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Disease-modifying effects of a novel cathepsin K inhibitor in osteoarthritis: A randomized, placebo-controlled study

Authors:

P.G. Conaghan[1], PhD; M.A. Bowes[2], PhD; S.R. Kingsbury[1], PhD; A. Brett[2], PhD; G. Guillard[2], PhD; B. Rizoska[3], PhD; N. Sjögren[3], PhLic; P. Graham[3], MBChB; Å. Jansson[3], MSc Pharm; C. Wadell[3], PhD; R. Bethell[3], D.Phill; J. Öhd[3]* MD, PhD.

Affiliations:

1. Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, & NIHR Leeds Biomedical Research Centre, Leeds, United Kingdom

2. Imorphics Ltd, Manchester, United Kingdom

3. Medivir AB, Huddinge, Sweden

* Current affiliation: Modus Therapeutics, Stockholm, Sweden

Corresponding author:

P.G. Conaghan. Leeds Institute of Rheumatic and Musculoskeletal Medicine, Chapel Allerton Hospital, Chapeltown Road, Leeds, LS7 4SA, United Kingdom. Email: P.Conaghan@leeds.ac.uk; Tel: +44 113 3924883

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Abstract

Background: MIV-711 is a novel selective cathepsin K inhibitor with beneficial effects on bone and cartilage in preclinical osteoarthritis models.

Objective: To evaluate the efficacy, safety and tolerability of MIV-711 in participants with symptomatic, radiographic knee osteoarthritis.

Design: 26-week randomized, double-blind, placebo-controlled Phase IIa study with 26-week open-label safety extension sub-study.

Setting: Six European sites.

Participants: 244 participants with primary knee osteoarthritis, Kellgren-Lawrence Grade 2/3, and pain ≥4–10 on numeric rating scale (NRS).

Interventions: MIV-711 100 (n=82) or 200 mg (n=81) daily or matched placebo (n=77). Participants from the study (46 who initially received 200 mg; 4 who received placebo) received MIV-711 200 mg during the extension.

Measurements: The primary outcome was 26-week change in NRS pain score. The key secondary outcome was change in MRI bone area; other secondary endpoints: MRI quantitative cartilage thickness, Type I/II collagen C-telopeptide biomarkers. Outcomes assessed over 26 weeks.

Results: Change in NRS pain scores with MIV-711 treatment were not statistically significant (placebo: -1.4; MIV-711 100 mg: -1.7; MIV-711 200 mg: -1.5). MIV-711 significantly reduced medial femur bone area progression (100 mg: p=0.002; 200 mg: p=0.004) and medial femur cartilage thinning (100 mg: p=0.023; 200 mg: p=0.125) vs placebo and substantially reduced bone and cartilage biomarker levels. Nine serious adverse events occurred in six participants (placebo: one participant; 100 mg: three participants; 200 mg: two participants), none considered treatment-related.

Limitations: The trial duration was relatively short.

Conclusion: MIV-711 was not more effective than placebo for pain, but it significantly reduced bone and cartilage progression with a reassuring safety profile. This treatment may merit further evaluation as a disease-modifying osteoarthritis drug.

Trial registration: EudraCT: 2015-003230-26/2016-001096-73.

Funding source: Medivir AB.

Keywords: osteoarthritis, MIV-711, disease modifying osteoarthritis drug, MRI, cathepsin K

Introduction

Osteoarthritis is a major worldwide problem, affecting 9.6% of men and 18.0% of women over the age of 60 (1, 2). As osteoarthritis progresses, multiple structural changes occur including increases in subchondral bone area (3, 4) and loss of cartilage (5-7). Drugs that inhibit degenerative processes in both tissues have potential as disease modifying osteoarthritis drugs (DMOADs) (8, 9).

Cathepsin K is a cysteine protease involved in bone resorption and cartilage degradation through the breakdown of key bone matrix proteins (10-12). Little is known about inhibiting cathepsin K in osteoarthritis although several inhibitors have been tested in other indications (13-16). MIV-711 is a potent, selective and reversible cathepsin K inhibitor, that has undergone Phase I testing (12). Results from preclinical *in vivo* models and the single/multiple dose study in humans demonstrated that MIV-711 substantially reduces biomarkers of bone resorption (Type I collagen C-telopeptide, CTX-I) and cartilage loss (CTX-II) (12, 17, 18).

