Efficacy and safety of LEVI-04 in patients with osteoarthritis of the knee: a randomised, double-blind, placebo-controlled, phase 2 trial

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Summary

Background Current therapies for osteoarthritis have limitations. LEVI-04 is a p75 neurotrophin receptor (p75NTR) fusion protein that inhibits neurotrophin-3. We assessed the efficacy and safety of LEVI-04 in individuals with knee osteoarthritis.

Methods This randomised, placebo-controlled, double-blind, phase 2 trial enrolled participants from Denmark, Hong Kong, Poland, Moldova, and the Czech Republic with painful (≥4/10 Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] pain scores) and radiographic knee osteoarthritis. Participants were randomised 1:1:1:1 to receive a monthly intravenous placebo or LEVI-04 0·3 mg/kg, 1·0 mg/kg, or 2·0 mg/kg through to week 16, with safety follow-up to week 30. The primary endpoint was change in WOMAC pain from randomisation to week 17 in the intention-to treat population. Safety analyses included all participants who received the study drug. This trial is registered with ClinicalTrials.gov, NCT05618782, and EU Clinical Trials database, EudraCT 2021-006540-28.

Findings Between Oct 19, 2022, and Oct 23, 2023, of 1598 participants screened, 518 (292 female and 226 male; mean age 64·0 years [SD 8·07]) were randomly assigned to receive LEVI-04 0·3 mg/kg (n=130), 1·0 mg/kg (n=130), or 2·0 mg/kg (n=129) or placebo (n=129). One person who did not receive the study treatment was excluded from the safety analysis. At week 17, least squares mean difference in WOMAC pain versus placebo were −0·51 (95% CI −0·96 to −0·07), p=0·023; −0·62 (−1·07 to −0·17), p=0·015; and −0·79 (−1·24 to −0·35) p=0·0024 in the LEVI-04 0·3 mg/kg, 1·0 mg/kg, and 2·0 mg/kg groups, respectively. Effect sizes (standardised mean difference) at week 17 were 0·28 (95% CI 0·52 to 0·04), 0·33 (0·58 to 0·09), and 0·43 (0·68 to 0·19) for the 0·3 mg/kg, 1·0 mg/kg, and 2·0 mg/kg groups, respectively. LEVI-04 showed no increased incidence in serious adverse events, treatment-emergent adverse events (75 [58%], 86 [66%], 83 [64%] in the 0·3 mg/kg, 1·0 mg/kg, and 2·0 mg/kg dose groups, respectively, and 87 [67%] placebo), or joint pathologies, including rapidly progressive osteoarthritis.

Interpretation LEVI-04 was well tolerated and showed significant improvements in pain and function. These results support supplementing endogenous p75NTR in treating osteoarthritis.

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See **Comment** page 1210

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Introduction

Novel therapies for the treatment of osteoarthritis are urgently required. Current pharmacological options are limited by efficacy, tolerability, and adverse effects.[1,2] Nerve growth factor (NGF) and neurotrophin-3 (NT-3) belong to a family of neurotrophins that regulate peripheral pain pathways.[3,4] NGF binds to tropomyosin receptor kinase A (TrkA) and p75 neurotrophin receptor (p75NTR), whereas NT-3 binds to all neurotrophin receptors (TrkA, TrkB, TrkC, and p75NTR), with highest affinity for TrkC and lowest affinity for p75NTR.[5–7] In addition to its role in pain signalling, NT-3 has a prominent role in cartilage and bone metabolism, inducing osteoclastogenesis and resorptive activity.[7] In contrast, NGF regulates bone cells, influencing osteoblast and osteoclast differentiation and osteocyte activity, as well as homeostasis of articular chondrocytes.[8–10] Antibodies to NGF provide analgesia in individuals with osteoarthritis but this treatment has been associated with dose-dependent increases in joint safety events, including rapidly progressive osteoarthritis.[11–13]

LEVI-04 is a fusion protein comprising two extracellular domains of the human p75NTR coupled to the fragment crystallisable component of human immunoglobulin G1, acting as a stable analogue of the endogenous neurotrophin binding protein, p75NTR. LEVI-04 supplements circulating concentrations of p75NTR and, like soluble p75NTR, binds to all the neurotrophins with differing affinities, with low picomolar affinity to NT-3 and with low nanomolar and reversible affinity to NGF.[14] LEVI-04 is an antagonist of neurotrophin-induced activation of Trk receptors with and without co-expression

Research in context

Evidence before this study

We searched PubMed from database inception up to Nov 27, 2025, using the search terms "p75NTR", "osteoarthritis", and "randomised clinical trial" for publications in English. This search yielded no results. There remains a huge unmet need for efficacious and well tolerated therapies for osteoarthritis. Excess neurotrophins are implicated, and previous analgesic therapies targeting nerve growth factor (NGF) inhibition provided analgesia but were dose-dependently associated with substantial joint pathologies, including rapidly progressive osteoarthritis. LEVI-04 is a first-in-class fusion protein comprising two extracellular domains of the human p75 neurotrophin receptor (p75NTR) coupled via a glycine linker to the fragment crystallisable component of human immunoglobulin G1. LEVI-04 provides analgesia via supplementation of the endogenous p75NTR binding protein and inhibition of neurotrophin-3 activity. A phase 1 study (NCT03227796) conducted in healthy volunteers and a small number of participants with osteoarthritis showed LEVI-04 to be well tolerated, with a pharmacokinetic profile that supported the doses and dose frequency explored in this phase 2 study.

Added value of this study

This is the first clinical study demonstrating analgesic efficacy of p75NTR supplementation, supporting a novel mechanism of action for targeting chronic pain in knee osteoarthritis. Significant improvements in pain, function, and patient global outcomes were shown. LEVI-04 was well tolerated and exhibited a favourable safety profile, especially in terms of joint safety outcomes, with no increase in joint safety events including rapidly progressive osteoarthritis.

Implications of all the available evidence

LEVI-04 has the potential to provide clinically meaningful analgesia without the treatment-limiting side effects of current therapies and without the serious joint safety side effects seen with anti-NGF antibodies.

of p75NTR. However, the responses induced by brain-derived neurotrophic factor, NT-4 and NGF, in cells expressing Trk receptors and cells co-expressing Trk receptors and p75NTR are not fully inhibited by LEVI-04. In contrast, NT-3-induced activity in cells expressing TrkA and TrkC receptors is fully inhibited by LEVI-04 and close to full inhibition is seen with p75NTR co-expression.[14]

We hypothesised that modulating neurotrophin excess with p75NTR supplementation would maintain NGF signalling and provide pain relief without side effects such as rapidly progressive osteoarthritis. This phase 2 trial evaluated the efficacy, safety, and tolerability of LEVI-04 compared with placebo in participants with knee osteoarthritis.

