	Exclusion criterion #2 rephrased for clarity Exclusion criterion #3 rephrased for clarity Exclusion criterion #7 rewritten to exclude participants with prior knee allosplasty Exclusion criterion #21 rewritten to clarify which of the subscores of the scale the criterion refers to and cut-off increased to include a score of 3. Exclusion criterion #27 rewritten to clarify contraindication to MRI also includes any inferences of significance to image quality	Phrasing ambiguous. Clarification and specification of which conditions if present should be excluded and which joints it would apply. Clarification that prior alloplasty of target knee to be excluded. Based on the screening data emerging and the background literature on the SAS, a cut-off of over 3 is considered appropriate. Clarification of rationale for exclusion criterion.
Section 5.5: Criteria for Initiation of Trial Treatment	To allow submission of screening knee x-rays for central read if acquired within 3 months of screening.	To reduce unnecessary radiographic imaging for the participants
Section 5.6.1: Process for Early Termination	Section added	To provide guidance on handling of early termination
Section 5.6.1: Process for Early Termination	Text added to clarifify process for rescreening	To provide transparency for site
Section 6.4.2: Permitted Concomitant Medications, Non-Pharmaceutical Supplements, and Therapies	Oral mulitivitamins and Selective Serotonin Receptor Inhibitors (SSRIs) added to list of permitted medications	To clarify
Section 7.9: Patient-Reported Outcome Instruments	Elaboration of the study used patient-reported outcomes	To clarify the correct use of the measures
Section 7.10: Laboratory Tests	Time window for post-dosing IMP PK sample removed Discrepancies between text and SoE corrected	To clarify procedures and facilitate site logistics
Section 8: Schedule of Events	Clarification of procedures at each visit and correction of discrepancies to SoE	To clarify visit procedures
Section 8.2.3: Diary Run-In Period	The possibly to extend the Diary-Run In period added	To facilitate site logistics and technical errors

Throughout the protocol	Minor editorial changes and clarifications	To correct minor inconsistencies or clarify relevant paragraphs

Version 2.0 (05OCT2022)

Overall rationale for the Amendment:

To implement a follow-up safety telephone visit at week 30 to ensure at least 87 days follow-up from last dosing of IMP and extend the Screening window to facilitate site logistics.

Tabulated List of Changes – Version 2.0 (05OCT2022)

Section # and Name	**Description of Change**	**Brief Rationale**
Title Page Document headers **Section 2**: Synopsis Appendix III: Signature Pages and Responsible Persons for the Trial	Update protocol date/version.	To incorporate new protocol date and version number.
Section 14.2: Appendix II: Protocol Amendment List of Changes	New section	To facilitate review of protocol amendment(s) and associated changes.
Section 5.4.2: Exclusion Criteria **Section 2:** Synopsis	Specification of use for females of highly effective contraception for at least 3 months after last dosing of IMP. Specification of inclusion of participants with non-acute gout. Removed pre-specified definition of substance abuse	To ensure safety of unexcepted pregnancy in female participants To avoid unnecessary exclusion of participants with gout flares that do not require NSAIDs. To avoid unnecessary site staff assessments of substance abuse according to pre-defined criteria.

Section 5: Investigational Plan **Section 8.4.9:** Visit 12 **Section 9.1.7:** Definition of the Adverse Event Reporting Period **Section 9.4:** Monitoring of Participants with Adverse Events **Section 12.6** Clinical Trial Report and Publication Policy	Addition of Follow-up Safety Phone Visit 12 at week 30	To ensure at least 87 days follow-up from last dosing of IMP
Section 6.2: Dosage, Administration of Post-infusion monitoring	Addition of a minimum 30-minute post-infusion monitoring of participants	To ensure sufficient monitoring of participants post-infusion
Section 6.3: Assignment to Treatment Groups	Clarification of randomization process previously described in other section	To clarify the use of central randomization process.
Section 7.11: Laboratory Tests **Section 9.8.2** Pharmacodynamics	Specification of blood samples to be taken	To clarify sufficient inclusion of all organ function tests necessary to ensure adequate safety monitoring and clarify use of samples to be collected
Section 9: Assessment of Safety	Clarification of study monitoring plans and charters in place for safety monitoring	To ensure adequate description of monitoring of safety
Throughout the protocol	Minor editorial changes and clarifications	To correct minor inconsistencies or clarify relevant paragraphs

14.3 Appendix III: Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Trial Title:	LEVI-04-21-02
EudraCT Number:	2021-006540-28
Clinical Trial Protocol Date/ Version:	07FEB2023/version 3.0

Protocol Lead:

I approve the design of the clinical trial:

_____ _____

Signature Date of Signature

Name, degree:

Function / Title:

Institution:

Address:

Telephone number:

E-mail address:

Signature Page – Coordinating Investigator

Trial Title	LEVI-04-21-02
EudraCT Number	2021-006540-28
Clinical Trial Protocol Date / Version	07FEB2023/version 3.0

I approve the design of the clinical trial and I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Conference on Harmonization Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

_____ _____

Signature Date of Signature

Name, degree:

Function / Title:

Institution:

Address:

Telephone number:

E-mail address:

Signature Page – CRO Representative

Trial Title:	LEVI-04-21-02
EudraCT Number:	2021-006540-28
Clinical Trial Protocol Date/ Version:	07FEB2023/version 3.0

I approve the design of the clinical trial and I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Conference on Harmonization Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

_____ _____

Signature Date of Signature

Name, degree:

Function / Title:

Institution:

Address:

Telephone number:

E-mail address:

Signature Page – Trial Biostatistician

Trial Title	LEVI-04-21-02
EudraCT Number	2021-006540-28
Clinical Trial Protocol Date / Version	07FEB2023/version 3.0

I approve the design of the clinical trial and I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Conference on Harmonization Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

_____ _____

Signature Date of Signature

Name, degree:

Function / Title:

Institution:

Address:

Telephone number:

E-mail address:

Signature Page – Principal Investigator

Trial Title	LEVI-04-21-02
EudraCT Number	2021-006540-28
Clinical Trial Protocol Date / Version	07FEB2023/version 3.0

Center Number

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Conference on Harmonization Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also affirm that I understand that Health Authorities may require the Sponsors of clinical trials to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for the purpose of complying with the regulatory requirements. I therefore agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

Signature	Date of Signature

Name, degree:

Function / Title:

Institution:

Address:

Telephone number:

E-mail address: