ORIGINAL RESEARCH

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Disease-Modifying Effects of a Novel Cathepsin K Inhibitor in Osteoarthritis

A Randomized Controlled Trial

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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 2a study with a 26-week open-label safety extension substudy. (EudraCT: 2015-003230-26 and 2016-001096-73)

Setting: Six European sites.

Participants: 244 participants with primary knee osteoarthritis, Kellgren–Lawrence grade 2 or 3, and pain score of 4 to 10 on a numerical rating scale (NRS).

Intervention: MIV-711, 100 (n = 82) or 200 (n = 81) mg daily, or matched placebo (n = 77). Participants (46 who initially received 200 mg/d and 4 who received placebo) received 200 mg of MIV-711 daily during the extension substudy.

Measurements: The primary outcome was change in NRS pain score. The key secondary outcome was change in bone area on magnetic resonance imaging (MRI). Other secondary end points included cartilage thickness on quantitative MRI and type I and II collagen C-telopeptide biomarkers. Outcomes were assessed over 26 weeks.

Results: Changes in NRS pain scores with MIV-711 were not statistically significant (placebo, −1.4; MIV-711, 100 mg/d, −1.7; MIV-711, 200 mg/d, −1.5). MIV-711 significantly reduced medial femoral bone area progression (P = 0.002 for 100 mg/d and 0.004 for 200 mg/d) and medial femoral cartilage thinning (P = 0.023 for 100 mg/d and 0.125 for 200 mg/d) versus placebo and substantially reduced bone and cartilage biomarker levels. Nine serious adverse events occurred in 6 participants (1 in the placebo group, 3 in the 100 mg group, and 2 in the 200 mg group); none were considered to be treatment-related.

Limitation: The trial 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.

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Osteoarthritis is a major worldwide problem, affecting 9.6% of men and 18.0% of women older than 60 years (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 (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 inhibition of 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 1 testing (12). Results from preclinical in vivo models and single- and multiple-dose studies in humans showed 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 disease-modifying osteoarthritis drugs have been limited by a lack of sensitive and responsive markers of structural progression (19, 20). New quantitative biomarkers on magnetic resonance imaging (MRI) using supervised machine learning have demonstrated construct validity and are more responsive than radiographic joint space narrowing (4, 19, 20). In addition, changes in 3-dimensional bone shape and cartilage thickness can predict subsequent knee replacement (19–24). Although the relationship between changes in these measures and pain is less clear, increases in bone area and changes in shape have been associated with clinically relevant progression over a 2-year period (19). Of note, the responsiveness of these novel imaging methods enables shorter and smaller studies than are possible using radiographic assessments (25, 26).

To test the hypothesis that a cathepsin K inhibitor could alleviate osteoarthritis symptoms by reducing degeneration of bone and cartilage, we evaluated the efficacy, safety, and tolerability of orally administered

See also:

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Web-Only
Supplement

MIV-711 in participants with symptomatic and radiographic knee osteoarthritis.

METHODS

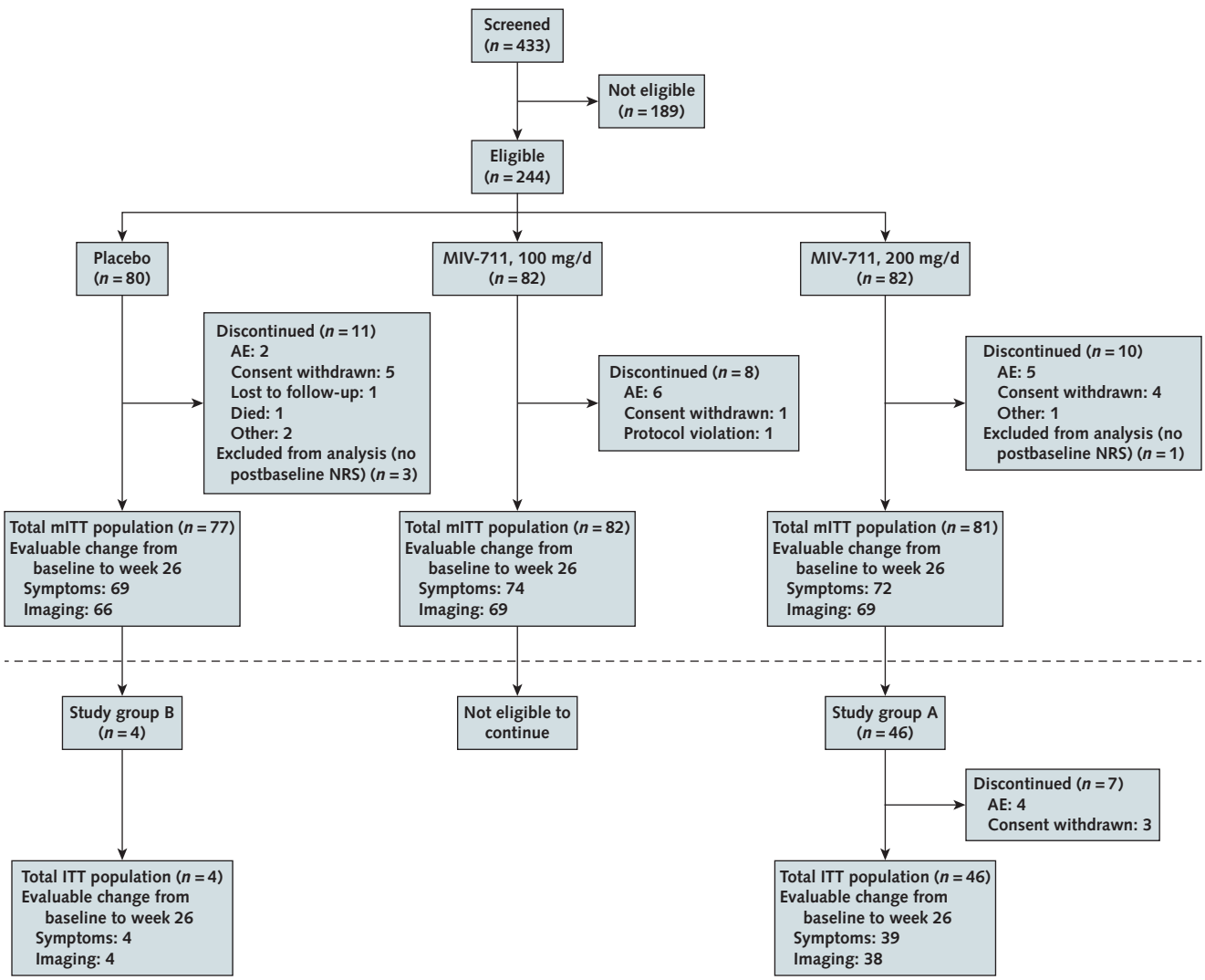
Design Overview

We conducted a 26-week, multicenter, randomized, placebo-controlled, double-blind, 3-group, parallel phase 2a study (MIV-711-201) followed by a 26-week open-label extension substudy (MIV-711-202) (Figure 1 of Supplement 1, available at Annals.org). The placebo-controlled study was done between January 2016 and May 2017. The protocols (Supplement 2, available at Annals.org) were approved by the appropriate independent ethics committees and regulatory agencies and were registered on ClinicalTrials.gov (NCT02705625 and NCT03037489) and EudraCT (European Union Drug Regulating Authorities Clinical Trials Database) (2015-003230-26 and 2016-001096-73). All participants provided written informed consent. The methods for the extension substudy are provided in the Methods 1 section of Supplement 1.

Setting and Participants

Participants were recruited from 6 European sites (1 each in Bulgaria, Georgia, Germany, Moldova, Romania, and the United Kingdom). Eligible participants were aged 40 to 80 years, had a diagnosis of primary knee osteoarthritis that met the American College of Rheumatology clinical and radiographic criteria (27), had a Kellgren–Lawrence grade of 2 or 3 based on a radiograph taken locally within the previous 12 months, had an average knee pain score of at least 4 on a numerical rating scale (NRS) of 0 to 10, had a stable analgesic regimen (including nutraceuticals) for 4 weeks before consent, were not pregnant, and were able to adhere to the protocol and give informed consent. Patients could have unilateral or bilateral knee osteo-

Figure 1. Study flow diagrams for the placebo-controlled study (*top*) and the extension substudy (*bottom*).



AE = adverse event; ITT = intention-to-treat; mITT = modified intention-to-treat; NRS = numerical rating scale.

