14L: MIV-711, a Novel Cathepsin K Inhibitor Demonstrates Evidence of Osteoarthritis Structure Modification: Results from a 6 Month Randomised Double-Blind Placebo-Controlled Phase IIa Trial

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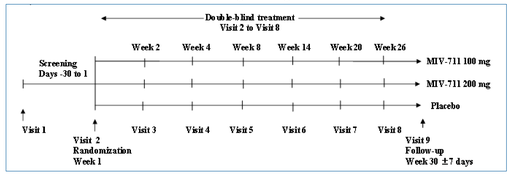
Background

- 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.
- Osteoarthritic joints are characterized by cartilage loss, subchondral bone pathology and synovial inflammation.
- Cathepsin K is a cysteine protease that is intimately involved in bone resorption and degrades key bone matrix proteins such as type I collagen as well as collagen type II and aggrecan, leading to cartilage degradation.
- Inhibition of cathepsin K is therefore a logical approach to attempt OA structure modification acting on bone as well as cartilage tissues
- MIV-711 is a potent, selective and reversible inhibitor of cathepsin K , with an attractive preclinical and early clinical profile.

Methods: Study Design

- MIV-711-201 (EudraCT no 2015-003230-26) was a multicentre, randomised, placebo-controlled, double-blind, three arm, parallel, Phase IIa study. All patients were permitted to remain on their current stable analgesic regimen.



Primary endpoint

- Change in target knee average pain over 26 weeks as measured by an 11-point NRS (1 week recall).

Key secondary endpoint

- To assess the effect of MIV-711 on MRI target knee bone area.

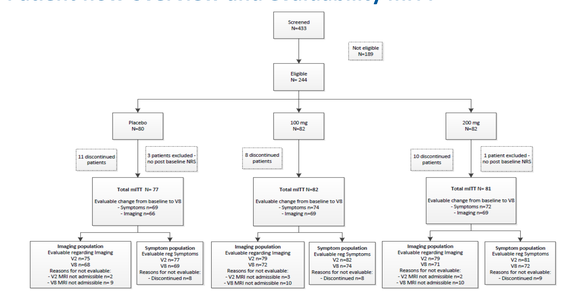
Secondary endpoints (not exhaustive)

- To assess the effect of MIV-711 on cartilage thickness and further MRI measurements of bone as well as: NRS scores assessing additional pain parameters; WOMAC; daily NRS for pain and daily analgesic use (via e-diary); biomarkers; QoL.
- To assess the safety and tolerability of MIV-711.

Key Inclusion criteria

- Current average knee pain ≥4, <10 on a 0 to 10 NRS.
- X-ray evidence within the last 12 months for K-L classification grade 2 or 3.

Patient flow overview and evaluability mITT

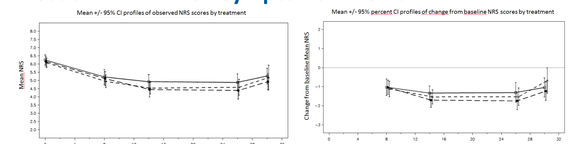


Demographics

	Statistic	Placebo	100 mg	200 mg	Overall
	n	77	82	81	240
Age (years)	Mean	62.3	61.2	62.0	61.8
BMI (kg/m^2)	Mean	32.49	31.98	32.02	32.16
Female	NA	62 (80.5%)	64 (78.0%)	58 (71.6%)	184 (76.7%)
Male	NA	15 (19.5%)	18 (22.0%)	23 (28.4%)	56 (23.3%)
Discontinuations	NA	11	8	10	29

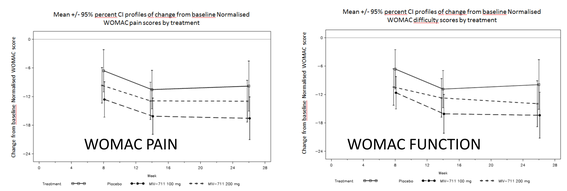
Treatment groups well-balanced overall also including but not shown here; height, weight, ethnicity and race.

Effect of MIV-711 on Symptoms: NRS Pain



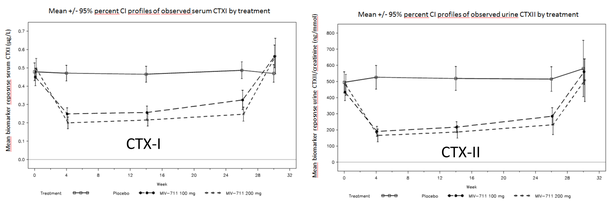
- No statistically significant effect by treatment (unadjusted p=0.41 for 200 mg and p=0.15 for 100 mg).
- Tendency to less pain in the MIV-711 treated arms compared to placebo.

Effect of MIV-711 on Symptoms: WOMAC



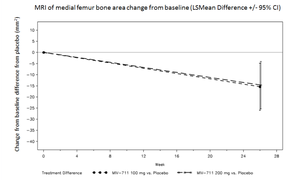
- The tendency of a treatment effect was more pronounced in WOMAC scales (including placebo around 12 weeks versus treatment arms)

Effect of MIV-711 on Biomarkers: CTX-I and CTX-II



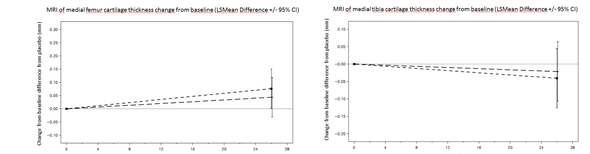
- The reductions in both serum CTX-I and urine CTX-II were rapid and sustained over 26 weeks of treatment with a slight climb consistent with the literature.
- The biomarker data suggest robust target engagement with ca. 30% and 50% reductions for 100 mg and 200 mg groups, respectively for both biomarkers.