Methods

Study design

This was a multiple-arm, multicentre, prospective, parallel group, randomised, double-blind, placebo-controlled, phase 2 study of LEVI-04 intravenous infusion for the treatment of knee osteoarthritis. Participants were enrolled at 13 clinical research centres in Denmark, Hong Kong, Poland, Moldova, and the Czech Republic. Regulatory and ethical approvals were obtained in each country. The trial participation involved ten study visits over a 30-week period, following a screening period of up to 56 days (two study visits). The study was conducted in accordance with all applicable regulations, including the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines on current good clinical practice, and the Declaration of Helsinki as amended in October 2013. All participants provided written informed consent.

See Online for appendix

Participants

Adults aged 40–80 years with a history of knee pain on most days for at least 3 months before screening and confirmed osteoarthritis of the target knee were enrolled. Diagnosis was confirmed radiographically as Kellgren–Lawrence grade 2 or greater (scale 0–4, read centrally) and by American College of Rheumatology clinical and radiographic diagnostic criteria.[15] The target knee had to score at least 20/50 (4/10 on transformed 0–10 scale) on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) numerical rating scale (NRS) version 3.1 pain subscale at screening and baseline visits, with average daily pain NRS scores of between 4·0 and 9·0 (range 0–10, 10 indicating the worst pain), with mean variability (SD) of 1·5 or less, collected on at least six of the last 7 days before randomisation using a daily electronic diary. Participants had to be willing to withdraw from all analgesic medication for osteoarthritis.

Exclusion criteria focused on comorbidities or concomitant medication that could interfere with assessment of target knee pain, systemic illness known to be significantly associated with arthritis or joint pathology affecting any joint, and pathological conditions significantly affecting joint and bone health. Full list of inclusion and exclusion criteria are provided in the appendix (pp 3–5).

Randomisation and masking

Participants were randomised (block size of four centrally balanced across the study) by an interactive web-based randomisation system to one of four treatment arms: LEVI-04 0·3 mg/kg, 1·0 mg/kg, 2·0 mg/kg, or placebo, in a 1:1:1:1 ratio (figure 1). Study site staff and participants did not have access to the random allocation sequence.

The treatment was prepared at each site by an unblinded delegate who was not involved in other aspects of the study. The placebo was indistinguishable from the active treatment. Participants, study site investigators, study site personnel giving the interventions, those assessing outcomes, and those analysing the data were unaware of the treatment allocation.

Procedures

After the screening period and randomisation, study visits were performed at weeks 0, 2, 4, 5, 8, 12, 16, 17, 20, and 30 (with week 2 and week 30 being telephone visits). Participants received monthly intravenous infusions of LEVI-04 or saline control (placebo) during the first 16 weeks. All on-site visits involved safety assessments, including blood monitoring, electrocardiograms (ECGs), and vital signs. Efficacy measures were conducted at visits one week after dose 2 (week 5) and dose 5 (week 17). Efficacy assessments at these visits were the WOMAC, patient global assessment (PGA), and an evoked pain-on-movement assessment, the Staircase-Evoked Pain Procedure (StEPP), in which participants rate their pain on a scale of 0–10 (with 10 being the worst pain) after climbing up and down a single standardised step on alternate legs a total of 24 times.[16] Pain was assessed in both knees during screening, but once the target knee was selected at baseline, only pain in that knee was rated throughout the study. Pain scores (NRS) for the previous 24 h were collected daily using an electronic diary, starting from the screening period and continuing throughout the trial.

Standing x-rays of bilateral knees (posteroanterior fixed-flexion), hips (pelvis anteroposterior weight-bearing and mediolateral view), and shoulders (Grashey's view), followed by MRI (1·5 T) of bilateral knees, were obtained during screening and read by an independent central reader to confirm eligibility (see imaging inclusion and exclusion criteria, appendix pp 3–5). Follow-up MRI of the target knee and follow-up x-rays of bilateral knees, hips, and shoulders were performed at week 20.

Blood samples for anti-drug antibodies were taken pre-dose at visits on day 1, and week 4 and week 20.

Rescue medication (paracetamol [acetaminophen] 1000 mg per dosing with a maximum total of 4000 mg per 24 h) was permitted, dispensed at sites, and use recorded via an electronic daily diary.

Outcomes

The primary endpoint was the change in WOMAC NRS 3.1 pain subscale from baseline to week 17. Secondary efficacy endpoints included change in WOMAC pain