Table 1. Baseline Demographic Characteristics in the Modified Intention-to-Treat Population

Characteristic	Placebo (n = 77)	MIV-711, 100 mg/d (n = 82)	MIV-711, 200 mg/d (n = 81)
Female, *n (%)*	62 (80.5)	64 (78.0)	58 (71.6)
Mean age (SD), *y*	62.3 (6.6)	61.2 (6.6)	62.0 (7.3)
Mean weight (SD), *kg*	87.1 (16.8)	86.0 (14.2)	86.6 (14.7)
Mean body mass index (SD), kg/m^2	32.5 (5.8)	32.0 (5.5)	32.0 (5.5)
Local Kellgren–Lawrence score of 2 or 3, *n*	77	82	81
Kellgren–Lawrence score on independent review, *n (%)*			
0	1 (1.3)	0	0
1	14 (18.2)	17 (20.7)	23 (28.4)
2	33 (42.9)	38 (46.3)	28 (34.6)
3	28 (36.4)	27 (32.9)	29 (35.8)
4	1 (1.3)	0	0
Missing	0	0	1 (1.2)
Duration of knee pain in previous 12 mo, *n (%)*			
8–30 d	1 (1.3)	0	0
31–92 d	19 (24.7)	18 (22.0)	15 (18.5)
>92 d	57 (74.0)	64 (78.0)	66 (81.5)
Prior medications, *n (%)*			
Analgesics	0	0	1 (1.2)
Other analgesics and antipyretics	5 (6.5)	8 (9.8)	4 (4.9)

arthritis; the right knee was prioritized if eligibility criteria were met for both knees. Key exclusion criteria included inflammatory arthritis, use of intra-articular or oral corticosteroids within 2 months, intra-articular hyaluronic acid in the target knee within 3 months, significant target knee injury or surgery within 6 months, history of partial or complete joint replacement in the target knee, or being listed for or anticipating knee surgery during the study.

Independent radiologist assessment of Kellgren–Lawrence grades was subsequently obtained for verification of local scoring. Two groups of participants were potentially eligible for the extension substudy: those who received MIV-711, 200 mg/d, and whose pain had stabilized or improved (study group A), and those who received placebo and whose pain had worsened (study group B). A full list of eligibility criteria is provided in the Methods 2 section of Supplement 1.

Randomization and Interventions

Participants were randomly assigned in a 1:1:1 ratio to receive 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 were randomly assigned to treatment groups via an automated assignment system. MIV-711 and placebo were supplied in identical hard gelatin capsules. All parties, including radiologists doing semiquantitative scoring and technicians involved with the machine learning assessments, remained blinded to treatment allocation throughout the trial and the extension substudy. To reduce loss to follow-up, participants were allowed to continue their stable usual analgesic regimen, with increased use permitted as rescue medication.

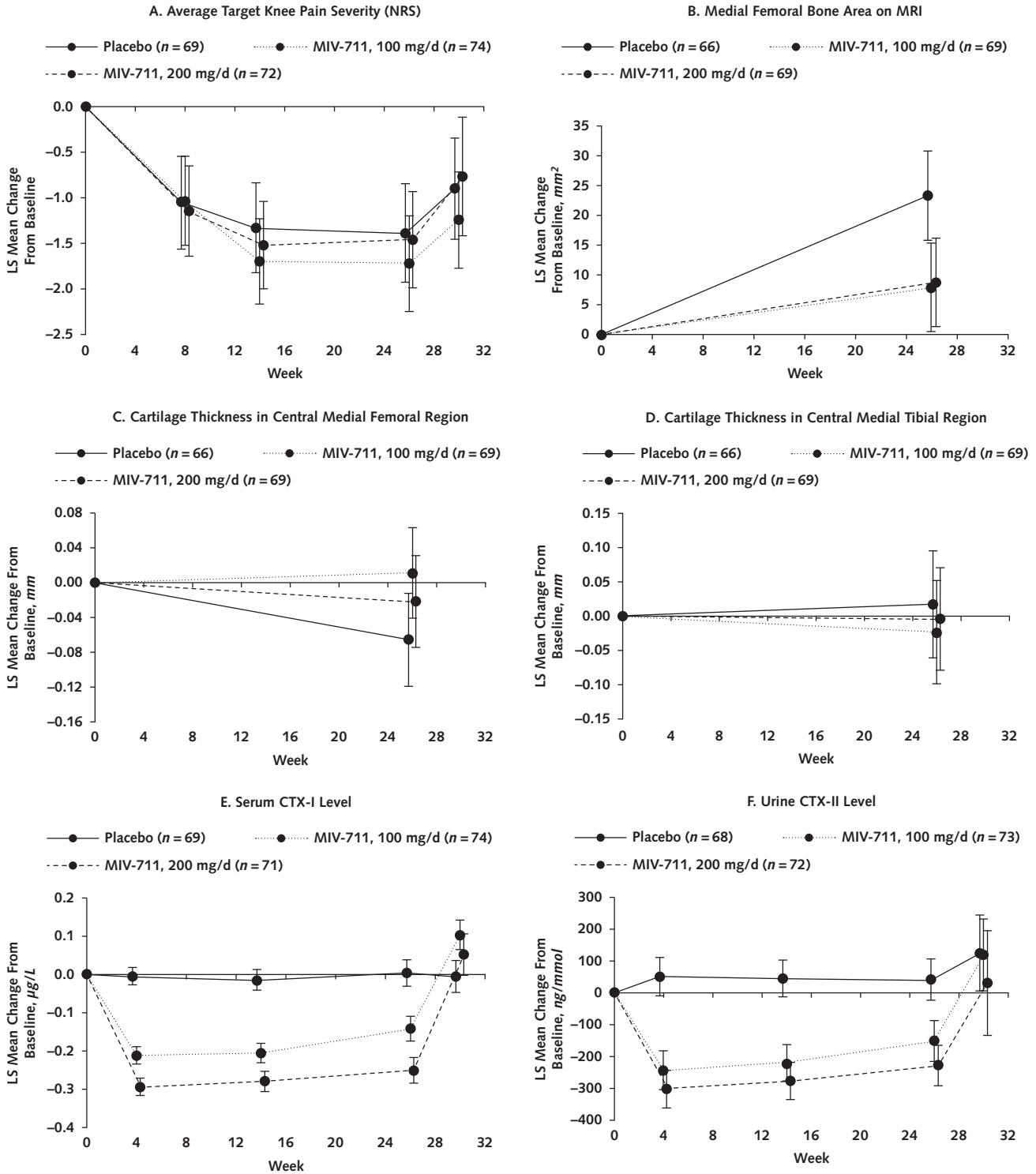
Because week 26 data from the placebo-controlled study were among the inclusion criteria for the extension substudy, there was a break in treatment between studies. All participants took the last dose in week 26 of the placebo-controlled study, and dosing in the extension substudy started after a screening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

