# Intraarticular Injection of MM-II Liposomes Lubricates Cartilage *in-vivo* and Reduces Friction and Wear in *ex-vivo* Cartilage Models

**Gadi Sarfati[1], Ronny Pinkus[1]**

[1] Moebius Medical LTD, 27th Habarzel street, Tel- Aviv, Israel

## INTRODUCTION

MM-II is a suspension of large multilamellar liposomes for intra-articular administration, under development for treatment of osteoarthritic pain. Due to their unique characteristics, MM-II liposomes are retained on the cartilage surface, providing long-term lubrication and leading to a reduction in wear of the cartilage. As previously reported in a first-in-human clinical trial, MM-II, when injected intraarticularly, was shown to reduce pain up to 3 months post injection.

## OBJECTIVE

This study aims to illustrate MM-II's mechanism of action by studying the localization of the liposomes in the joint following an intraarticular injection into rabbits and using 2 *ex-vivo* cartilage models for evaluation of MM-II's lubrication capabilities and its effect on reduction of friction and wear of the cartilage.

## METHODS

Three different studies were conducted for the evaluation of MM-II's localization in the knee post injection and its effect on reduction of cartilage wear and friction.

### MM-II knee localization after intraarticular injection into rabbits

Tritium-labeled MM-II liposomes were injected into the knee joint of New Zealand white rabbits at a volume of 350µL per knee. Analysis of the biodistribution of radioactivity in the knee joint was performed at selected time points following administration, up to 70 days. Imaging of the distribution of radioactivity in the knee joint was undertaken using quantitative whole-body autoradiography (QWBA) and micro-autoradiography (MARG) techniques.

### *Ex-vivo* friction measurement

Friction measurement was conducted using a cartilage-on-cartilage rotation friction test setup, using a pair of osteochondral equine cores (12 mm bottom core and 7.8 mm upper core) immersed in a bath containing the tested lubricant maintained at 37°C. Friction measurement was performed using a mechanical tester equipped with a multiple-axis load cell, as shown in Figure 1. Static and kinetic friction coefficients obtained using MM-II as a lubricant were compared with healthy synovial fluid (SF, positive control) and phosphate buffered saline (PBS, negative control).

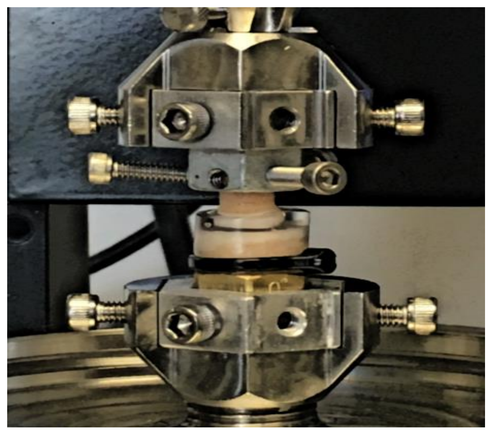

**Figure 1.** Cartilage-on-Cartilage in Rotation Test Setup

### *Ex-vivo* wear measurement

Wear tests were carried out using a pin-on-disc setup with porcine cartilage pins sliding against Cobalt-Chromium-Molybdenum (CoCrMo) discs immersed in a bath containing the tested lubricant maintained at 37°C. Wear assessment was performed by measurement of cartilage pin height and weight before and after application of wear cycles under a predetermined load. The effect of MM-II on wear of the cartilage pin was evaluated against a protein-based lubricant commonly used for wear testing of prostheses.

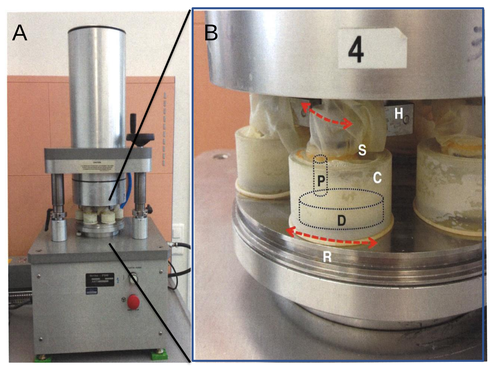


**Figure 2.** A. Wear Testing Apparatus. B. Zoom in of The Rotation Plate (R) and 1 station including CoCr Disc (D), Cartilage Pin (P), Holding Harm (H), Lubricant Container (C) and Rubber Sealing (S)

## RESULTS

### MM-II knee localization after intraarticular injection into rabbits

Distribution of radioactivity following intraarticular injection of MM-II into rabbit knee showed high concentrations of radioactivity in the articular space after injection (Figure 3 A and B). Seven days post injection, radioactivity concentration was found to be reduced in the synovial cavity and a high radioactivity concentration was observed on the cartilage, implying that MM-II is selectively bound to the surfaces of the cartilage (Figure 3 C and D). Radioactivity was detected on the cartilage surface for up to 56 days post injection (Figure 4).