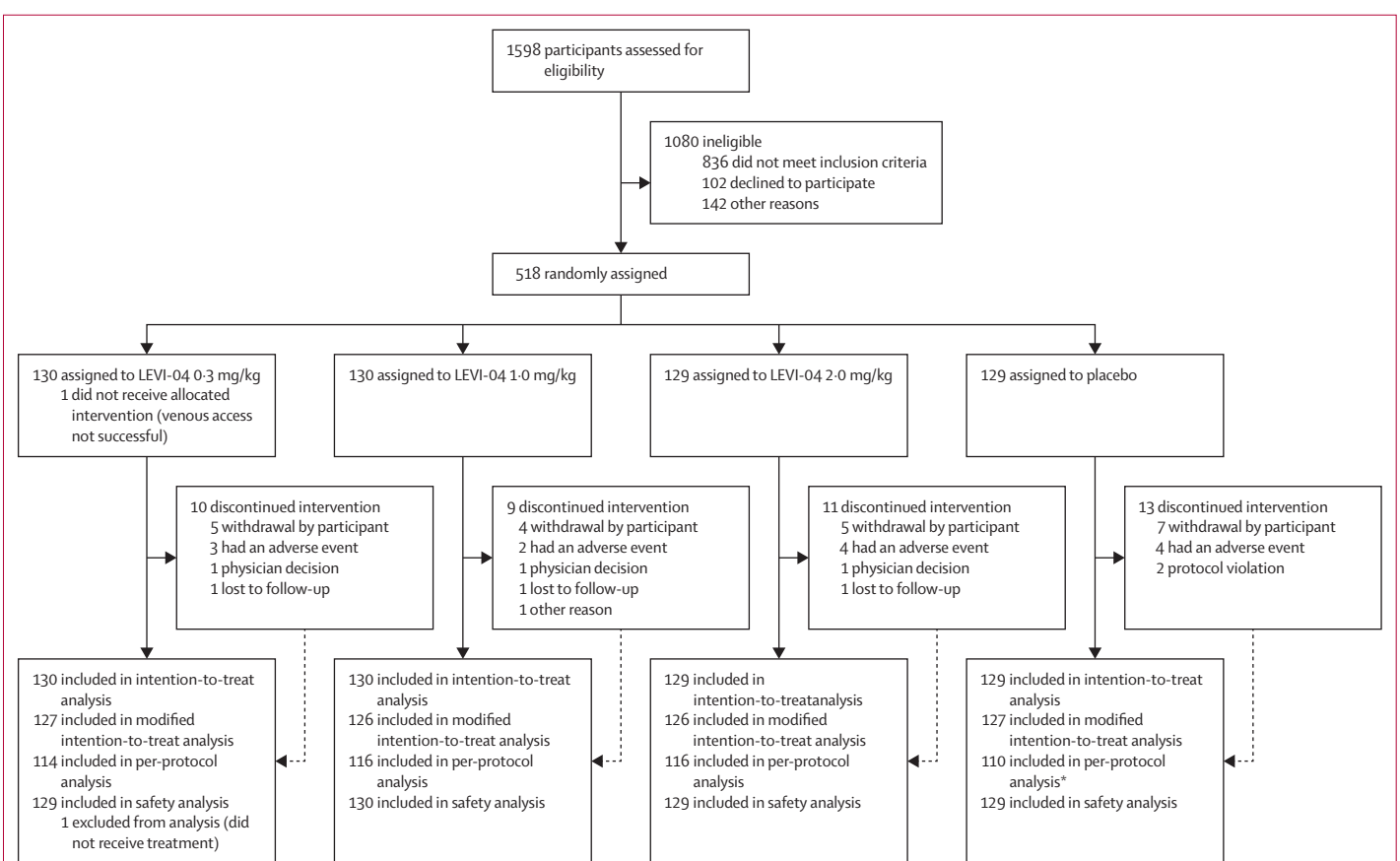

Figure 1: **Trial profile**

subscale from baseline to week 5 and change from baseline to week 5 and week 17 in WOMAC physical function and stiffness subscales, PGA, and StEPP. Changes in average weekly NRS pain score from baseline to week 5 and week 17, the proportion of participants achieving 30% and 50% reduction in WOMAC pain subscale at week 5 and week 17, the area under the curve of average daily NRS pain from baseline to week 20, and rescue medication usage during the trial were all prespecified secondary efficacy endpoints. The change from baseline in WOMAC pain at week 17 was also assessed by Kellgren–Lawrence grade.

Post-hoc efficacy analyses included the proportion of participants achieving 70% reduction and 90% reduction in WOMAC pain subscale at week 5 and week 17, and change from baseline in daily pain NRS scores on day 1 through to day 10.

Safety was assessed from the screening visit up to week 30 (follow-up safety phone visit). Adverse events between treatment arms (count and severity) were recorded and analysed. Any serious adverse event was reported as soon as site staff became aware of it. The safety profile of LEVI-04 was assessed through analysis of adverse events, physical examination findings, including vital signs, laboratory tests and procedures, ECGs during screening and before each dosing, and radiographic and MRI imaging at screening and week 20 (or as indicated clinically). Joint safety surveillance was in line with that used in anti-NGF antibody studies. Adverse events of special interest included new or worsening peripheral neuropathy or abnormal peripheral sensation, and joint events. Joint events, detected by treatment-blinded central reader on x-ray or MRI, or upon investigator request as a result of an unexplained increase in joint pain, were reviewed by an independent Adjudication Committee (appendix p 2).

Self-reported mean change from baseline in Boston Carpal Tunnel Questionnaire by treatment, subscale, and timepoint (intention-to-treat analysis set) were assessed at week 8 and week 20. The presence and impact of autonomic symptoms were assessed using the Survey for Autonomic Symptoms (SAS), stratified by treatment, timepoint (week 8 and week 20), and gender (intention-to-treat analysis set).

Statistical analysis

The sample size calculations assumed an SD of 19·2 and a reduction in the WOMAC pain score that was 10 units more than the placebo group in a minimum of one dose group (scale 0–100, all transformed to 0–10). With a sample size of 416, the power to detect at least one statistical difference from placebo ranged from 86% (only one dose different from placebo) to 90% (reductions of 10, 7·5, and 5 greater than placebo in the high, mid, and low dose groups, respectively). These power calculations were based on an adjusted critical value due to Dunnett's test at a per-comparison two-sided α of 0·0189 to account for three comparisons against a common control. Overall type-1 error was two-sided 0·05. The drop-out rate was assumed to be 15%, distributed evenly over the duration of the study. A predefined interim analysis to confirm the adequacy of sample size and variability assumptions was planned for when the first 208 participants either completed the week 5 visit or discontinued after randomisation, with approximately 80 participants passing week 17. The prespecified options were to continue the study with the originally planned sample size or recruit up to an additional 208 participants (a 50% increase) to a maximum of 624 participants, with the objective of achieving 90% power. All study personnel remained unaware of the interim analysis, and the statistician who performed the interim analysis was recused from any interactions with study personnel until the database lock of May 28, 2024.

All data collected were used in the final analysis. Missing data for the primary endpoint were imputed using multiple imputations methodology. Imputations were performed separately for each treatment and only the primary endpoint results for non-missing visits (baseline, week 5, and week 17) were used to impute the visits with missing results. Neither site nor any other additional covariates were used in the multiple imputation modelling. Missing data attributable to reasons plausibly related to treatment (eg, adverse events or lack of efficacy) were not assumed to be missing at random and were imputed using the jump-to-control principle. All other missing data were considered missing at random and imputed using the randomised treatment assignment as the projected treatment effect.

The primary population of all efficacy analyses was the intention-to-treat population defined as all randomised participants. The modified intention-to-treat analysis set included all participants from the intention-to-treat analysis set who had baseline and at least one post-treatment WOMAC pain sub-score assessment available. The per-protocol analysis set included all participants from the modified intention-to-treat analysis set who had been treated according to the trial protocol and had an absence of major clinical trial protocol deviations (determined in a blinded manner). Sensitivity analyses for assessing the jump-to-control imputation of the primary population were performed using observed data. Additionally, the modified intention-to-treat and per-protocol populations were analysed without imputation using only observed data.

The primary efficacy analyses of continuous data were analysed using the analysis of covariance (ANCOVA) model of the change from baseline in score, with treatment, study centre, and baseline score as covariates. The final primary endpoint analysis was conducted between the three treatment arms and placebo using a simple inverse normal combination test with weights of 1/2 on the interim Z, and 1/2 on the post-interim z-statistics. A step-down Dunnett's test was used to

control type-1 error and compare the three active arms with placebo. The same ANCOVA model used for the primary endpoint was used to assess the treatment effect on continuous secondary endpoints, but without weighting for the interim analysis, and without a step-down test. Logistic regression analysis was used to assess the treatment effect on the binary efficacy endpoints such as responder rate. The logistic regression model included main effect treatment and covariates study centre and baseline value. Point estimates for the pairwise comparison and corresponding CIs and p values were provided. WOMAC pain scores (0–50 scale) were transformed to a 0–10 scale. For the primary endpoint, effect size was calculated as Cohen's d[17] from an analysis of covariance of pooled interim and post-interim data.