Outcomes and Follow-up

The primary outcome measure was change from baseline to week 26 in average pain severity in the target knee over the previous week, assessed using an NRS of 0 to 10 (28, 29). A clinically important effect for change in pain on an NRS of 0 to 10 has previously been estimated as 1.0 point (30). The key secondary outcome was change from baseline to week 26 in medial femoral bone area in the target knee joint on MRI. The medial femoral region was selected because it is the most responsive region for bone change, although changes in all regions are correlated (20). Additional secondary imaging outcomes included 26-week change in cartilage thickness and bone marrow lesion volume on MRI. Scans of the target knee were acquired at baseline and week 26 using 1.5/3T systems with the following sequences: high-resolution 3-dimensional 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 methods for MRI statistical shape modeling (Imorphics) (20, 31–34).

Secondary clinical and laboratory outcomes included change from baseline to week 26 in participant-reported knee joint pain, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) 3.1 score (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 2 weeks before baseline and weeks 14 and 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 (Methods 3 section of Supplement 1).

Figure 2. Estimated mean change from baseline, by treatment, in average pain severity in the target knee (NRS) (primary outcome) (*A*), medial femoral bone area on MRI (*B*), cartilage thickness in the central medial femoral (*C*) and central medial tibial (*D*) regions, serum CTX-I level (*E*), and urine CTX-II level (corrected for creatinine level) (*F*).



Data are LS means and 95% CIs from the modified intention-to-treat population of the placebo-controlled study (*n* = 240). Change from baseline was analyzed using a linear mixed model, with baseline score as the covariate; fixed factors for treatment, time, interaction of treatment by time, and baseline analgesic use; and a random effect for clinical site. No follow-up data from week 30 were available for the 50 participants who participated in the extension substudy. Numbers are for week 26. Data points are offset for clarity. Error bars indicate 95% CIs. CTX-I = type I collagen C-telopeptide; CTX-II = type II collagen C-telopeptide; LS = least-squares; MRI = magnetic resonance imaging; NRS = numerical rating scale.

Table 2. Estimated Mean Changes From Baseline to Week 26 in Primary and Secondary Efficacy Outcomes in the Modified Intention-to-Treat Population*