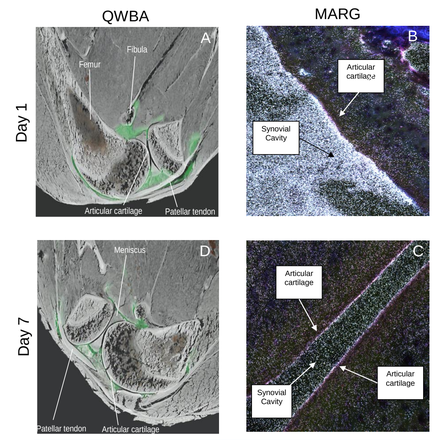


**Figure 3.** MM-II Knee Localization 1 and 7 Days Post Intraarticular Injection Imaged Using QWBA and MARG

| | | PC µg equivalents/g | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Animal no: | 01M | 02M | 03M | 04M | 05M | 06M | 07M | 08M | 09M |
| Tissue | Time-point: | 1 d | 3 d | 7 d | 14 d | 21 d | 28 d | 42 d | 56 d | 70 d |
| Articular cartilage | | 37.3 | 97.0 | 125 | 117 | 63.3 | 17.4 | 51.0 | 20.3 | BLQ |
| Bone marrow | | BLQ | 14.3 | 15.5 | 14.1 | BLQ | BLQ | BLQ | 13.1 | BLQ |
| Compact bone | | BLQ | BLQ | 18.4 | 12.2 | BLQ | BLQ | ND | ND | ND |
| Ligament | | 1177 | NS | NS | 286 | 34.3 | 11.2 | ND | ND | ND |
| Meniscus | | 19.8 | 200 | 112 | 52.8 | 81.8 | BLQ | BLQ | ND | ND |
| Muscle | | BLQ | BLQ | 13.8 | 14.0 | 100 | 28.9 | 16.8 | BLQ | BLQ |
| Muscle fascia | | 145 | 139 | 3099 | 1610 | 886 | 422 | 202 | 43.7 | 41.7 |
| Patella tendon | | 237 | 219 | 175 | NS | BLQ | BLQ | ND | ND | ND |
| Spongy bone | | BLQ | 13.6 | 23.5 | 12.7 | BLQ | BLQ | BLQ | ND | ND |
| Synovial bursa | | 47787† | 45473† | 6066 | NS | NS | NS | NS | 23.4 | ND |
| Synovial cavity | | 92857† | 32696† | 6268 | 90.0 | 119 | 22.9 | BLQ | ND | ND |

†: Above limit of accurate quantification (>31087 µg equivalents/g), extrapolated value reported
BLQ: Below limit of accurate quantification (<9.96 µg equivalents/g)
ND: Radioactivity not detected
NS: No sample

**Figure 4.** Concentrations of Radioactivity in the Knee Following Intraarticular Administration of MM-II

### Ex-vivo friction measurement

Evaluation of the friction coefficient was performed at a static phase and kinetic phase. For the static friction coefficients, MM-II presented a statistically significant lower coefficient when compared to Phosphate Buffered Saline (0.11versus 0.16, respectively; p<0.0001) or to synovial fluid (0.11versus 0.15, respectively; p=0.05). For Kinetic friction coefficient, MM-II showed a statistically significant lower coefficient than Phosphate Buffered Saline (0.028 versus 0.035, respectively; p=0.008), but statistically higher than synovial fluid (0.028 versus 0.022, respectively; p=0.002), as presented in Figure 5.

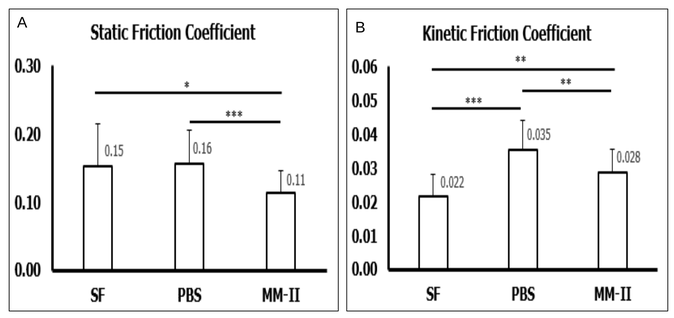


**Figure 5.** Static (A) and Kinetic (B) Friction Coefficient of Cartilage Pins in Different Lubricant Baths (N=10). * p≤0.05; ** p≤0.01 and *** p≤0.001.

### Ex-vivo wear measurement

MM-II was shown to reduce the mass and height loss when compared to protein-based liquid (14 mg versus 26 mg mass decrease, respectively, and 0.3 mm versus 1.1 mm length decrease, respectively; P<0.01 and p<0.1 respectively), as presented in Figure 6.

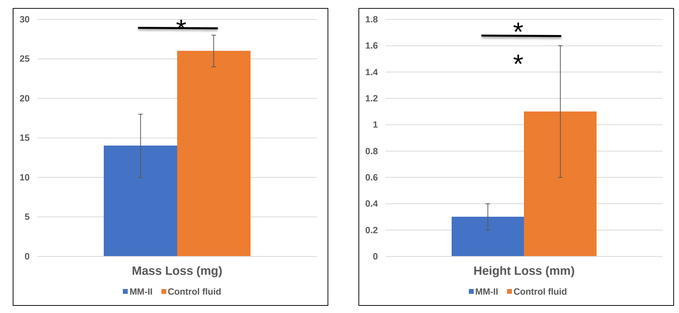


**Figure 6.** Comparison of Mass and Height Loss of Cartilage Pins in Different Lubricant Baths After Application of Wear Pattern. * p<0.01; ** p<0. 1.

## CONCLUSIONS

**Our data illustrates the role that MM-II liposomes can play in lubrication of the knee joint. Due to their unique characteristics, after intraarticular injection MM-II liposomes adsorb to the cartilage surface and provide lubrication for movement between the cartilage surfaces. This lubrication leads to reduction in friction that reduces the wear of the cartilage surfaces.**

## CONTACT

Gadi Sarfati, PhD: gadi@moebiusmedical.com