Safety data, including joint safety events, were summarised descriptively overall and by treatment group using the safety analysis set (all participants who had been administered at least one dose of trial treatment). Participants were analysed according to the actual treatment they received. No statistical inference was applied to safety endpoints. The incidence rate, severity, and relationship to treatment for all adverse events were summarised by Medical Dictionary for Regulatory Activities version 25.0 system organ classes and preferred term. Descriptive statistics were presented for clinical laboratory tests, vital signs, and physical examinations.

NBCD was responsible for medical monitoring, operational management, site monitoring, and data management. Statistical analyses were performed by Prosoft Clinical (Chesterbrook, PA, USA) using SAS

	LEVI-04 0·3 mg/kg (n=130)	LEVI-04 1·0 mg/kg (n=130)	LEVI-04 2·0 mg/kg (n=129)	Placebo (n=129)
Age, years	63·2 (7·68)	64·5 (8·37)	63·1 (8·26)	65·4 (7·80)
Sex				
Female	67 (52%)	80 (62%)	69 (53%)	76 (59%)
Male	63 (48%)	50 (38%)	60 (47%)	53 (41%)
Ethnicity				
Hispanic or Latino	0	1 (1%)	1 (1%)	0
Not Hispanic or not Latino	130 (100%)	128 (98%)	128 (99%)	129 (100%)
Not reported	0	0	0	0
Unknown	0	1 (1%)	0	0
Race				
American Indian or Alaska Native	1 (1%)	0	0	0
Asian	12 (9%)	15 (12%)	17 (13%)	22 (17%)
White	117 (90%)	115 (88%)	112 (87%)	107 (83%)
BMI, kg/m²	30·3 (4·50)	29·4 (4·40)	29·3 (4·31)	30·3 (4·65)
Selected medical history				
Hypertension	70 (54%)	55 (42%)	63 (49%)	62 (48%)
Hypercholesterolaemia	26 (20%)	30 (23%)	25 (19%)	24 (19%)
Type 2 diabetes	10 (8%)	11 (8%)	13 (10%)	12 (9%)
WOMAC pain subscale score				
Target knee	5·74 (1·12)	5·80 (1·05)	5·76 (1·07)	5·82 (1·03)
Non-target knee	3·98 (1·97)	3·73 (1·96)	3·79 (2·05)	3·95 (2·12)
Kellgren–Lawrence grade, target knee				
0 and 1	0	0	0	0
2	22 (17%)	30 (23%)	34 (26%)	25 (19%)
3	64 (49%)	60 (46%)	60 (47%)	65 (50%)
4	44 (34%)	40 (31%)	35 (27%)	39 (30%)
Kellgren–Lawrence grade, non-target knee*				
0	13 (10%)	5 (4%)	7 (6%)	8 (6%)
1	12 (9%)	20 (16%)	16 (13%)	17 (13%)
2	33 (26%)	42 (33%)	30 (24%)	32 (25%)
3	47 (36%)	48 (38%)	50 (40%)	50 (39%)
4	24 (19%)	12 (9%)	23 (18%)	20 (16%)

Data are n (%) or mean (SD). WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index numerical rating scale. Sex, ethnicity, and race were self-reported by participants. *Patient numbers for Kellgren–Lawrence grade of non-target knees were 129, 127, 126, 127 across the LEVI-04 0·3 mg/kg, 1·0 mg/kg, 2·0 mg/kg dose groups, and placebo, respectively, due to existing arthroplasties.

Table 1: **Demographics and baseline characteristics of the intention-to-treat population**

(version 9.44). Both organisations are independent of the trial sponsor. This trial was registered with ClinicalTrials.gov, NCT05618782, and the EU Clinical Trials database, EudraCT 2021-006540-28.

Role of the funding source

The study funder was involved in the study design, data collection, data interpretation, and writing of the report.

Results

Between Oct 19, 2022, and Oct 23, 2023, 1598 participants were screened and 518 were randomly assigned to receive LEVI-04 0·3 mg/kg (n=130), LEVI-04 1·0 mg/kg (n=130), LEVI-04 2·0 mg/kg (n=129), or placebo (n=129); the intention-to-treat analysis set (figure 1). The main reasons for exclusion were radiology findings other than Kellgren–Lawrence grade (including meniscal root tear in 255 individuals), insufficient pain in the target knee (151 individuals), and Kellgren–Lawrence grade less than 2 in the target knee (108 individuals). The interim analysis estimated a conditional power of 85% with no change to the sample size, or 90% with a 25% increase. Therefore, according to the predefined interim analysis plan, the independent statistician recommended a 25% increase in the sample size. In total, 517 received at least one dose of treatment (safety analysis set), and 475 participants (92%) completed the study.

Participant demographic and baseline characteristics were similar across the treatment groups (table 1). The mean age of participants was 64·0 years (SD 8·07), 292 (56%) were female and 226 (44%) were male, and the mean BMI was 29·8 (SD 4·48) kg/m². All participants had evidence of target knee osteoarthritis with a Kellgren–Lawrence grade 2 or greater. Target knee

	LEVI-04 0·3 mg/kg (n=130)	LEVI-04 1·0 mg/kg (n=130)	LEVI-04 2·0 mg/kg (n=129)	Placebo (n=129)
WOMAC pain, week 5				
N	127	124	125	127
LSM change from baseline (SE)	−2·24 (0·15)	−2·18 (0·15)	−2·43 (0·16)	−1·57 (0·15)
LSM difference (95% CI)	−0·67 (−1·09 to −0·26)	−0·62 (−1·04 to −0·20)	−0·87 (−1·29 to −0·45)	..
p value	0·0016	0·0038	<0·0001	..
WOMAC pain, week 17 (primary endpoint, multiple imputations)				
N	130	130	129	129
LSM change from baseline (SE, SD)*	−2·77 (0·16, 1·86)	−2·87 (0·17, 1·88)	−3·05 (0·17, 1·89)	−2·26 (0·17, 1·87)
LSM difference (95% CI)	−0·51 (−0·96 to −0·07)	−0·62 (−1·07 to −0·17)	−0·79 (−1·24 to −0·35)	..
Adjusted p value†	0·023	0·015	0·0024	..
WOMAC physical function, week 5				
N	127	124	125	127
LSM change from baseline (SE)	−1·72 (0·15)	−1·81 (0·15)	−2·14 (0·15)	−1·16 (0·15)
LSM difference (95% CI)	−0·56 (−0·96 to −0·15)	−0·64 (−1·05 to −0·23)	−0·98 (−1·38 to −0·57)	..
p value	0·0073	0·0021	<0·0001	..
WOMAC physical function, week 17				
N	118	119	116	113
LSM change from baseline (SE)	−2·40 (0·16)	−2·49 (0·16)	−2·75 (0·16)	−1·84 (0·16)
LSM difference (95% CI)	−0·56 (−1·00 to −0·12)	−0·65 (−1·09 to −0·21)	−0·90 (−1·34 to −0·46)	..
p value	0·012	0·0038	<0·0001	..
WOMAC stiffness, week 5				
N	127	124	125	127
LSM change from baseline (SE)	−1·92 (0·16)	−1·98 (0·16)	−2·35 (0·16)	−1·15 (0·16)
LSM difference (95% CI)	−0·77 (−1·21 to −0·33)	−0·83 (−1·27 to −0·39)	−1·20 (−1·64 to −0·76)	..
p value	0·0006	0·0003	<0·0001	..
WOMAC stiffness, week 17				
N	118	119	116	113
LSM change from baseline (SE)	−2·60 (0·18)	−2·82 (0·18)	−3·20 (0·18)	−1·75 (0·19)
LSM difference (95% CI)	−0·85 (−1·34 to −0·35)	−1·07 (−1·56 to −0·57)	−1·45 (−1·95 to −0·95)	..
p value	0·0009	<0·0001	<0·0001	..

