

The Potential Clinical Relevance of Imaging Biomarker Data from Short-Term Interventional Trials in Osteoarthritis: A Comparison of the Cathepsin K Inhibitor MIV-711 Phase 2a MRI Knee Joint Data and KL-Matched 5577 Knee Control Data from the Osteoarthritis Initiative

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Background

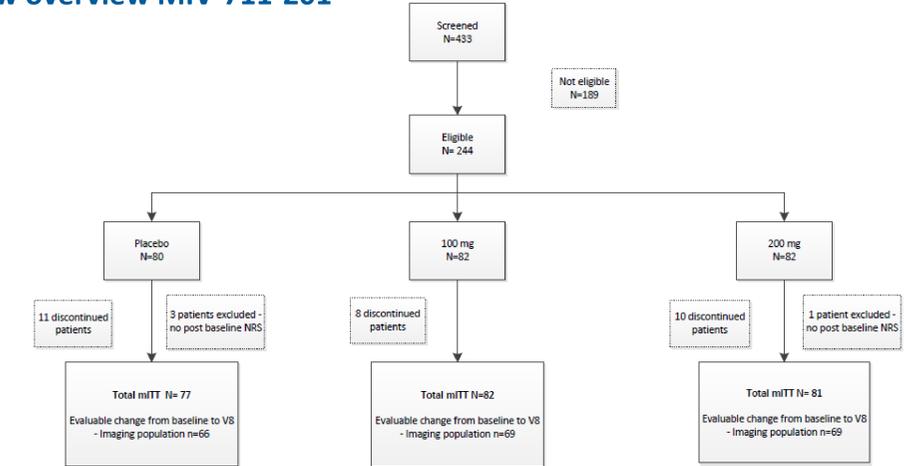
- Osteoarthritis (OA) is the fastest growing chronic pain disease worldwide.
- Current treatments available for OA are aimed at controlling pain. There is a need for new therapies, so called Disease Modifying Osteoarthritis Drugs (DMOADs), that can prevent joint structural degeneration.
- New imaging biomarkers using supervised machine learning offer opportunities to demonstrate effects of potential DMOADs on joint structure in short, small trials based on superior reliability.
- MIV-711, a cathepsin K inhibitor, demonstrated substantial effects vs placebo on both joint bone area and cartilage thickness following 6 months' treatment in the MIV-711-201 study^{1,2}. This study was the first to apply these highly sensitive imaging biomarkers in an interventional setting.
- Structural and clinical progression data from the Osteoarthritis Initiative (OAI) provide an opportunity to compare the outcome data from the MIV-711-201 study with data on the natural history of OA from a large prospective cohort.

Demographics

Statistics	MIV-711-201			OAI cohort		
	Placebo	100 mg	200 mg	KL0	KL2	KL3
N	77	82	81	2789	1870	918
Age (years)	Mean 62.3	Mean 61.2	Mean 62.0	59.2	61.7	64.2
BMI (kg/m ²)	Mean 32.49	Mean 31.98	Mean 32.02	27.0	29.5	30.0
Female	NA 62 (80.5%)	64 (78.0%)	58 (71.6%)	1542 (55.3%)	1182 (63.2%)	479 (52.2%)
Discontinuations	NA 11	8	10	NA	NA	NA

- Treatment groups well-balanced overall in Study MIV-711-201 also including but not shown here; height, weight, ethnicity and race.
- The average BMI in the MIV-711-201 study was slightly higher than in the OAI cohort. In addition, the MIV-711-201 study had a higher proportion of females compared to the OAI cohort.