Variable	Placebo (n = 77)		MIV-711, 100 mg/d (n = 82)		
	Participants, *n*	LS Mean Change (95% CI)	Participants, *n*	LS Mean Change (95% CI)	Difference vs. Placebo (95% CI)
Primary outcome					
Overall pain severity score (NRS)	69	−1.4 (−1.9 to −0.8)	74	−1.7 (−2.3 to −1.2)	−0.3 (−1.0 to 0.3) (P = 0.146)
Secondary outcomes					
Bone area on MRI, mm^2	66	23.3 (15.7 to 30.9)	69	7.9 (0.5 to 15.3)	−15.4 (−26.0 to −4.8) (P = 0.002)
Cartilage thickness on MRI, *mm*					
Femoral region	66	−0.066 (−0.119 to −0.013)	69	0.011 (−0.042 to 0.063)	0.076 (0.002 to 0.150) (P = 0.023)
Tibial region	66	0.017 (−0.061 to 0.095)	69	−0.024 (−0.099 to 0.052)	−0.041 (−0.125 to 0.044) (P = 0.83)
Total bone marrow lesion volume on MRI, *μL*	66	−811 (−1900 to 282)	69	−1160 (−2230 to −84.4)	−347 (−1880 to 1190) (P = 0.33)
E-diary NRS scores					
Morning response	69	−1.0 (−1.4 to −0.6)	72	−1.4 (−1.8 to −0.9)	−0.4 (−1.0 to 0.2)
Evening response	67	−1.2 (−1.6 to −0.7)	67	−1.5 (−2.0 to −1.1)	−0.3 (−1.0 to 0.3)
Overall response	69	−1.1 (−1.6 to −0.6)	72	−1.4 (−1.9 to −1.0)	−0.3 (−1.0 to 0.3)
Normalized WOMAC scores					
Pain	69	−11.3 (−16.9 to −5.7)	74	−15.9 (−21.3 to −10.5)	−4.6 (−10.8 to 1.7) (P = 0.075)
Function	69	−11.9 (−18.1 to −5.7)	74	−15.7 (−21.8 to −9.6)	−3.8 (−10.3 to 2.7) (P = 0.126)
Stiffness	69	−11.0 (−17.8 to −4.2)	74	−15.9 (−22.6 to −9.3)	−5.0 (−12.1 to 2.2) (P = 0.086)
Biomarkers					
Serum CTX-I level, *μg/L*	69	0.003 (−0.031 to 0.037)	74	−0.143 (−0.175 to −0.110)	−0.145 (−0.193 to −0.098) (P < 0.001)
Urine CTX-II, *ng/mmol*†	68	41.9 (−23.0 to 107)	73	−151 (−215 to −87.6)	−193 (−262 to −124) (P < 0.001)

CTX-I = type I collagen C-telopeptide; CTX-II = type II collagen C-telopeptide; LS = least-squares; MRI = magnetic resonance imaging; NRS = numerical rating scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
* Change from baseline was analyzed using a linear mixed model, with baseline score as the covariate; fixed factors for treatment, time, interaction of treatment by time, and baseline analgesic use; and a random effect for clinical site.
† Corrected for creatinine concentration.

Safety and tolerability of MIV-711 were assessed over 26 weeks and were the primary outcomes of the extension substudy. 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 were recorded. Serious AEs (SAEs) were defined according to prespecified criteria (**Supplement 2**), assessed for causality and expectedness by a physician, and reported within 24 hours (Methods 3 section of **Supplement 1**). Possible AE sources (patient reports, vital signs, electrocardiogram, clinical chemistry or hematologic testing, and urinalysis) were evaluated at screening; baseline; and weeks 2, 4, 8, 14, 20, 26, and 30. For all AEs, unblinded interim safety data were reviewed by a data monitoring committee after 50, 100, 150, and 200 participants had completed week 14. Treatment adherence was assessed by counting unused capsules at weeks 8, 14, and 26.

All investigated outcomes and assessments are described in the study protocol (**Supplement 2**).

Statistical Analysis

Using a previously reported between-patient SD of 2.256 for change in pain score (36), we determined that 192 participants were needed to provide the primary outcome measurement. Assuming 20% loss to follow-up by week 26, we required 80 participants per group (240 total) to provide 80% power at a 1-sided significance level of 0.05.

All analyses were conducted according to the prespecified statistical analysis plan using SAS, version 9.4 (SAS Institute). The primary efficacy analysis population was based on the original randomization for all participants with an NRS pain score value at baseline and at least 1 point afterward (referred to as the "modified intention-to-treat population"). Missing values were not imputed because the statistical analyses that were used allowed inclusion of participants with incomplete data. Change from baseline was analyzed using a linear mixed model, with baseline score as the covariate; fixed factors for treatment, visit, interaction of treatment by visit, and baseline analgesic use; and a random effect for clinical site. Least-squares 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 was used to estimate the denominator degrees of freedom for the tests of fixed effects. A fixed-sequence multistep testing procedure (MIV-711, 200 mg/d, vs. placebo, followed by MIV-711, 100 mg/d, vs. placebo) was performed to control the type I error rate to 5% for the primary end point. The second step was considered confirmatory only if the first step was statistically significant at a 1-sided 5% level (P < 0.05); otherwise, the analysis of the second step was considered descriptive. No multiplicity correction was applied for any of the other end points, and these are therefore reported with unadjusted P values.