From an ANCOVA model with main effect treatment and covariates study centre and baseline score with missing scores imputed using multiple imputations methodology. ANCOVA=analysis of covariance. LSM=least squares mean. WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index numerical rating scale. *SD=SE*sqrt(n). †p values are from separately analysing interim and post-interim participants. Z statistics from the interim and post-interim comparisons against placebo are created using the inverse normal transformation of the *t* statistics and combined using a weighted sum and used for an overall comparison against placebo. p values are adjusted according to a step-down Dunnett's test.

Table 2: **Primary and selected secondary efficacy endpoints at week 5 and week 17 in the intention-to-treat population**

Kellgren–Lawrence grades at baseline were grade 2 (21%), grade 3 (48%), and grade 4 (31%). Overall target knee baseline mean WOMAC pain subscale score was 5·78 (SD 1·07).

All doses of LEVI-04 met the primary endpoint, demonstrating greater improvements in change from baseline in WOMAC pain than placebo at week 17: least squares mean change from baseline were –2·77 (SD 1·86), –2·87 (1·88), and –3·05 (1·89) in the LEVI-04 0·3 mg/kg, 1·0 mg/kg, and 2·0 mg/kg groups, respectively, versus –2·26 (1·87) with placebo. The least squares mean differences from placebo in the LEVI-04 0·3 mg/kg, 1·0 mg/kg, and 2·0 mg/kg groups, respectively, were –0·51 (95% CI –0·96 to –0·07), p=0·023; –0·62 (–1·07 to –0·17), p=0·015; and –0·79 (–1·24 to –0·35), p=0·0024 (table 2). Modified intention-to-treat and per-protocol analyses showed consistent results (data not shown). Limited influence of missingness on treatment effect estimation was confirmed in sensitivity analyses of observed data (no imputation). The effect sizes (standardised mean difference) of each dose group versus placebo at week 17 were 0·28 (95% CI 0·52 to 0·04), 0·33 (0·58 to 0·09), and 0·43 (0·68 to 0·19) for the 0·3 mg/kg, 1·0 mg/kg, and 2·0 mg/kg groups, respectively.

LEVI-04 also met the secondary endpoints, of WOMAC physical function and WOMAC stiffness at week 5 and week 17 for all doses (table 2). The differences between all LEVI-04 dose groups and placebo were significant at all timepoints for WOMAC physical function: p=0·0073, p=0·0021, and p<0·0001 for LEVI-04 0·3 mg/kg, 1·0 mg/kg, and 2·0 mg/kg, respectively, at week 5; and p=0·012, p=0·0038, and p<0·0001, respectively, at week 17. Similarly, for WOMAC stiffness, the differences between the LEVI-04 dose groups and placebo were significant at both week 5 and week 17 for all doses and timepoints (p=0·0006, p=0·0003, and p<0·0001 at week 5, and p=0·0009, p<0·0001, and p<0·0001 at week 17, for LEVI-04 0·3 mg/kg, 1·0 mg/kg, and 2·0 mg/kg, respectively).

Additional secondary endpoints are shown in figure 2. All LEVI-04 doses showed significant improvement in PGA and in the StEPP pain intensity scores compared with placebo at week 5 and week 17 (figure 2). Responder analyses showed that a significantly higher proportion of participants in all LEVI-04 groups experienced at least 30% reduction in WOMAC pain scores versus placebo at week 5 (80 of 127, p<0·0006 in the 0·3 mg/kg; 74 of 124, p<0·0033 in the 1 mg/kg; and 77 of 125, p<0·0001 in the 2 mg/kg dose groups), although at week 17 this difference was not significant (appendix p 7). The proportion of participants who experienced at least 50% reduction in WOMAC pain scores compared with placebo was significantly higher in all LEVI-04 groups at week 5 (45 of 127, p=0·0027 for 0·3 mg/kg; 44 of 124, p=0·0037 for 1 mg/kg; and 57 of 125, p<0·0001 for 2·0 mg/kg), indicating sustained duration of effect from weeks 5 to 17 with these doses (figure 3A).

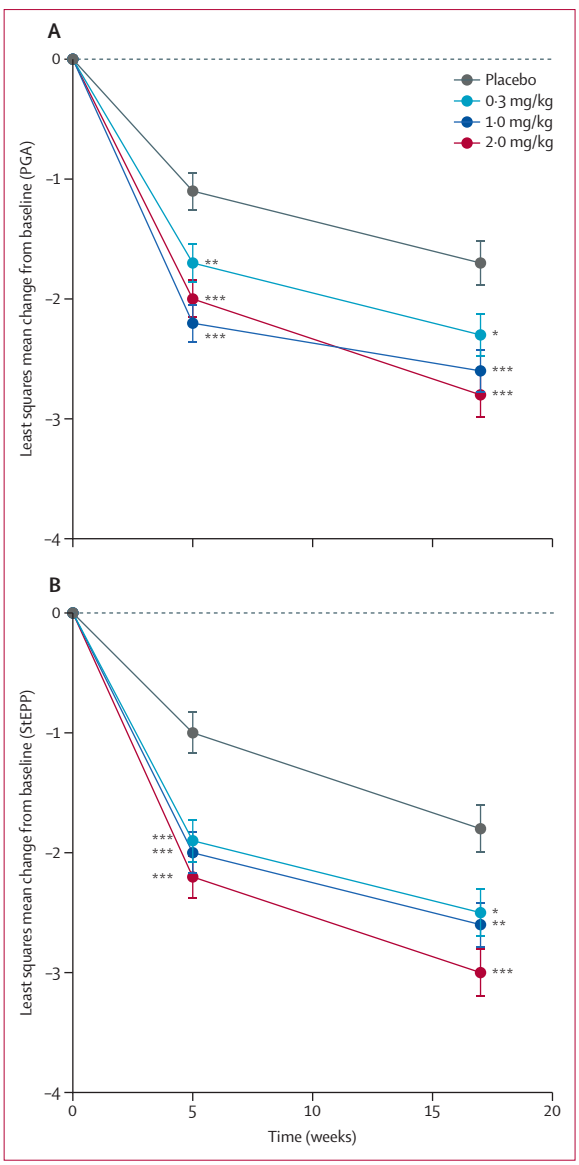

Figure 2: **Least squares mean change from baseline in (A) PGA score and (B) StEPP score through to week 17 in the intention-to-treat population**
PGA=patient global assessment. StEPP=Staircase-Evoked Pain Procedure. *p<0·05; **p<0·01; ***p<0·001. p values are adjusted according to a step-down Dunnett's test.