Investigations into DMOADs have been limited by a lack of sensitive and responsive markers of structural progression (19, 20). New quantitative magnetic resonance imaging (MRI) biomarkers using supervised machine learning have demonstrated construct validity and are much more responsive than the previous radiographic joint space narrowing (4, 19, 20). In addition, changes in 3D bone shape and cartilage thickness can predict subsequent knee replacement (19-24). While the relationship between changes in these measures and pain is less clear, increases in bone area/shape have been associated with clinically-relevant progression over a 2-year period (19). Importantly the responsiveness of these novel imaging methods enable shorter duration and smaller studies than is possible using X-ray assessments (25, 26).

We tested the hypotheses that a cathepsin K inhibitor could reduce degeneration of osteoarthritis bone and cartilage resulting in symptom reduction. We therefore evaluated the

efficacy, safety, and tolerability of orally administered MIV-711 in participants with symptomatic and radiographic knee osteoarthritis.

Materials and methods

Design overview

This was a 26-week, multicenter, randomized, placebo-controlled, double-blind, three-arm parallel Phase IIa study (MIV-711-201) followed by a 26-week open-label extension sub-study (MIV-711-202) (Supplementary Figure 1). The placebo-controlled study was conducted between January 2016 and May 2017. The protocols (Supplement 1) were approved by the appropriate Independent Ethics Committees and regulatory agencies and registered on ClinicalTrials.gov (NCT02705625/NCT03037489) and EudraCT (2015-003230-26/2016-001096-73). All participants provided written informed consent. Methodology for the extension sub-study is given in Supplementary Methods 1.

Setting and participants

Participants were recruited from six European (Bulgaria, Georgia, Germany, Moldova, Romania, and United Kingdom) sites. Eligible participants were 40–80 years old with a diagnosis of primary knee osteoarthritis fulfilling the American College of Rheumatology Clinical and Radiographic criteria (27); Kellgren-Lawrence (K-L) classification Grade 2 or 3 based on local radiology using an X-ray taken within the last 12 months; average knee pain severity score of $\geq$4 and <10 on a 0–10 numeric rating scale (NRS); stable analgesic regimen (including nutraceuticals) for 4 weeks prior to consent; non-pregnant; and able to comply with the protocol and give informed consent. Patients could have uni- or bilateral knee osteoarthritis; the right knee was prioritized if fulfilling eligibility for both knees.

Key exclusion criteria included: inflammatory arthritis; intra-articular or oral corticosteroids within 2 months; intra-articular hyaluronic acid in the target knee within 3 months; significant target knee injury/surgery within 6 months; and history of partial/complete joint replacement in the target knee, listed for, or anticipating, knee surgery during the study.

Independent radiologist assessment of K-L Grade was subsequently obtained for verification of local scoring. Two groups of participants were potentially eligible for the extension sub-study: those who received MIV-711 200 mg and had stable or improved pain (Study Group A), and those who received placebo and had worsened pain (Study Group B). A full list of eligibility criteria can be found in Supplementary Methods 2.

Randomization and interventions

Participants were randomized 1:1:1 to receive either MIV-711 100 mg, MIV-711 200 mg, or placebo once daily. Eligible participants were assigned a unique number through a third-party centralized automated code holder and randomized to treatment groups using an automated assignment system. MIV-711 and placebo were supplied as identical hard gelatin capsules. All parties (including radiologists doing semi-quantitative scoring and technicians involved with the machine learning assessments) remained blinded to treatment allocation throughout the trial. This blind was maintained during the extension sub-study.

In order to reduce loss to follow-up in a 6-month study, participants were allowed to continue on stable usual analgesia, with increased use permitted as rescue medication.

As week 26 data from the placebo-controlled study were among the inclusion criteria for the extension sub-study, there was a break in treatment between studies. All participants took the last dose in week 26 of the placebo-controlled study and dosing in the extension sub-study started after a screening period of 10±5 days. Patients that did not continue in the extension sub-study had a 28-day follow-up visit instead.

