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ABSTRACT SUBMISSION
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Prevention of Synovial Membrane Inflammation & Cartilage Degradation by a Novel Chitosan Hydrogel in a Rabbit Model of Osteoarthritis

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Keywords: Osteoarthritis, CHITOSAN hydrogel, Animal model, Biomaterials

1. Abstract

Purpose:

Current treatments of osteoarthritis (OA) are mainly based on the alleviation of painful symptoms but they are unable to prevent or to reverse cartilage degradation. The development of new hydrogels for intra-articular viscosupplementation is a promising approach. Herein, we reported the effects of a novel chitosan hydrogel in OA induced surgically in rabbit.

Methods and Materials:

A biodegradable thermosensitive hydrogel was prepared with ultrapure and animal-free chitosan according to a proprietary formulation and process (VI002, Vegetech inside, Synolyne Pharma, Herstal, Belgium). OA was surgically induced by section of the anterior cruciate ligament (ACLT) in rabbits. One week after surgery, animals were randomly divided into 2 groups and injected intra-articularly (right knee) with 600 microliters saline solution (control; n =9) or with 600 microliters VI002 hydrogel (n=10). The standard radiographs were acquired in extension and scored with the Kellgren and Lawrence (K&L) scale. Animals were euthanized 9 weeks after surgery and the right knee joint was dissected. A macroscopic evaluation of cartilage was done. Histological sections of cartilage and of synovial membrane were stained with Safranine-O/fast green or hematoxylin/eosin respectively. All evaluations were done according to the OARSI guidelines.

Results:

The X-ray analysis showed a significant decrease ($p=0.0079$) of the k&L score in rabbits injected with VI002 hydrogel compared with controls. The size and the severity of the macroscopic OA cartilage lesions significantly decreased in the lateral compartment in animals treated with VI002 compared to controls ($p = 0.0041$). The synovitis histological scores, mostly synoviocytes hyperplasia and inflammatory cells infiltrate criteria, were significantly reduced by VI002 hydrogel ($p = 0.0040$). Finally, the injection of VI002 significantly improved the structure of cartilage ($p = 0.0017$).

Conclusion:

The VI002 hydrogel was found to prevent cartilage degradation and to decrease synovitis in OA rabbit. The results confirm the high potential of a chitosan-based hydrogel in preventing OA.

2. Purpose

Current treatments of osteoarthritis (OA) are mainly based on the alleviation of painful symptoms but they are unable to prevent or to reverse cartilage degradation. The development of new hydrogels for intra-articular viscosupplementation is a promising approach. Herein, we reported the effects of a novel chitosan hydrogel in OA induced surgically in rabbit.

3. Methods and Materials

A biodegradable thermosensitive hydrogel was prepared with ultrapure and animal-free chitosan according to a proprietary formulation and process (VI002, Vegetech inside, Synolyne Pharma, Herstal, Belgium).

OA was surgically induced by the transection of the anterior cruciate ligament (ACLT) of the right knee of female Hyla albino rabbits aged 20 weeks. One week after surgery, animals were randomly divided into 2 groups and injected intra-articularly (right knee) with 600 microliters saline solution (control; n =10) or with 600 microliters VI002 hydrogel (n=10) (Figure 1, Table 1).

study design_chart.jpg

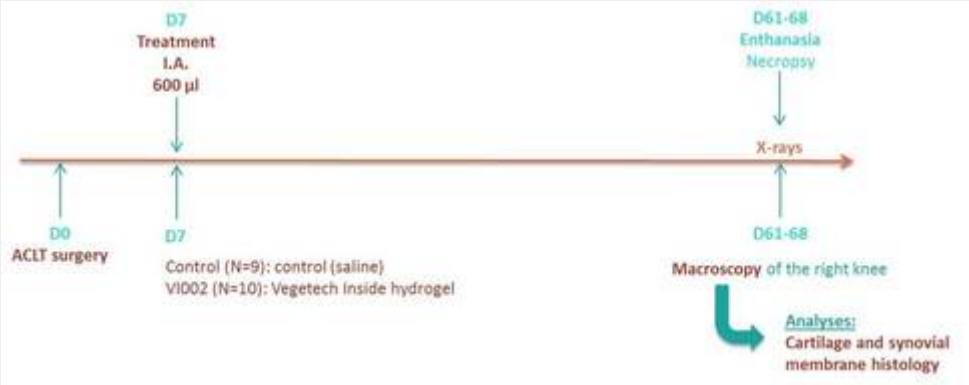

Figure 1: Study design (D: day; ACLT: anterior cruciate ligament transection; I.A.: intra-articular)