Mean change from baseline in average weekly NRS score was significantly improved for the 2·0 mg/kg LEVI-04 group compared with placebo at week 5 (p=0·028) and week 17 (p=0·0036). There was a trend for numerically greater reductions in the LEVI-04 0·3 mg/kg and 1·0 mg/kg dose groups versus placebo, but the differences were not significant (appendix p 8). Reduction in the mean area under the curve of average daily pain was statistically significant (p=0·0066) for the LEVI-04 2·0 mg/kg group compared with placebo (appendix p 8).

The average daily rescue medication use in all dose groups was low, with no significant differences observed

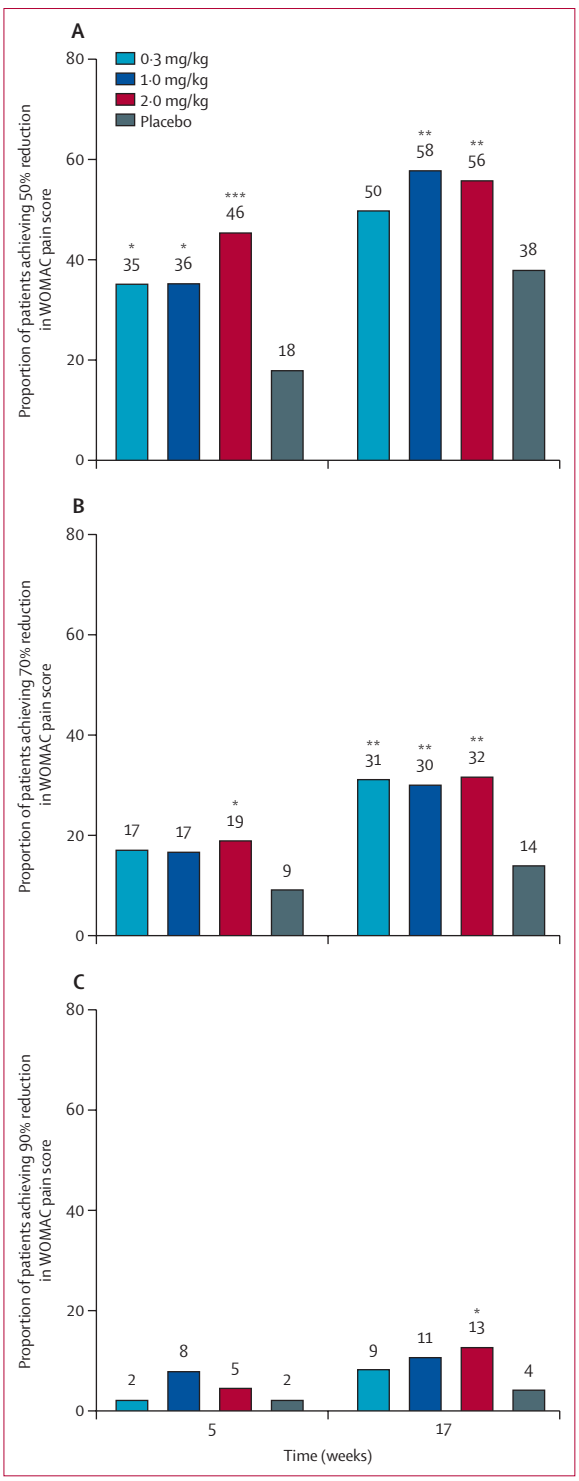

Figure 3: **Proportion of participants achieving (A) at least 50%, (B) at least 70%, and (C) at least 90% reduction in WOMAC pain score through week 17 in the intention-to-treat population**
WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index numerical rating scale. *p<0·05; **p<0·01; ***p<0·001.

for LEVI-04 groups compared with placebo (appendix p 9). Similarly, differences in the mean proportion of days on rescue medication with LEVI-04 were not statistically significant versus placebo (appendix p 9).

Further post-hoc analyses showed improvements in outcomes with LEVI-04 versus placebo. A significantly higher proportion of participants in all LEVI-04 groups versus placebo achieved at least 70% reduction in WOMAC pain scores at week 17 (p=0·004, p=0·003, and p=0·001 in the 0·3 mg/kg, 1·0 mg/kg, and 2·0 mg/kg dose groups, respectively), and the proportion of participants achieving at least 90% reduction in mean WOMAC pain scores was significant for the 2·0 mg/kg dose group versus placebo at week 17 (p=0·022; figure 3). LEVI-04 showed a rapid time to reduction in least squares mean change from baseline in daily NRS pain score, with a significant difference versus placebo by day 3 for the 1·0 mg/kg and 2·0 mg/kg dose groups (p=0·028 and p=0·017, respectively; appendix p 7). Similar improvements in WOMAC pain scores were observed with LEVI-04 treatment across all Kellgren–Lawrence grades (2–4) at week 17 (appendix p 10).

LEVI-04 was well tolerated, with a similar frequency of observed serious adverse events, treatment-emergent adverse events, and joint pathologies, including rapidly progressive osteoarthritis, between the treatment groups (table 3). The incidence of treatment-emergent adverse events reported as severe, treatment-related, causing discontinuation, or of special interest was low, with similar rates between active LEVI-04 and placebo treatment groups (table 3). The most common treatment-emergent adverse events across the LEVI-04 0·3 mg/kg, 1·0 mg/kg, and 2·0 mg/kg dose groups, and placebo, respectively, were: arthralgia, 11 (9%), 15 (12%), 15 (12%), and 20 (16%); nasopharyngitis, six (5%), eight (6%), 13 (10%), and 13 (10%); and back pain, three (2%), five (4%), eight (6%), and three (2%) participants (table 3).