Outcomes and follow-up

The primary outcome measure was the change from baseline to week 26 in NRS average target knee pain over the past 1 week, assessed using a 0–10 NRS (28, 29). A clinically important effect for change in pain on a 0–10 NRS has previously been estimated as 1.0 point (30). The key secondary outcome was change from baseline to week 26 in target knee

joint medial femoral bone area as assessed by MRI. The medial femoral bone region was selected as this is the most responsive region for bone change (though changes in all regions are correlated) (20). Additional secondary imaging outcomes included the 26-week change in MRI cartilage thickness and MRI bone marrow lesion volume. MRIs of the target knee were acquired at baseline and week 26 using 1.5/3T systems with the following sequences: high resolution 3D sagittal proton density (PD) fast spin echo (FSE) with fat saturation; sagittal PD FSE intermediate-weighted with fat-saturation; and sagittal PD FSE without fat-suppression. Imaging outcomes were quantitatively assessed using previously reported MRI statistical shape modelling methods (Imorphics Ltd) (20, 31-34).

Secondary clinical and laboratory outcomes included change from baseline to week 26 in: subject-reported knee joint pain; the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) 3.1 (35); and levels of serum CTX-I and urine CTX-II. Knee joint pain was assessed and recorded by participants twice daily in an e-diary during the two-weeks prior to baseline and weeks 14, 26. WOMAC scores were recorded at baseline and weeks 8, 14, 26, and 30. Levels of serum CTX-I and urine CTX-II were measured at baseline and weeks 4, 14, 26, and 30 (Supplementary Methods 3).

Safety and tolerability of MIV-711 was assessed over 26 weeks and was the primary outcome of the extension sub-study. Participants were monitored for new or previously reported adverse events (AEs) at each visit. Incidence, severity, relatedness to the study intervention, and outcome of each AE was recorded. Serious AEs were defined according to pre-specified criteria (Supplement 1); assessed for causality and expectedness by a physician; and reported within 24 hours (Supplementary Methods 3). Possible AE sources (patient reports, vital signs, electrocardiogram, clinical chemistry/hematology, and urinalysis) were measured at screening, baseline and weeks 2, 4, 8, 14, 20, 26, and 30. For all AEs, unblinded interim safety data was reviewed by a data monitoring committee after 50, 100, 150, and 200 participants had completed week 14.Treatment compliance was assessed by counting unused capsules at weeks 8, 14, and 26.

All investigated outcomes and assessments are described in the study protocol (Supplement 1).

Statistical analysis

Using a previously reported between-patient standard deviation for change in pain score of 2.256 (36), 192 participants were required to provide the primary outcome measurement. Assuming 20% loss to follow-up by week 26, 80 participants were required per group (240 total) to provide 80% power at a 0.05 one-sided significance level.

All analyses were conducted according to the pre-specified statistical analysis plan using the SAS® software Version 9.4 (SAS Institute Inc, North Carolina, USA). The primary efficacy analysis population was based on the original randomization for all participants with both a baseline and at least one post-baseline NRS pain score value (referred to as 'modified intent-to-treat'). Missing values were not imputed as the statistical analyses used allowed inclusion of participants with incomplete data; change from baseline was analyzed using a linear mixed model with baseline score as covariate and fixed factors for treatment, visit, interaction for treatment-by-visit, baseline analgesic user, and random effect for clinical site. Least square (LS) means were estimated in the linear mixed model. An unstructured covariance matrix was used for the residuals (allowing covariance between repeated measures within patients). The residual maximum likelihood method was used to estimate covariance parameters and the Kenward-Roger method to estimate the denominator degrees of freedom for the tests of fixed effects. A fixed-sequence multiple-testing procedure was performed to control the type I error rate to 5% for the primary endpoint:

1) MIV-711 200 mg versus placebo
2) MIV-711 100 mg versus placebo.

The second step was only considered as confirmatory provided the previous step was statistically significant at a one-sided 5%-level ($p<0.05$). If the first step was not statistically significant, the analysis of the second step was considered descriptive. No multiple

comparison correction was applied for any of the other endpoints and these are therefore reported with unadjusted p-values. Secondary endpoints were analyzed using the same statistical model, adjusting for the same factors as the primary analysis. Post-hoc sensitivity analyses were performed for the primary and secondary outcomes using the same model as the primary efficacy analysis but with clinical site as a fixed-factor instead of a random-effect. Change from baseline for MRI bone area and cartilage thickness in the medial femur region was analyzed post-hoc using an ANOVA model with factors for baseline analgesic use, clinical site and treatment. MRI imaging analysis is described in Supplementary Methods 3.

The daily e-diary scores were averaged into one score per visit before they were analyzed statistically (Supplementary Methods 3).