Table 1: Study details ($^{+}$ one rabbit lost during narcose)

study design_table.jpg

	Control	VI002
Species & strain	Adult female HYLA albino rabbit	
Age on delivery	*20 weeks*	
Weight at surgery	*3.5-4.0 kg*	
Number of rabbits	9^{+}	10
Treatment administration	Single I.A. 600 µl 7 days after surgery	
Follow-up period (days)	61-68	61-68

Standard radiographs were acquired in extension and scored with the Kellgren and Lawrence (K&L) scale 9 weeks after surgery. Animals were euthanized at that time and the right knee joint was dissected. A macroscopic evaluation of cartilage was done. The size and severity of the lesions were recorded according to the OARSI recommended scores (1). Synovial membrane and cartilage (femoral condyles) were processed for histologic evaluation. Synovial membrane sections were stained with hematoxylin/eosin and cartilage with Safranine-O/fast green. Histologic evaluation was performed according to the OARSI scores (1).

Data were analyzed using Mann-Whitney U test. They are presented as box and whisker plots. Results

are given either as global (entire joint) or for specified compartment or parameter. P value below 0.05 was considered significant.

4. Results

Tolerance and safety

Except one rabbit lost during narcose, no loss was recorded throughout the whole duration of the study. The I.A. treatment was well tolerated. No adverse reaction was reported.

Imaging

Standard X-rays showed characteristic OA manifestations (Figure 2). The analysis showed a significant decrease (p=0.0079) of the k&L score in rabbits injected with VI002 hydrogel compared with controls (Figure 3).

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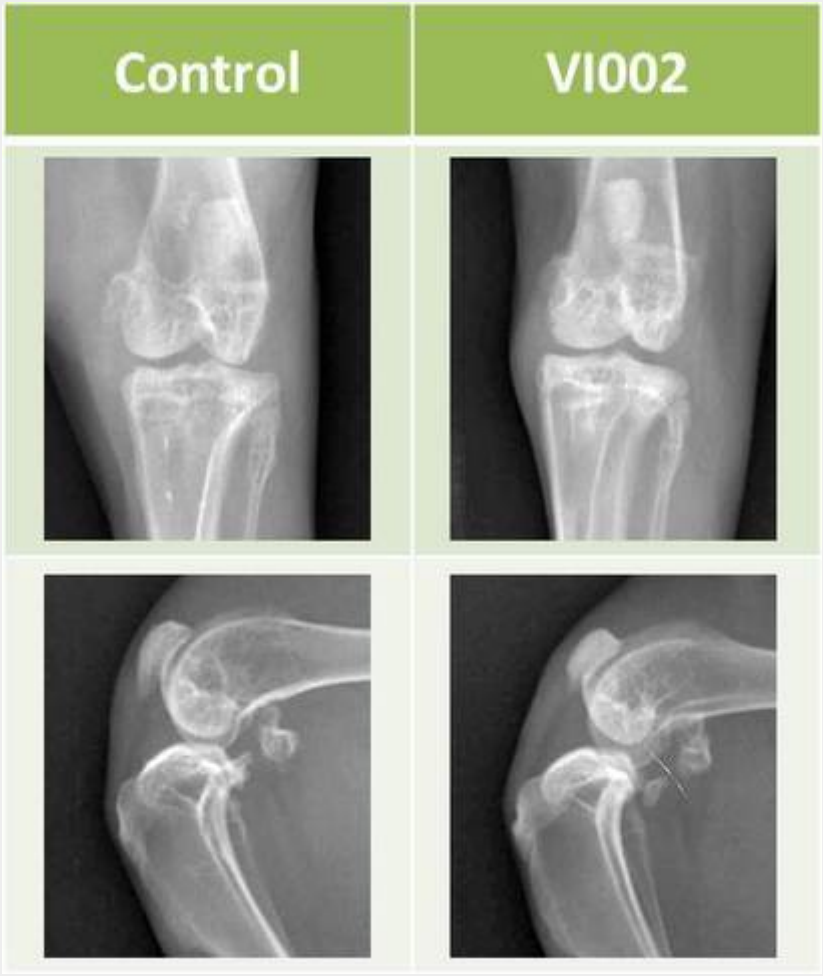