Serious treatment-emergent adverse events were reported in seven participants: none, one (1%), three (2%), and three (2%) in the LEVI-04 0·3 mg/kg, 1·0 mg/kg, 2·0 mg/kg, and placebo groups, respectively. All serious treatment-emergent adverse events were considered unrelated to the study medication, and none resulted in death. A total of 13 participants reported 17 treatment-emergent adverse events leading to study discontinuation (table 3). Of the 17 treatment-emergent adverse events, eight (five participants) were considered related to study medication (LEVI-04 0·3 mg/kg, mild rash, moderate joint effusion, mild joint effusion, moderate arthralgia, mild arthralgia, and moderate muscle weakness; LEVI-04 1·0 mg/kg, moderate microscopic colitis and mild skin burning sensation). No clinically important observations were noted in physical examinations, vital signs, laboratory parameters, ECG findings, or x-ray results. Concerning the Boston Carpal Tunnel Questionnaire, no change in functional status subscale score or symptom severity subscale score was observed at week 8 or week 20

	LEVI-04 0·3 mg/kg (n=129)	LEVI-04 1·0 mg/kg (n=130)	LEVI-04 2·0 mg/kg (n=129)	Placebo (n=129)
Any treatment-emergent adverse event	75 (58%)	86 (66%)	83 (64%)	87 (67%)
Study medication-related* treatment-emergent adverse events	9 (7%)	9 (7%)	8 (6%)	10 (8%)
Serious treatment-emergent adverse events	0	1 (1%)	3 (2%)	3 (2%)
Severe treatment-emergent adverse events	0	3 (2%)	4 (3%)	4 (3%)
Treatment-emergent adverse events leading to study discontinuation	3 (2%)	2 (2%)	4 (3%)	4 (3%)
Treatment-emergent adverse event of special interest†	5 (4%)	10 (8%)	7 (5%)	4 (3%)
Abnormal peripheral sensation	3 (2%)	4 (3%)	2 (2%)	1 (1%)
Traumatic fracture	0	2 (2%)	3 (2%)	1 (1%)‡
Total joint replacement§	1 (1%)¶	1 (1%)¶	1 (1%)	0
Subchondral insufficiency fracture§	0	1 (1%)‡	0	1 (1%)
Suspected neuropathy	1 (1%)	0	0	0
Narrowing of joint space width (rapidly progressive osteoarthritis type 1)§	0	2 (2%)||	1 (1%)||	1 (1%)||
Non-traumatic fracture	1 (1%)	0	0	0
Destructive arthropathy (including rapidly progressive osteoarthritis type 2§	0	0	0	0
Osteonecrosis§	0	0	0	0
Bone marrow infiltration	0	0	0	0
Treatment-emergent adverse events in ≥5% participants in any treatment group (preferred term)				
Arthralgia	11 (9%)	15 (12%)	15 (12%)	20 (16%)
Nasopharyngitis	6 (5%)	8 (6%)	13 (10%)	13 (10%)
Back pain	3 (2%)	5 (4%)	8 (6%)	3 (2%)
Headache	4 (3%)	3 (2%)	8 (6%)	6 (5%)
COVID-19	5 (4%)	2 (2%)	4 (3%)	8 (6%)
Upper respiratory tract infection	4 (3%)	4 (3%)	5 (4%)	7 (5%)
Pain in extremity	3 (2%)	7 (5%)	5 (4%)	5 (4%)

Data are n (%). Participants experiencing multiple adverse events are only counted once within a given cell. *Adverse events with missing relatedness are considered related. †Participants experiencing multiple adverse events are only counted once within a given cell. ‡Osteoarthritis present at baseline. §All joint events Kellgren–Lawrence grade 2–4 on entry, all total joint replacements Kellgren–Lawrence grade 4 on entry. ¶Elective surgery. ||Meniscal extrusion reported.

Table 3: **Treatment-emergent adverse events in the safety population**

(appendix p 11). Similarly, for the SAS, no change from baseline was observed in SAS score at week 8 or week 20 (appendix p 12).

The incidence rates of treatment-emergent adverse events of special interest are reported in table 3. The most frequently reported was abnormal peripheral sensation with three (2%), four (3%), two (2%), and one (1%) participant reporting this event in the LEVI-04 0·3 mg/kg, 1·0 mg/kg, 2·0 mg/kg, and placebo groups, respectively. There were no patterns related to the time of onset or duration of these events, and most resolved spontaneously. One non-traumatic fracture of L4/L5 in a female participant aged 70 years with longstanding lumbar pain and osteoporosis was reported (0·3 mg/kg group). Six traumatic fractures, all classified as unrelated, were reported as adverse events of special interest (two, three, and one in the LEVI-04 1·0 mg/kg, 2·0 mg/kg, and placebo groups, respectively). None of these were reported to be associated with prior dizziness or changes in proprioception.

Irrespective of the Adjudication Committee decision regarding normal or rapid progression of osteoarthritis, all cases reviewed by the Committee are reported. There was no increase in the observed incidence of joint-related events with LEVI-04 at any dose. Rapidly progressive osteoarthritis type 1 was reported in none, two (2%), one (1%), and one (1%) participants in the LEVI-04 0·3 mg/kg, 1·0 mg/kg, 2·0 mg/kg, and placebo groups, respectively (table 3). There were two subchondral insufficiency fractures reported, one in a shoulder joint in the 1 mg/kg group (1%), and one in a knee joint in the placebo group (1%). There were no events of rapidly progressive osteoarthritis type 2. Three participants had joint replacements during the 30-week study period (one in each active arm, 1%), all of which were Kellgren–Lawrence grade 4 on study entry. One participant had surgery 3 weeks after starting the study and was adjudicated as normal progression of osteoarthritis, one was on a waiting list before the study start (protocol deviation), and one was performed during the follow-up period.

Detection of anti-drug antibodies was low (<2% of participants treated with LEVI-04). Anti-drug antibodies to LEVI-04 were detected at randomisation in two (2%), five (4%), and two (2%) participants, and at week 20 in zero, four (3%), and two (2%) participants in the LEVI-04 0·3 mg/kg, 1·0 mg/kg, and 2·0 mg/kg groups, respectively. All positive anti-drug antibody results were at the limit of detection (data not shown).

Discussion

This is the first report of a trial of supplementation of p75NTR in individuals with osteoarthritis. The primary endpoint, the mean change from baseline in WOMAC pain scores compared with placebo at week 17, was met for all LEVI-04 dose groups. Significant improvements with LEVI-04 were also observed across secondary endpoints, including patient-reported and observed function, stiffness, and PGA. The severity of knee pain has been associated with the severity of Kellgren–Lawrence grade;[18] LEVI-04 treatment demonstrated similar efficacy across all Kellgren–Lawrence grades (Kellgren–Lawrence grade 2–4).

Interpreting the clinical meaningfulness of these analgesic responses requires interpretation of a range of outcomes, as outlined by the IMMPACT guidelines.[19,20] For the two highest doses of LEVI-04, the magnitude of between-group differences in WOMAC pain scores was similar to that in previous trials of existing therapies, and the effect sizes—another measure of meaningfulness—were in the range of those previously reported for effective therapies, with the higher doses above the 0·37 threshold that reflects the median reported minimum clinically important difference.[21] Furthermore, the reduction in daily pain score from baseline was rapid (within 3 days). In terms of responder analyses, a 30% reduction in pain is considered clinically meaningful;[22] significantly more participants on the top two LEVI-04 doses achieved at least 50% reduction in WOMAC pain compared with placebo at weeks 5 and week 17. Sustained duration of effect was seen with the top two doses, although not for the lowest dose in the at least 30% responder analysis.