Secondary end points were analyzed using the same statistical model and with adjustment for the same factors as in 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

Table 2–Continued

MIV-711, 200 mg/d (*n* = 81)		
Participants, *n*	**LS Mean Change (95% CI)**	**Difference vs. Placebo (95% CI)**
72	−1.5 (−2.0 to −0.9)	−0.1 (−0.7 to 0.6) (*P* = 0.41)
69	8.6 (1.1 to 16.1)	−14.7 (−25.3 to −4.0) (*P* = 0.004)
69	−0.022 (−0.074 to 0.031)	0.044 (−0.031 to 0.118) (*P* = 0.125)
69	−0.005 (−0.080 to 0.071)	−0.022 (−0.107 to 0.063) (*P* = 0.69)
69	−1050 (−2130 to 34.8)	−234 (−1770 to 1300) (*P* = 0.38)
71	−1.4 (−1.9 to −1.0)	−0.5 (−1.1 to 0.2)
70	−1.5 (−2.0 to −1.1)	−0.4 (−1.0 to 0.3)
71	−1.5 (−1.9 to −1.0)	−0.4 (−1.0 to 0.3)
72	−13.1 (−18.6 to −7.6)	−1.8 (−8.0 to 4.5) (*P* = 0.29)
72	−13.8 (−19.9 to −7.7)	−1.8 (−8.4 to 4.7) (*P* = 0.29)
72	−14.1 (−20.8 to −7.4)	−3.1 (−10.2 to 4.1) (*P* = 0.20)
71	−0.251 (−0.285 to −0.218)	−0.254 (−0.302 to −0.206) (*P* < 0.001)
72	−228 (−292 to −165)	−270 (−339 to −201) (*P* < 0.001)

instead of a random effect. Changes from baseline in bone area and cartilage thickness in the medial femoral region on MRI were analyzed post hoc using an analysis of variance model with factors for baseline analgesic use, clinical site, and treatment. Analysis of MRI imaging is described in the Methods 3 section of **Supplement 1**. The daily e-diary scores were averaged into 1 score per visit before they were analyzed statistically (Methods 3 section of **Supplement 1**).

Role of the Funding Source

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

RESULTS

A total of 433 persons were screened, of whom 244 were eligible and randomly assigned to MIV-711, 100 mg/d (*n* = 82); MIV-711, 200 mg/d (*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 in the placebo group, 82 in the 100-mg group, and 81 in the 200-mg group) in the prespecified primary analysis of the modified intention-to-treat population.

Demographic characteristics were generally well balanced among groups (**Table 1**). Most participants were female (*n* = 184 [76.7%]) and white (*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 a Kellgren–Lawrence grade of 2 or 3 on local scoring, only 77% had a grade of 2 or 3 on independent radiologist review, and 22% had a grade of 1.

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

Primary Outcome

Average pain severity in the target knee decreased in all treatment groups (**Figure 2**, *A*). At week 26, the estimated mean change from baseline in NRS score was −1.4 (95% CI, −1.9 to −0.8) for placebo; −1.7 (CI, −2.3 to −1.2) for MIV-711, 100 mg/d; and −1.5 (CI, −2.0 to −0.9) for MIV-711, 200 mg/d (**Table 2**). The difference in least-squares means between the 200 mg group and the placebo group was not statistically significant, which precluded confirmatory statistical testing of the primary end point at the lower dose (**Table 2**).

Secondary Outcomes

Joint Structure

Data from MRI scans were available for 204 participants. Bone area in the target knee increased in all groups over 26 weeks (**Table 2**). There was attenuation of bone area progression in the medial femoral region on MRI for both MIV-711 groups (**Figure 2**, *B*; **Table 2**; **Figure 2** of **Supplement 1**). At 26 weeks, the estimated mean change from baseline in bone area on MRI was 23.3 mm^2 (CI, 15.7 to 30.9 mm^2) for placebo; 7.9 mm^2 (CI, 0.5 to 15.3 mm^2) for MIV-711, 100 mg/d; and 8.6 mm^2 (CI, 1.1 to 16.1 mm^2) for MIV-711, 200 mg/d. The difference in estimated means compared with placebo was statistically significant for both MIV-711 groups in unadjusted analyses (**Table 2**).