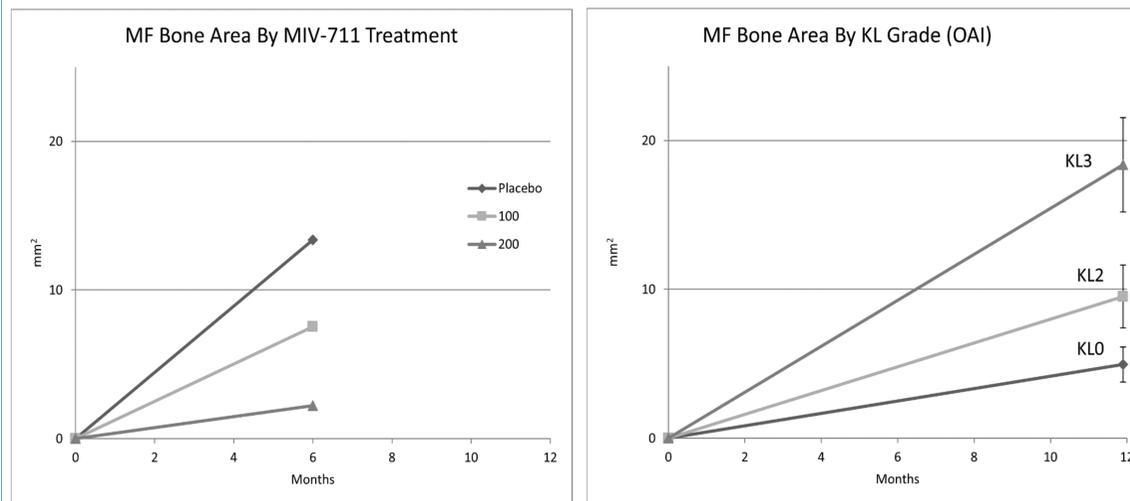
Patient flow overview MIV-711-201



Methods

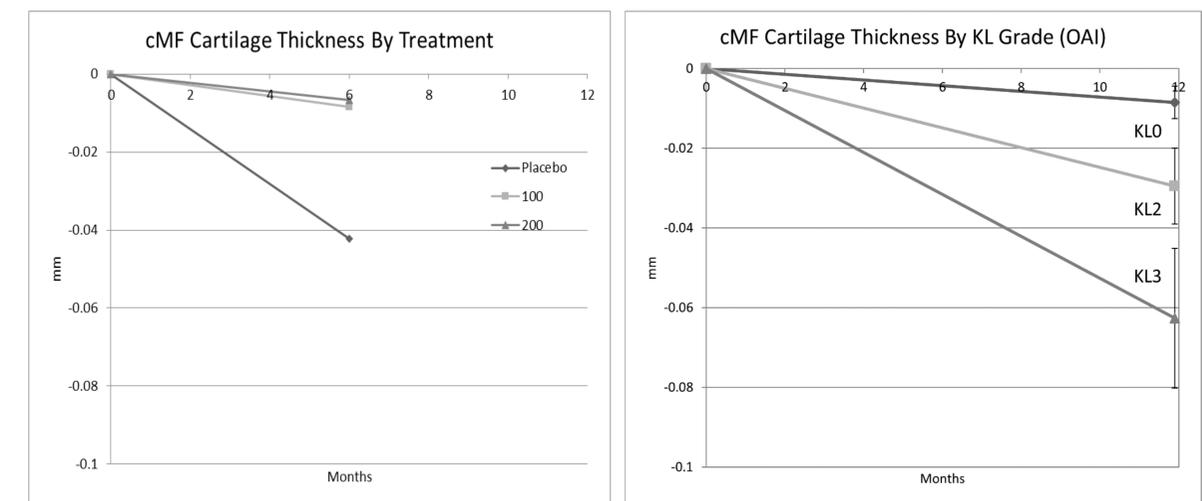
- MIV-711-201 (EudraCT no 2015-003230-26) was a multicentre, randomised, placebo-controlled, double-blind, three arm, parallel, Phase 2a study.
- Key inclusion criteria for MIV-711-201 study patients:
 - ACR knee OA
 - K-L classification grade 2 or 3 (local radiologist's assessment based X-ray taken within the last 12 months)
 - Current average target knee pain ≥ 4 & < 10 on a 0 to 10 NRS
- Patients were randomised to receive MIV-711 100 mg, MIV-711 200 mg or placebo once daily for 26 weeks. A total of 240 patients were included in the mITT population (placebo=77; MIV-711 100 mg=82, MIV-711 200 mg=81).
- 3D bone area of the medial femoral condyle (MF) and cartilage thickness in the central medial femur (cMF) were measured using automated segmentation of Magnetic Resonance Images (MRI) and active appearance modelling^{3,4}.
- Rates of change were compared against annual change from all knees from the OAI (3,334 individuals, 5,577 knees) with K-L grade 0 (normal), 2 or 3, and a baseline and 12 month image, using the same methods of bone and cartilage segmentation as used in the MIV-711-201 study.

Effect of MIV-711 on Joint structure compared with the OAI cohort: Bone Area



- In the MIV-711-201 quantitative MRI data, mean changes in MF bone area (mm²) were 13.4 (7.48, 19.28); 7.54 (-1.19, 16.27); 2.22 (-3.92, 8.37) for the placebo, 100 mg and 200 mg groups respectively (95% CI). This is in good agreement with the corresponding published data based on manual segmentation^{1,2}.
- OAI MF bone area change (mm²) over 12 months was 4.26, 9.177, 20.09 (mm²) for KL0, 2 and 3 respectively (equates to 2.13, 4.59, 10.05 over 6 months assuming linear change).

Effect of MIV-711 on Joint structure compared with the OAI cohort: Cartilage thickness



- In the MIV-711-201 quantitative MRI data cMF cartilage thickness (mm) mean changes were -0.042 (0.001, -0.085), -0.008 (0.034, -0.051), -0.007 (0.044, -0.058) for the placebo, 100 mg and 200 mg respectively (95% CI), also this in good agreement with the data based on manual segmentation^{1,2}.
- OAI cMF cartilage change over 12 months was -0.005, -0.024, -0.060 (mm) for KL0, 2 and 3 respectively (equates to -0.0025, -0.012, -0.03 over 6 months assuming linear change).

Conclusions

- This comparison suggests that patients in the placebo arm of the MIV-711-201 study had a similar structural progression rate to untreated KL2/KL3 patients in the OAI cohort.
- The effects of 6 months treatment with MIV-711 on bone area and cartilage thickness are relevant when compared to the natural progression seen over 12 months in OAI K-L 2/3 patients, establishing the relevance of these endpoints for use in prospective interventional studies
- Benefits on clinical symptoms could become manifest if MIV-711's positive effects on joint structure can be maintained over time.

References

1. Conaghan PG et al. MIV-711, a Novel Cathepsin K Inhibitor Demonstrates Evidence of Osteoarthritis Structure Modification: Results from a 6 Month Randomized Double-Blind Placebo-Controlled Phase IIA Trial [abstract]. Arthritis Rheumatol. 2017; 69 (suppl 10).
2. Conaghan PG et al. Six months' treatment with MIV-711, a novel Cathepsin K inhibitor induces osteoarthritis structure modification: results from a randomized double-blind placebo-controlled phase IIA trial. Osteoarthritis Cartilage. 2018; 26 (Suppl 1): S25-S26.
3. Bowes MA, Vincent GR, Wolstenholme CB, Conaghan PG. A novel method for bone area measurement provides new insights into osteoarthritis and its progression. Ann Rheum Dis. 2015;74(3):519-25.
4. Coates TF, Taylor CJ, Cooper, DH; Graham, J. Active Shape Models-Their Training and Application. Computer Vision and Image Understanding. 1995;61(1):38-59.