Figure 2: Representative X-ray images from Control and VI002 hydrogel groups

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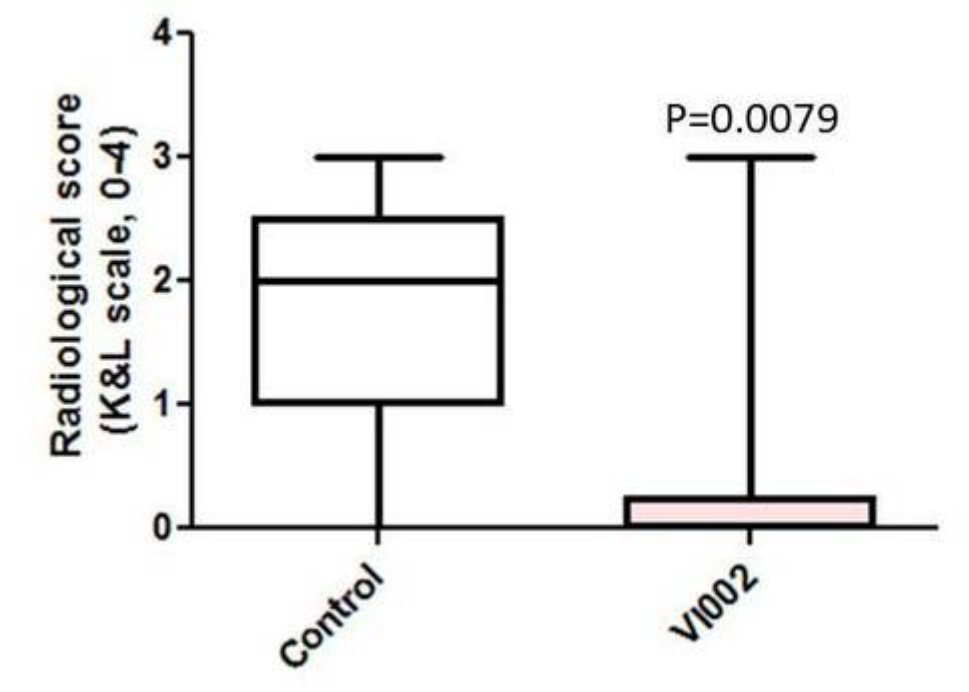

Figure 3: K&L score in Control and VI002 hydrogel groups

Macroscopic analysis

All animals developed OA lesions. The observation of the joint structures revealed lesions with different grade and size on the different compartments (Figure 4). The size and the severity of the macroscopic OA cartilage lesions significantly decreased in the lateral compartment in animals treated with VI002 compared to controls ($p = 0.0041$) (Figure 5). The same tendency was observed with the global score. This result is in favor of a protective effect of VI002 against the development of OA lesions.