Attenuation of thinning of medial femoral joint cartilage was observed in the MIV-711 groups compared with placebo, with a mean reduction in cartilage thickness of 0.066 mm (**Figure 2**, *C*; **Table 2**; **Figure 3** of **Supplement 1**). Compared with placebo, the difference in the estimated mean change from baseline to week 26 in loss of femoral cartilage thickness on MRI was statistically significant with 100 but not 200 mg of MIV-711 daily (**Table 2**). There was no statistically significant difference in medial tibial cartilage loss (**Figure 2**, *D*) or estimated mean change in bone marrow lesion volume on MRI between the MIV-711 groups and placebo (**Table 2**).

Symptoms

The difference in estimated mean change from baseline to week 26 in participant-reported overall pain severity (assessed via the NRS) compared with placebo was −0.3 (CI, −1.0 to 0.3) with MIV-711, 100 mg/d, and −0.4 (CI, −1.0 to 0.3) with MIV-711, 200 mg/d (**Table 2**). Estimated mean changes from baseline to week 26 in WOMAC scores for pain, function, and stiffness were not statistically significant between the MIV-711 groups and placebo (**Table 2**).

Biomarkers

At week 26, statistically significant changes from baseline in serum CTX-I and urine CTX-II levels were observed in both MIV-711 groups compared with placebo

Table 3. Adverse Events Reported in the Safety Analysis Population

Adverse Events	Placebo (n = 80)	MIV-711, 100 mg/d (n = 82)	MIV-711, 200 mg/d (n = 82)
Any adverse event, *n (%)*	44 (55.0)	45 (54.9)	43 (52.4)
Adverse events occurring in ≥2% of participants overall, *n (%)*			
Nasopharyngitis	6 (7.5)	8 (9.8)	7 (8.5)
Osteoarthritis	7 (8.8)	7 (8.5)	6 (7.3)
Headache	6 (7.5)	5 (6.1)	5 (6.1)
Back pain	3 (3.8)	1 (1.2)	6 (7.3)
Diarrhea	3 (3.8)	4 (4.9)	2 (2.4)
Arthralgia	2 (2.5)	5 (6.1)	2 (2.4)
Nausea	2 (2.5)	1 (1.2)	4 (4.9)
Muscle spasms	1 (1.3)	6 (7.3)	0
Paresthesia	3 (3.8)	1 (1.2)	3 (3.7)
Hypertension	4 (5.0)	0	1 (1.2)
Increased γ-glutamyltransferase level	4 (5.0)	1 (1.2)	0
Myalgia	1 (1.3)	2 (2.4)	2 (2.4)
Any serious adverse event, *n (%)*	1 (1.3)	3 (3.7)	2 (2.4)
Atrial fibrillation	0	1 (1.2)	0
Cardiac failure	1 (1.3)	0	0
Prinzmetal angina	0	1 (1.2)	0
Acute cholecystitis	0	0	1 (1.2)
Chronic pyelonephritis	0	1 (1.2)	0
Compression fracture	0	1 (1.2)	0
Contusion	0	1 (1.2)	0
Cerebral infarction	0	0	1 (1.2)
Hematoma	0	1 (1.2)	0

($P < 0.001$ for all) (Figure 2, *E* and *F*; Table 2). Compared with baseline, levels of CTX-I and CTX-II were reduced by 27.8% and 34.4%, respectively, with MIV-711, 100 mg/d, and by 50.3% and 51.6%, respectively, with MIV-711, 200 mg/d (Figure 4 of Supplement 1). Levels of both biomarkers returned to baseline values after treatment stopped at week 26 (Figure 2, *E* and *F*).

Observed mean values for primary and secondary end points are presented in Figure 4 of Supplement 1. Results were similar in the post hoc sensitivity analyses that used clinical site as a fixed factor instead of a random effect (Table 1 of Supplement 1). We found results similar to those in the primary efficacy analysis for post hoc analyses of medial femoral bone area and cartilage thickness on MRI using an analysis of variance model (Table 2 of Supplement 1). Results for all other secondary outcomes are presented in Tables 3 to 6 of Supplement 1.

Safety

Similar proportions of participants reported treatment-emergent AEs across groups (55.0% for placebo; 54.9% for MIV-711, 100 mg/d; and 52.4% for MIV-711, 200 mg/d) (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%]). Nine SAEs were reported among 6 participants (Table 3), and incidence was similar across treatment groups. No SAEs occurred in more than 1 participant, and none were considered to be treatment-related. Only 1 resulted in death (cardiac failure in a participant in the placebo group).