Effect of MIV-711 on Joint Structure: Bone Area



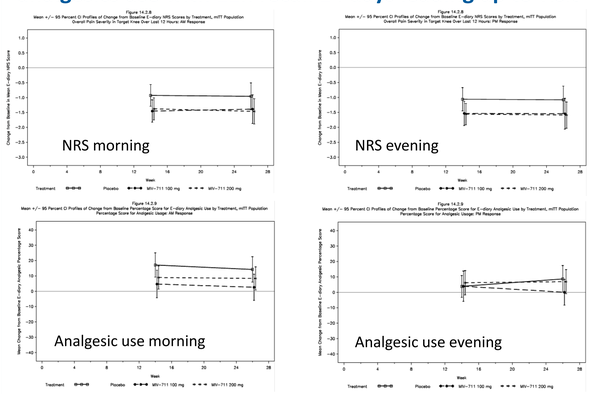
- Pronounced attenuation with both doses on medial femur bone area progression (~0,3%/6 months) compared to that of placebo (~1%/ 6 months)
- Unadjusted p-values= 0.002 (100 mg), 0.004 (200 mg)

Effect of MIV-711 on Joint Structure: Cartilage Loss



- Both treatment arms showed a benefit on the attenuation of cartilage thinning in the central medial femoral region (~0%/6 months) compared to that of placebo (~4%/6 months). No significant effect was seen on the tibial side.
- Unadjusted p-values = 0.023 (100 mg) and 0.125 (200 mg).

Effects of MIV-711 on symptoms: E-diary assessed NRS & analgesics use with 12h recall 14 days leading up to visit



Discussion

- Despite substantial effects on medial femur bone area and cartilage loss over 6m, the length of time over which the observed effects on these markers need to be sustained to detect effects on patient-reported symptoms remains uncertain.
- Data from the OAI cohort indicate that changes in joint bone markers over 24 months are associated with radiographic and pain progression over 48 months (Hunter *et al*., Ann Rheum Dis. (2016) 75:1607-14)

Safety & Tolerability

	Treatment		
	Placebo N = 80 nn (%) E	100 mg MIV-711 N = 82 nn (%) E	200 mg MIV-711 N = 82 nn (%) E
All TEAEs	44 (55.0%) 107	45 (54.9%) 120	43 (52.4%) 118
'Related' TEAEs	17 (21.3%) 39	17 (20.7%) 34	20 (24.4%) 37
Mild TEAEs	14 (17.5%) 54	11 (13.4%) 48	17 (20.7%) 57
Moderate TEAEs	29 (36.3%) 52	32 (39.0%) 68	21 (25.6%) 55
Severe TEAEs	1 (1.3%) 1	2 (2.4%) 4	5 (6.1%) 6
Deaths	1 (1.3%) 1	0	0
SAEs	1 (1.3%) 1	3 (3.7%) 6	2 (2.4%) 2
TEAEs Leading to early Discontinuation from Study	3 (3.8%) 3	6 (7.3%) 6	4 (4.9%) 10

Overall safety summary

- MIV-711 showed acceptable tolerability; overall AEs were balanced across arms. A DMC gave go ahead at 4 preplanned unblinded safety reviews.
- Slight increase in numbers of patients reporting skin disorders (2.5%, 12.2%, 7.3%), infections (11.3%, 18.3%, 22.0%), and musculoskeletal events (16.3%, 15.9%, 23.2%) in the placebo, 100 mg and 200 mg arms respectively.
- Infections and skin events were generally mild to moderate and non-specific.
- Three patients presented with allergic drug eruptions.
- No instances of morphea/scleroderma.
- Slight increase in number of patients with severe AEs and AEs leading to discontinuation in 100 (2.4%; 7.3%) and 200 mg (6.1%; 4.9%) arms vs placebo (1.3%; 3.8%).
- There were 9 SAEs in 6 patients: None were reported related to study medication
  - Placebo: cardiac failure (death).
  - 100 mg arm: atrial fibrillation, prinzmetal angina, pyelonephritis, compression fracture, contusion, haematoma (last 4 events all in one patient).
  - 200mg: cholecystitis, cerebral infarction (CI).
- Independent experts assessed cases with atrial fibrillation and CI as unrelated to treatment due to comorbidities and preexisting conditions. Prinzmetal angina was preexisting undisclosed condition diagnosed during study.
- Transient shifts in calcium and parathyroid hormone (PTH) were seen in line with the mode of action of study drug. These shifts however, did not appear to be associated with any AEs or ECG changes. No other clinically significant changes in labs, vitals or ECGs.

Conclusions

Symptoms

- Primary endpoint of knee pain not met, however consistent tendency favors treated arms in all symptom measures
- Analgesic use showed tendency to be lower in treated arms

Joint structure

- MRI measures demonstrated joint protection after 6 months of treatment

Biomarkers

- Significant depressions of both CTX-I and CTX–II show clear target engagement

Safety & Tolerability

- Acceptable safety and tolerability at both doses

<u>Overall conclusion</u>

- Even with a short treatment period (6 m), MIV-711 demonstrated significant reductions in OA bone disease and cartilage disease (100mg dose) progression in the femur.
- The treatment duration required to demonstrate a corresponding reduction in patient-reported symptoms was not reached.
- Further evaluation of MIV-711 in longer and larger DMOAD trials is therefore warranted.

Medivir AB is the Sponsor of the study, contact person *john.ohd@medivir.com*