



UNIVERSITY OF LEEDS

This is a repository copy of *Disease-Modifying Effects of a Novel Cathepsin K Inhibitor in Osteoarthritis: A Randomized Controlled Trial*.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/153052/>

Version: Supplemental Material

Article:

Conaghan, PG orcid.org/0000-0002-3478-5665, Bowes, MA, Kingsbury, SR orcid.org/0000-0002-9917-1269 et al. (9 more authors) (2020) Disease-Modifying Effects of a Novel Cathepsin K Inhibitor in Osteoarthritis: A Randomized Controlled Trial. *Annals of Internal Medicine*, 172 (2). pp. 86-95. ISSN 0003-4819

<https://doi.org/10.7326/M19-0675>

© 2019 American College of Physicians. All Rights Reserved. This is an author produced version of an article published in *Annals of Internal Medicine*. Reproduced with permission from the publisher.

Reuse

Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



eprints@whiterose.ac.uk
<https://eprints.whiterose.ac.uk/>

Table 1. Baseline demographics (modified intent-to-treat population).

	Placebo (n=77)	MIV-711 100 mg (n=82)	MIV-711 200 mg (n=81)
Female, n (%)	62 (80.5)	64 (78.0)	58 (71.6)
Age, years, mean (SD)	62.3 (6.6)	61.2 (6.6)	62.0 (7.3)
Weight, kg, mean (SD)	87.1 (16.8)	86.0 (14.2)	86.6 (14.7)
BMI, kg/m ² , mean (SD)	32.5 (5.8)	32.0 (5.5)	32.0 (5.5)
Local K-L score 2/3	77	82	81
Independent K-L score, 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 the last 12 months, n (%)			
8–30 days	1 (1.3)	0	0
31–92 days	19 (24.7)	18 (22.0)	15 (18.5)
More than 92 days	57 (74.0)	64 (78.0)	66 (81.5)
Prior medications			
Analgesics	0	0	1 (1.2)
Other analgesics and antipyretics	5 (6.5)	8 (9.8)	4 (4.9)

BMI, body mass index; K-L, Kellgren-Lawrence; SD, standard deviation.

Table 2. Estimated mean (LS mean; 95% CI) change from baseline (week 0) to week 26 in primary and secondary efficacy outcomes (modified intent-to-treat population).

	Change from baseline (week 0) to week 26 *, LS mean (95% CI)							
	Placebo (n=77)		MIV-711 100 mg (n=82)			MIV-711 200 mg (n=81)		
	n		n		n			
				Difference (vs placebo)			Difference (vs placebo)	
Primary outcome								
NRS overall pain severity score	69	-1.4 (-1.9, -0.8)	74	-1.7 (-2.3, -1.2)	-0.3 (-1.0, 0.3) (p=0.146)	72	-1.5 (-2.0, -0.9)	-0.1 (-0.7, 0.6) (p=0.41)
Secondary outcomes								
MRI of bone area (mm²)	66	23.3 (15.7, 30.9)	69	7.9 (0.5, 15.3)	-15.4 (-26.0, -4.8) (p=0.002)	69	8.6 (1.1, 16.1)	-14.7 (-25.3, -4.0) (p=0.004)
MRI of cartilage thickness (mm)								
Femur region	66	-0.066 (-0.119, -0.013)	69	0.011 (-0.042, 0.063)	0.076 (0.002, 0.150) (p=0.023)	69	-0.022 (-0.074, 0.031)	0.044 (-0.031, 0.118) (p=0.125)
Tibia region	66	0.017 (-0.061, 0.095)	69	-0.024 (-0.099, 0.052)	-0.041 (-0.125, 0.044) (p=0.83)	69	-0.005 (-0.080, 0.071)	-0.022 (-0.107, 0.063) (p=0.69)
MRI of total bone marrow lesion volume (µL)	66	-811 (-1900, 282)	69	-1160 (-2230, -84.4)	-347 (-1880, 1190) (p=0.33)	69	-1050 (-2130, 34.8)	-234 (-1770, 1300) (p=0.38)
E-diary NRS scores								
AM response	69	-1.0 (-1.4, -0.6)	72	-1.4 (-1.8, -0.9)	-0.4 (-1.0, 0.2)	71	-1.4 (-1.9, -1.0)	-0.5 (-1.1, 0.2)
PM response	67	-1.2 (-1.6, -0.7)	67	-1.5 (-2.0, -1.1)	-0.3 (-1.0, 0.3)	70	-1.5 (-2.0, -1.1)	-0.4 (-1.0, 0.3)
Overall response	69	-1.1 (-1.6, -0.6)	72	-1.4 (-1.9, -1.0)	-0.3 (-1.0, 0.3)	71	-1.5 (-1.9, -1.0)	-0.4 (-1.0, 0.3)
Normalized WOMAC scores								
Pain score	69	-11.3 (-16.9, -5.7)	74	-15.9 (-21.3, -10.5)	-4.6 (-10.8, 1.7) (p=0.075)	72	-13.1 (-18.6, -7.6)	-1.8 (-8.0, 4.5) (p=0.29)

Function score	69	-11.9 (-18.1, -5.7)	74	-15.7 (-21.8, -9.6)	-3.8 (-10.3, 2.7) (p=0.126)	72	-13.8 (-19.9, -7.7)	-1.8 (-8.4, 4.7) (p=0.29)
Stiffness score	69	-11.0 (-17.8, -4.2)	74	-15.9 (-22.6, -9.3)	-5.0 (-12.1, 2.2) (p=0.086)	72	-14.1 (-20.8, -7.4)	-3.1 (-10.2, 4.1) (p=0.20)
Biomarkers								
Serum CTX-I (µg/L)	69	0.003 (-0.031, 0.037)	74	-0.143 (-0.175, -0.110)	-0.145 (-0.193, -0.098) (p<0.0001)	71	-0.251 (-0.285, -0.218)	-0.254 (-0.302, -0.206) (p<0.0001)
Urine CTX-II/Creat(ng/mmol)	68	41.9 (-23.0, 107)	73	-151 (-215, -87.6)	-193 (-262, -124) (p<0.0001)	72	-228 (-292, -165)	-270 (-339, -201) (p<0.0001)

CI, confidence interval; LS, least-squares; MRI, magnetic resonance imaging; NRS, numeric rating scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

* 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.

Table 3. Adverse events reported (SAF population).

	Placebo (n=80)	MIV-711 100 mg (n=82)	MIV-711 200 mg (n=82)
Any AE, n (%)	44 (55.0)	45 (54.9)	43 (52.4)
AEs 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
Paraesthesia	3 (3.8)	1 (1.2)	3 (3.7)
Hypertension	4 (5.0)	0	1 (1.2)
Gamma-glutamyltransferase increased	4 (5.0)	1 (1.2)	0
Myalgia	1 (1.3)	2 (2.4)	2 (2.4)
Any SAE, 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
Cholecystitis acute	0	0	1 (1.2)
Pyelonephritis chronic	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

(S)AE, (serious) adverse event; SAF, safety analysis population.