Because development of 2 other cathepsin K inhibitors for osteoporosis was discontinued due to increases in the frequency of morphea or stroke and atrial fibrillation (14, 37), skin and cardiovascular events were considered AEs of special interest. Five cardiovascular events were reported: 2 cases of atrial fibrillation, 1 case of Prinzmetal angina, 1 stroke, and 1 case of cardiac failure. More participants reported skin disorders in the active treatment groups (100 mg/d: 7.3%; 200 mg/d: 12.2%) than the placebo group (2.5%), including 1 participant treated with 200 mg/d who had angioedema and urticaria that led to discontinuation of use of the study drug. In general, the reported skin events were mild to moderate and nonspecific.

There were no clinically meaningful changes in vital signs, including blood pressure and electrocardiographic assessments, or key laboratory measures (Figures 5 to 8 of Supplement 1). Increases in parathyroid hormone levels and decreases in calcium levels were observed, consistent with the expected mechanism of action of MIV-711.

Extension Substudy

Fifty participants were enrolled in the extension substudy (Figure 1): 46 in study group A (participants who initially received MIV-711, 200 mg/d), and 4 in study group B (participants who initially received placebo). Data on study group B are not shown because of the small number of participants. Baseline demographic characteristics and enrollment by site for the extension substudy are shown in Tables 7 and 8 of Supplement 1. Ten SAEs were reported by 2 participants in study group A; none were considered treatment-related, and only 1 led to study discontinuation (Table 9 of Supplement 1). Further results for the extension

substudy are reported in Tables 10 to 12 and the Results section of Supplement 1.

Discussion

We compared 2 doses of a novel cathepsin K inhibitor with placebo and did not find a significant difference in the primary outcome, pain, across the 3 groups. However, significant reductions in secondary outcomes were observed. Progression of medial femoral bone area was significantly reduced in both MIV-711 treatment groups compared with placebo, and medial femoral cartilage thinning was reduced in the group receiving 100 mg/d. Significant reductions in bone resorption and cartilage degradation biomarkers were also observed. MIV-711 was well tolerated, with 9 SAEs in 6 participants, none of which were considered to be treatment-related. MIV-711 showed an acceptable safety profile in the 26-week extension substudy, and the effects on bone area progression and CTX-I and CTX-II were maintained in participants who initially received the 200-mg dose and whose symptoms did not worsen during the placebo-controlled study.

Many studies assessing structural change in osteoarthritis have relied on radiographic methods to show improvement, but these assess cartilage thinning indirectly and do not assess bone morphology. Using highly sensitive MRI techniques (20, 31–33), we demonstrated statistically significant attenuation of bone area progression and reduction of cartilage thickness in the active treatment groups compared with placebo, consistent with the mechanism of action of MIV-711. However, although these techniques can detect significant structural changes within a relatively short period, data from the Osteoarthritis Initiative indicate that changes in bone shape over 24 months are related to progression of pain over 48 months (19). Therefore, this study may have been too short for the 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 in both biomarkers were observed, at a greater magnitude than has previously been shown with use of bone-acting agents in osteoarthritis (25, 40, 41). This includes the 3-year SEKOIA (Strontium Ranelate Efficacy in Knee Osteoarthritis Trial), 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 using cathepsin K inhibitors (13, 15), there was a noticeable rebound effect after withdrawal of MIV-711 at the end of the placebo-controlled study, and levels decreased again when dosing resumed in the extension substudy. The effects of MIV-711 on these biomarkers provide 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, and 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 groups in both studies, and given the small numbers, cardiovascular monitoring and relevant eligibility criteria should still be considered in future studies. Overall, MIV-711 had a reassuring safety and tolerability profile in this population.

Our study has several limitations. The eligibility criteria for the extension substudy may have resulted in positive selection bias, given that most participants were selected because their symptoms did not worsen, which suggests a treatment benefit. Treatment effects could not be explored in participants with confirmed symptom progression because of the small number of participants in study group B. We excluded MRI scans that did not meet the predefined quality criteria for analysis, resulting in a 15% loss of data for the imaging analysis. Finally, multiple comparisons were conducted in this study, and multiplicity correction was applied only for the primary end point. Therefore, all other reported *P* values are unadjusted and should be interpreted with caution. This applies especially to the significant difference found in femoral cartilage on MRI between participants in the 100 mg group and placebo recipients.

In conclusion, MIV-711 showed no beneficial effects on osteoarthritic knee pain in this study. However, statistically significant reductions in bone and cartilage osteoarthritis manifestations were observed, along with a reassuring safety profile. Further evaluation of MIV-711 in longer and larger trials to confirm the structural benefits observed here and whether these translate to more tangible benefits on symptoms is warranted.

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