Evoked pain has been proposed as a more sensitive assessment for determining treatment effects.[16] In the StEPP assessment, the improvement versus placebo was significant for all LEVI-04 doses at week 5 and week 17. This measure of pain on movement reflects the impact of osteoarthritis on daily functioning, and the efficacy of LEVI-04 on this measure parallels the significant improvements seen in PGA scores.

In this study, LEVI-04 was well tolerated with no observed safety concerns. Incident rates of treatment-emergent adverse events were similar in the active treatment and placebo groups. There was no increased incidence of treatment-related adverse events or serious adverse events compared with placebo. Few participants (five) discontinued the study due to treatment-emergent adverse events.

The incidence of joint pathologies was not increased, with a low number of events of rapidly progressive osteoarthritis type 1 recorded across the treatment and placebo groups; background rates of approximately 3% might be expected over a 12-month period.[23] At baseline, all knees with rapidly progressive osteoarthritis had moderate-to-severe meniscal extrusion, which is associated with progression of osteoarthritis.[24] Importantly, there was no dose-dependence of incidence of rapidly progressive osteoarthritis type 1, no cases of rapidly progressive osteoarthritis type 2 (the subchondral bone-destructive phenotype) or other joint findings, and no events in healthy joints (graded as Kellgren–Lawrence grade 0 or 1 at study entry). By contrast, in studies with anti-NGF antibodies of similar treatment duration, rapidly progressive osteoarthritis type 2 was reported[25–27] and joint safety events occurred in healthy joints,[27] suggesting NGF inhibition, even over a short duration, has detrimental effects on joint health. All three of the joint replacements that occurred during the 30-week period in this study were in knees that were Kellgren–Lawrence grade 4 at baseline, and two were elective.

Osteoarthritis is a chronic condition requiring long-term treatment and biological therapies may be associated with development of an immune response to the treatment. The incidence of anti-drug antibodies in this study was low, similar to pre-dose levels, supporting the absence of immunogenicity of LEVI-04. Incidence of anti-drug antibodies will continue to be monitored in future trials.

Limitations of this phase 2 study included absence of a quality-of-life measure, and a safety follow-up period of only 13 weeks after the primary endpoint. Greater ethnic and race diversity within the patient population would have allowed for improved generalisability. Longer term treatment is needed to show any potential benefits or harms. If successful in subsequent trials, further evaluations will determine the place of this therapy in cost-effective care pathways.

NT-3 is associated with pain,[28,29] but also has important effects on bone metabolism. NT-3 enhances expression of matrix metalloproteinase-9 and matrix metalloproteinase-13, and can augment osteoclastogenesis and bone resorption directly by activating the extracellular signal-regulated kinase 1/2 cascade and receptor activator for nuclear factor κB ligand-induced increased expression of osteoclastogenic signals in differentiating osteoclasts, and indirectly by inducing osteoclastogenic signals in osteoblasts.[7] NT-3 also induces cartilage proteases, leading to cartilage degradation.[7] Consequently, it is plausible that inhibition of NT-3, could have an effect on structural progression, in addition to treating the symptoms of knee osteoarthritis, which will be explored further in subsequent trials. As LEVI-04 is a large molecule, it is peripherally restricted in most individuals and likely to have limited central nervous system adverse events. It has a non-opioid mechanism of action, mitigating the potential for addiction.

Our results support the potential of LEVI-04 as a novel treatment for knee osteoarthritis, improving pain and physical function, and reducing disease burden, coupled with an acceptable side effect profile. Longer duration phase 3 trials will seek to replicate clinical efficacy and assess long-term joint health.

Contributors

PGC, NK, AG, ARB, DR, MCP, BH, CH, and SW were responsible for the study design. ARB, AG, and NK were involved in design of the data

acquisition tools. PGC, AG, ARB, MCP, CH, IB, and SW accessed, reviewed, and verified the data. DR is an employee of an independent statistics company (Prosoft) and conducted the statistical analysis. The team were blinded to all data until after database lock, which was performed by NBCD, according to GCP compliant procedures. All authors participated in data interpretation. All authors had final responsibility for the decision to submit the manuscript for publication, provided critical feedback on the manuscript, approved the final manuscript for submission, and were accountable for the accuracy and integrity of the manuscript.

Declaration of interests

Levicept provided support for medical writing. PGC has done consultancies or speaker bureaus for AbbVie, Eli Lilly, Enlivex, Formation Bio, Genascence, Grunenthal, Kolon TissueGene, Levicept, Moebius, Novartis, Orion, Pacira, Stryker & Takeda, and received support for attending meetings or travel from Novartis. NK is a consultant to Levicept, AbbVie, Biogen, Consano, EicOsis, Genentech, Grünenthal, GSK, Latigo Biotherapeutics, the Merck Group, Mesoblast, Noven Pharmaceuticals, Rapport Therapeutics, Scilex Pharmaceuticals, Sparian Biosciences, TLC BioSciences, Formation Bio (formerly TrialSpark), and Vertex Pharmaceuticals. ARB is an employee and shareholder of NBCD who were contracted by Levicept to provide medical monitoring, operational management, site monitoring, data management for the study. AG is a shareholder of Boston Imaging Core Lab, and a consultant for Levicept, Novartis, Kolon TissueGene, Medipost (UK), Formation Bio, Paradigm Biopharmaceuticals, Scarcell Therapeutics, Coval Biopharma (Shanghai), 4Moving Biotech, Peptinov, Pacira BioSciences, and holds stock or stock options in Boston Imaging Core Lab. DR received payment from NBCD to perform statistical analysis of the study and received consulting fees from Levicept for ad-hoc analyses and review of the study results. MCP is a consultant to Levicept, received Levicept support to attend the British Society of Rheumatology meeting, owns stock in Centessa Pharmaceuticals, and holds stock options for Levicept. BH is a consultant for and received payments for study-related meetings and relevant scientific meetings from Levicept, owns stock in Pfizer and Glaxo, and holds stock options in Levicept. CH is an employee of and holds stock options in Levicept. IB is an employee of Levicept. SW is Chief Scientific Officer, founder of, and holds stock options in Levicept.

Data sharing

The study sponsor will receive requests for individual participant data that underlie the results reported in this Article, after de-identification, from qualified researchers whose proposed use of the data has been approved by a Review Committee. The study protocol is available in the appendix (pp 13–109). Data requests can be submitted to: info@levicept.com.

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