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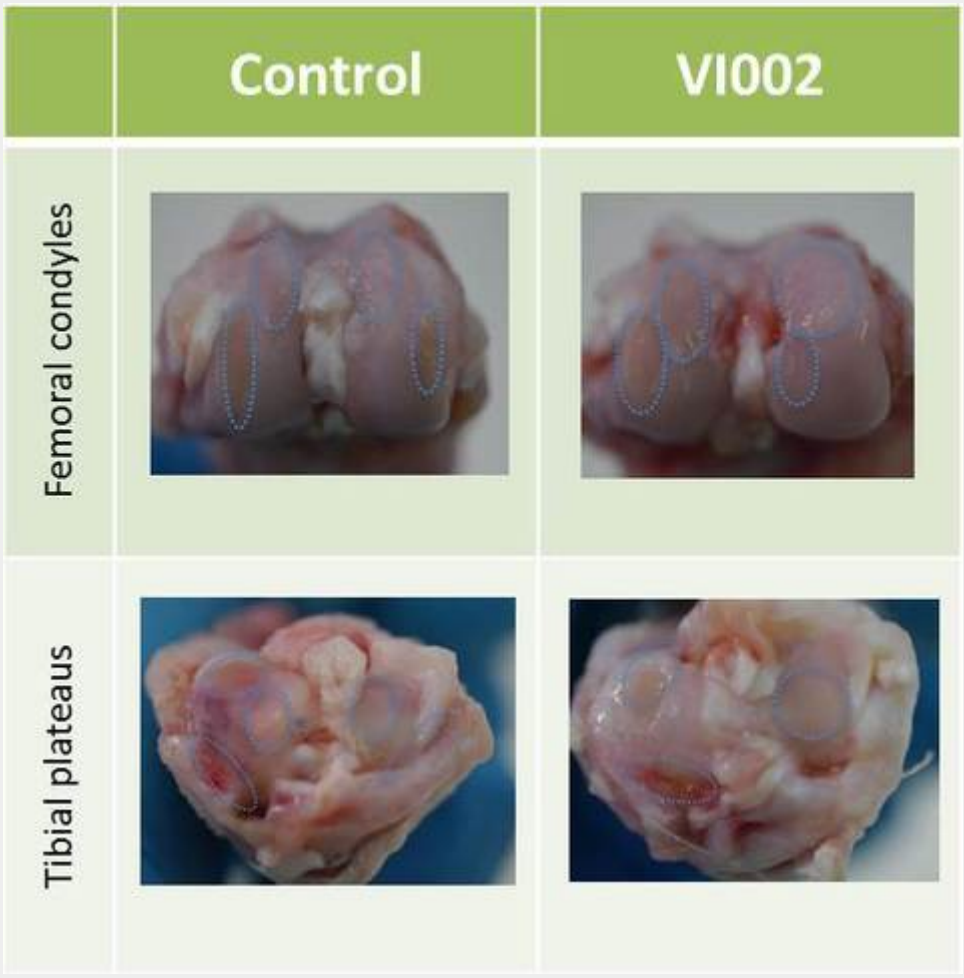

Figure 4: Representative macroscopic appearance of cartilage lesions on femoral condyles and tibial plateaus in Control and VI002 hydrogel groups

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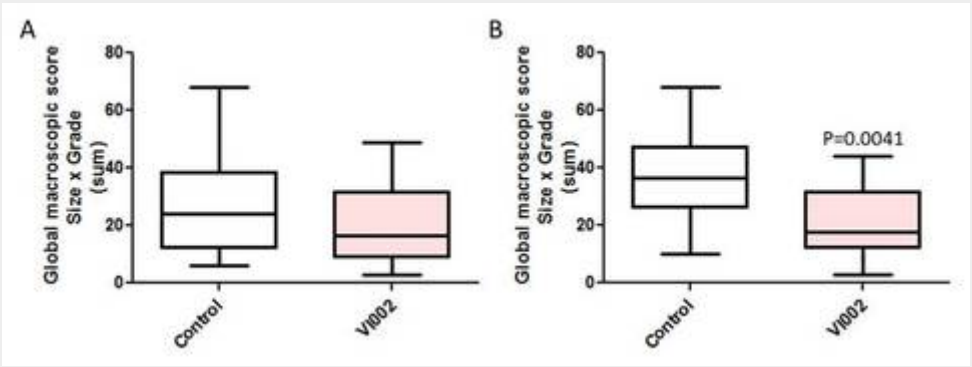

Figure 5: Macroscopic evaluation of the lesions of cartilage: A) Global score, B) Score in the lateral compartment (Sizexgade) Control and VI002 hydrogel groups

Histology of the synovial membrane

The synovial membrane is the site an inflammatory reaction characterized by synovial hypertrophy, villous hyperplasia and inflammatory infiltrate (Figure 6). VI002 hydrogel signicantly improved the global score of synovial membane (p = 0.0040) (Figure 7). This effect was mostly due to the significant reduction of synoviocytes hyperplasia and inflammatory cells infiltrate criteria (Figure 8). VI002 was indeed able to reduce the synovial inflammation.