Role of the funding source

This study was funded by Medivir AB and outsourced to Parexel. Medivir contributed to the design, data analysis, and data interpretation of the study together with PC, MB, and Parexel. Publication of study results was mandated in the protocol and all authors approved submission.

Results

A total of 433 subjects were screened, 244 of which were eligible and randomized to MIV-711 100 mg (n=82), MIV-711 200 mg (n=82), or placebo (n=80; Figure 1). Four participants had no post-baseline NRS values and were excluded, leaving 240 participants (98.4%; 77 placebo, 82 MIV-711 100 mg, 81 MIV-711 200 mg) in the pre-specified primary modified intent-to-treat analysis.

Demographic characteristics were generally well balanced between treatment groups (Table 1). Most participants were female (n=184; 76.7%) and Caucasian (n=238; 99.2%). The median age was 61 years in both MIV-711 groups and 62 years in the placebo group. Although all participants had K-L grade 2 or 3 on local scoring, only 77% had 2 or 3 on independent radiologist review, with 22% having K-L grade 1.

Median treatment compliance was 100% in all study groups. Two hundred and fifteen (88.1%) participants completed the study, with 29 participants discontinuing, primarily due to AEs (13 [5.3%] participants) and withdrawal of consent (10 [4.1%] participants).

Primary outcome

Average pain severity in the target knee decreased in all treatment groups (Figure 2a). At week 26, the estimated mean change (95% CI) from baseline in average target knee NRS pain severity was -1.4 (-1.9, -0.8) for placebo, -1.7 (-2.3, -1.2) for MIV-711 100 mg, and -1.5 (-2.0, -0.9) for MIV-711 200 mg (Table 2). The difference in LS mean between MIV-711 arms and placebo was not statistically significant for the 200 mg dose, which also precluded further confirmatory statistical testing of the primary endpoint at the lower dose (Table 2).

Secondary outcomes

Joint structure

MRI data were available for 204 participants. MRI bone area of the target knee increased in all treatment groups over 26 weeks (Table 2). There was an attenuation of MRI bone area

progression in the medial femur region for both MIV-711 treated groups (Figure 2b; Table 2; Supplementary Figure 2). After 26 weeks' treatment, the estimated mean change (95% CI) from baseline in MRI bone area was 23.3 (15.7, 30.9) mm^2 for placebo, 7.9 (0.5, 15.3) mm^2 for MIV-711 100 mg, and 8.6 (1.1, 16.1) mm^2 for MIV-711 200 mg. The difference of estimated means compared with placebo reached statistical significance for both MIV-711 treated groups in unadjusted analyses (Table 2).

Attenuation of medial femoral joint cartilage thinning was observed for the MIV-711 treated groups compared with placebo, in which there was a mean reduction in cartilage thickness of 0.066 mm (Figure 2c; Table 2; Supplementary Figure 3). The difference in the estimated mean change from baseline to week 26 in MRI cartilage thickness loss in the femur region was statistically significant for the MIV-711 100 mg group vs placebo but not the MIV-711 200 mg group vs placebo (Table 2). There was no statistically significant difference in medial tibia cartilage loss (Figure 2d) or estimated mean change in MRI bone marrow lesion volume between MIV-711 treated groups and placebo (Table 2).

Symptoms

The difference in estimated mean (95% CI) change from baseline to week 26 in subject-reported e-diary NRS overall pain severity compared with placebo was -0.3 (-1.0, 0.3) for the MIV-711 100 mg group and -0.4 (-1.0, 0.3) for the MIV-711-200 mg group (Table 2). Estimated mean changes from baseline to week 26 in WOMAC scores for pain, function, and stiffness were not statistically significant between MIV-711 treated groups and placebo (Table 2).

Biomarkers

At week 26, statistically significant changes from baseline in serum CTX-I and urine CTX-II were observed in both MIV-711 treated groups compared with placebo ($p<0.0001$ for all; Figure 2e&f; Table 2). Compared with baseline, levels of CTX-I and CTX-II were reduced by 27.8% and 34.4%, respectively in the MIV-711 100 mg group and by 50.3% and 51.6%,

respectively in the MIV-711 200 mg group (Supplementary Figure 4). Levels of both biomarkers returned to baseline values after MIV-711 treatment stopped at week 26 (Figure 2e&f).