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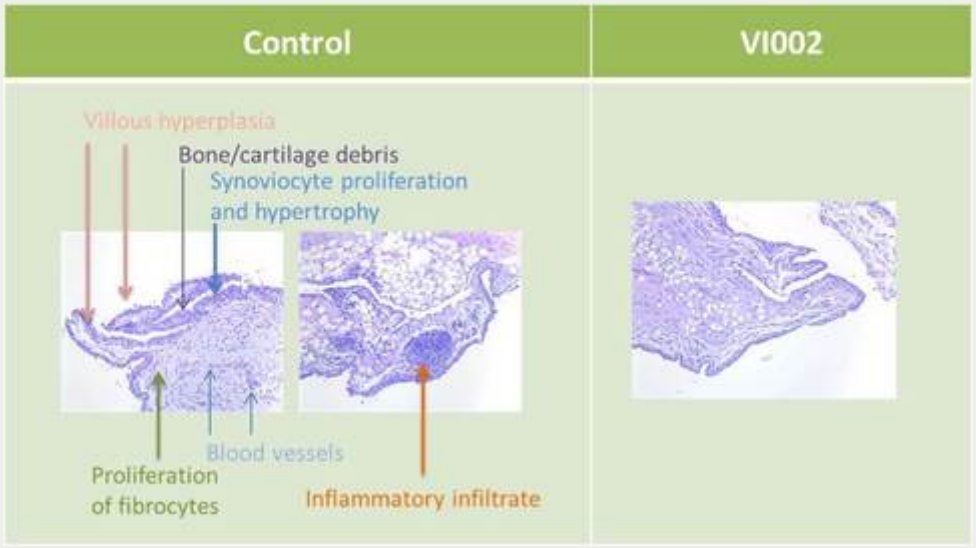

Figure 6: Representative sections of synovial membrane from Control and VI002 hydrogel groups

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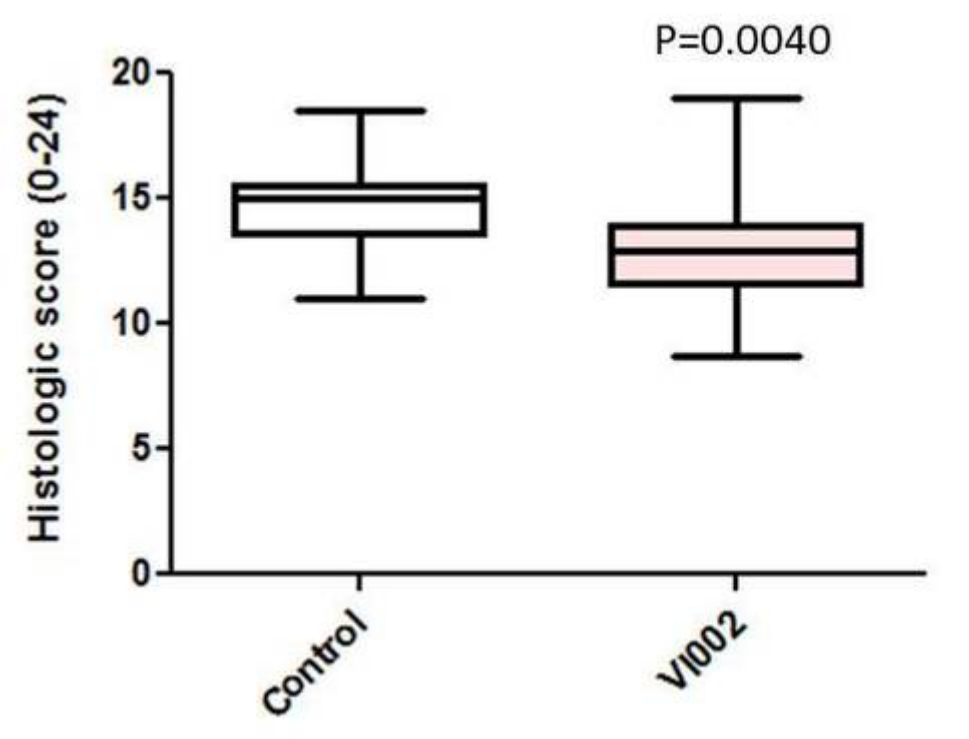