Observed mean values for primary and secondary endpoints are presented in Supplementary Figure 4. Results for primary and secondary endpoints were similar in the post-hoc sensitivity analyses that used clinical site as a fixed factor instead of a random effect (Supplementary Table 1). Similar results to the primary efficacy analysis were found for post-hoc analyses of MRI bone area and cartilage thickness in the medial femur region using an ANOVA model (Supplementary Table 2). Results for all additional secondary outcomes are presented in Supplementary Tables 3–6.

Safety

A comparable proportion of participants reported treatment-emergent AEs across groups (55.0% for placebo, 54.9% for MIV-711 100 mg, and 52.4% for MIV-711 200 mg; Table 3). A total of 345 treatment-emergent AEs were reported in 132 (54.1%) participants; most were mild (159; 46.1%) or moderate (175; 50.7%) in intensity. Nine serious AEs (SAEs) were reported by six participants in total (Table 3) and the incidence of SAEs was comparable across treatment groups. No SAE occurred in more than one participant and none were considered treatment related. Only one SAE resulted in death: cardiac failure in a participant in the placebo group.

As development of two other cathepsin K inhibitors for osteoporosis was discontinued due to increases in the frequency of either morphea or stroke and atrial fibrillation (14, 37), skin and cardiovascular events were considered AEs of special interest (AESIs). Five cardiovascular AESIs were reported: two atrial fibrillations, one prinzmetal angina, one stroke, and one cardiac failure. More participants in the active treatment groups reported skin disorders (100 mg: 7.3%, 200 mg: 12.2%) compared with the placebo group (2.5%), including one patient

280 treated with MIV-711 200 mg who had angioedema and urticaria which lead to study drug
281 discontinuation. In general, the reported skin events were mild-to-moderate and non-specific.

282 There were no clinically meaningful changes in vital signs, including blood pressure and
283 electrocardiogram assessments, or key laboratory measures (Supplementary Figures 5–8).
284 Increases in parathyroid hormone and decreases in calcium were observed, consistent with
285 the expected mechanism of action of MIV-711.

286 ***Extension sub-study (MIV-711-202)***

287 Overall, 50 participants were enrolled in the extension sub-study (Figure 1); 46 in Study
288 Group A (participants who initially received MIV-711 200 mg) and four in Study Group B
289 (participants who initially received placebo). Due to the low number of participants in Study
290 Group B, these data are not shown. Baseline demographics and enrolment by site for the
291 extension sub-study are shown in Supplementary Tables 7&8. Ten SAEs were reported by
292 two participants in Study Group A, none were considered treatment related and only one led
293 to study discontinuation (Supplementary Table 9). Further results for the extension sub-study
294 are reported in Supplementary Results 1 and Supplementary Tables 10–12.

295

Discussion

We compared two doses of a novel cathepsin K inhibitor to placebo and did not find a significant difference in the primary outcome, pain, across the three treatment groups. However, significant reductions in secondary outcomes were observed. Medial femur bone area progression was significantly reduced in both MIV-711 treatment groups compared to placebo. Medial femur cartilage thinning was also reduced in the 100 mg group. Significant reductions in bone resorption and cartilage degradation biomarkers were also observed. MIV-711 treatment was well tolerated, with nine SAEs in six participants, none considered treatment-related. MIV-711 demonstrated an acceptable safety profile in the 26-week extension and the effects on bone area progression, as well as CTX-I and CTX-II biomarkers, were maintained in participants who initially received MIV-711 200 mg and whose symptoms did not worsen during the placebo-controlled study.

Many studies assessing structural change in osteoarthritis have relied on X-ray methods to demonstrate improvement, but these assess cartilage thickness loss indirectly and do not assess bone morphology. Using highly sensitive MRI techniques (20, 31-33) we demonstrated statistically significant attenuation of MRI bone area progression and reduction of cartilage thickness in the active arms compared with placebo, consistent with the mechanism of action of MIV-711. However, while these quantitative MRI techniques can detect significant structural changes within a relatively short study period, data from the Osteoarthritis Initiative has indicated that changes in bone shape over a period of 24 months are related to progression of pain over 48 months (19). Thus, the duration of this study may have been too short for these improvements in joint structure to lead to statistically significant reductions in symptoms.

Levels of CTX-I and CTX-II have been shown to be predictive of osteoarthritis progression (38, 39). Sustained reductions of CTX-I and CTX-II were observed, of a greater magnitude than has previously been shown using bone-acting agents in osteoarthritis (25, 40, 41),

including the 3 year Strontium Ranelate in Knee Osteoarthritis study, the only interventional study in which statistically significant effects on both joint structure and symptoms have been observed (26). In line with previous clinical studies employing cathepsin K inhibitors, there was a noticeable rebound effect after MIV-711 withdrawal at the end of the placebo-controlled study, corresponding to the treatment break, and levels were reduced again on re-dosing (13, 15). The effects of MIV-711 on these biomarkers demonstrate convincing evidence for target engagement (12, 17).

The AE profile of MIV-711 did not differ from that of placebo. No cases of morphea were reported with MIV-711. The frequency of cardiovascular events was judged to be within the expected range for an elderly population with multiple comorbidities. However, in light of their distribution over the treatment arms in both studies and given the small numbers, cardiovascular monitoring and relevant eligibility criteria should still be considered in future studies. Overall, MIV-711 demonstrated a reassuring safety and tolerability profile in this population.

Our study has several limitations. The eligibility criteria for the extension study may have resulted in a positive selection bias, as most participants were selected because their symptoms did not worsen, possibly suggesting a benefit of treatment. The aim to explore treatment effects in participants with confirmed symptom progression could not be addressed due to the low number of participants in Study Group B with worsening of symptoms. MRIs that did not meet the predefined quality criteria for analysis were excluded, resulting in a 15% loss of data for the imaging analysis. Finally, multiple comparisons were conducted in this study. Multiplicity correction was only applied for the primary endpoint. Therefore, all p-values reported here other than those for the primary endpoint are unadjusted and should be interpreted with caution. In particular, this applies to the significant difference found in the femur region MRI cartilage between the MIV-711 100 mg group and placebo.

In conclusion, MIV-711 did not demonstrate any beneficial effects on osteoarthritic knee pain in this study. However, statistically significant reductions in bone and cartilage osteoarthritis manifestations were observed together with a reassuring safety profile. Further evaluation of MIV-711 in longer and larger trials to confirm the structural benefits observed here, as well as whether these translate to more tangible patient benefits on symptoms is therefore warranted.

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Conflicts of interest

PGC has acted as a consultant or speaker for AbbVie, AstraZeneca, Bristol Myers Squibb, Eli Lilly, EMD Serono, Flexion Therapeutics, Galapagos, GlaxoSmithKline, Medivir, Novartis, Pfizer, Samumed, and Stryker.

MB, AB, and GG have all been employed by Stryker Corporation.

ÅJ, RB, CW, BR, and JÖ have all been employed by Medivir AB. NS, PG, and SRK have acted as part time consultants to Medivir AB.

Reproducible research statement

Protocol: posted as an online supplement to this manuscript on the annals website

Statistical Code: not available

Data: not available

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Address for Reprint Requests:

Professor P.G. Conaghan. Leeds Institute of Rheumatic and Musculoskeletal Medicine, Chapel Allerton Hospital, Chapeltown Road, Leeds, LS7 4SA, United Kingdom.

Addresses for All Authors:

1 Leeds Institute of Rheumatic and Musculoskeletal Medicine and NIHR Leeds Biomedical Research Centre, 2nd Floor Chapel Allerton Hospital, Chapeltown Road, LS7 4SA, UK

2 Imorphics Ltd., Worthington House, Towers Business Park, Wilmslow Road, Manchester M20 2HJ, UK

3 Medivir AB, PO Box 1086, 141 22 Huddinge, Sweden

Figure legends

Figure 1. MIV-711-201 and MIV-711-202 CONSORT diagram.

Figure 2. Estimated mean (LS mean; ±95% CI) change from baseline (week 0)* by treatment in (a) average target knee pain severity (NRS) (primary outcome), (b) MRI bone area of the medial femur region, (c) cartilage thickness in the central medial femur region and (d) central medial tibia region, (e) serum CTX-I, and (f) urine CTX-II (corrected for creatinine). Study MIV-711-201; modified intent-to-treat population; n=240†. CI, confidence interval; MRI, magnetic resonance imaging. Data points are offset for clarity. * Change from baseline was analyzed using a linear mixed model with baseline score as covariate and fixed factors for treatment, time, interaction for treatment-by-time, baseline analgesic user, and random effect for clinical site. † No follow-up data from week 30 was available for the 50 participants who participated in the extension sub-study (MIV-711-202). N values are for week 26.