Figure 7: Global histologic score of the synovial membrane in Control and VI002 hydrogel groups

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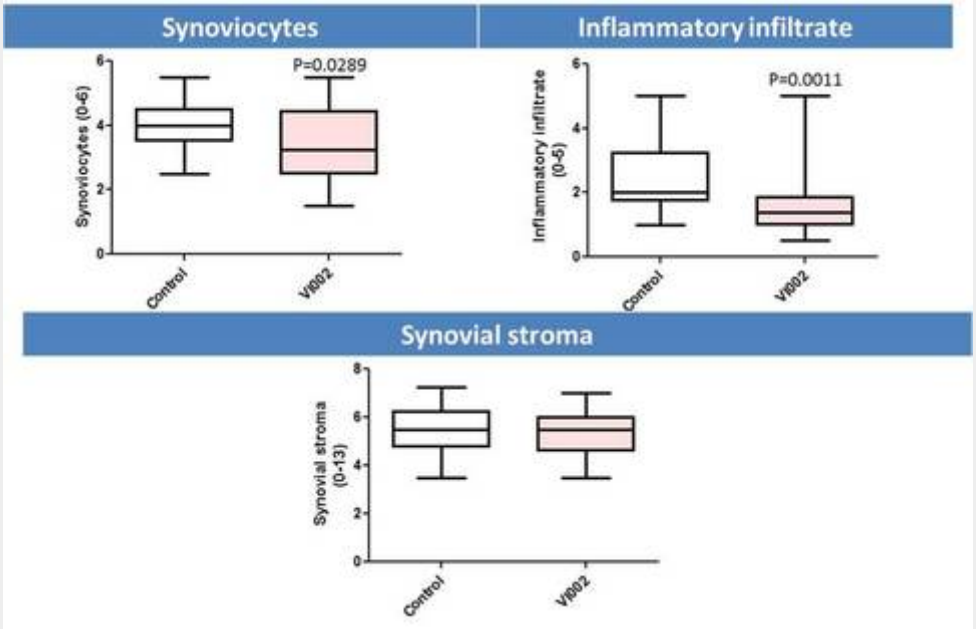

Figure 8: Detailed score of the synovial membrane

Histology of cartilage

Cartilage lesions were of mild to moderate intensity (Figure 9). VI002 treatment induced a slight but not significant improvement in the global score of cartilage (Figure 10). However a significant effect was shown on the cartilage structure score with VI002 treatment (p = 0.0017) (Figure 11).

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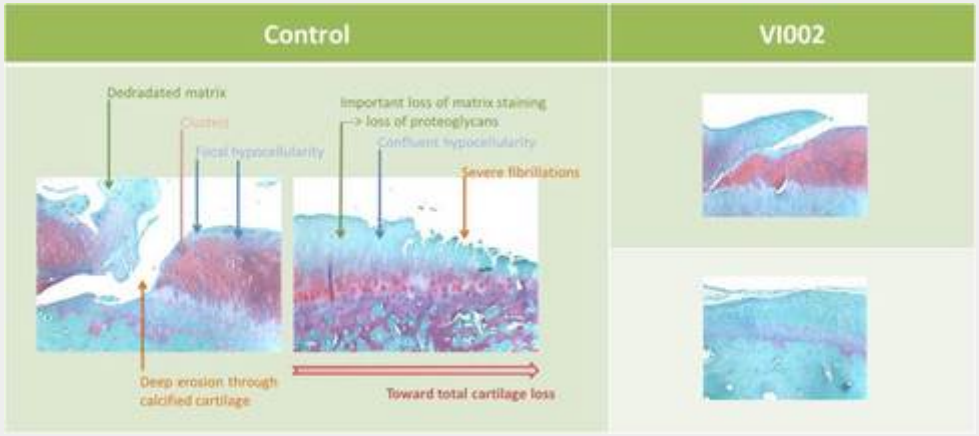

Figure 9: Representative lesion of cartilage in control and VI002 hydrogel groups

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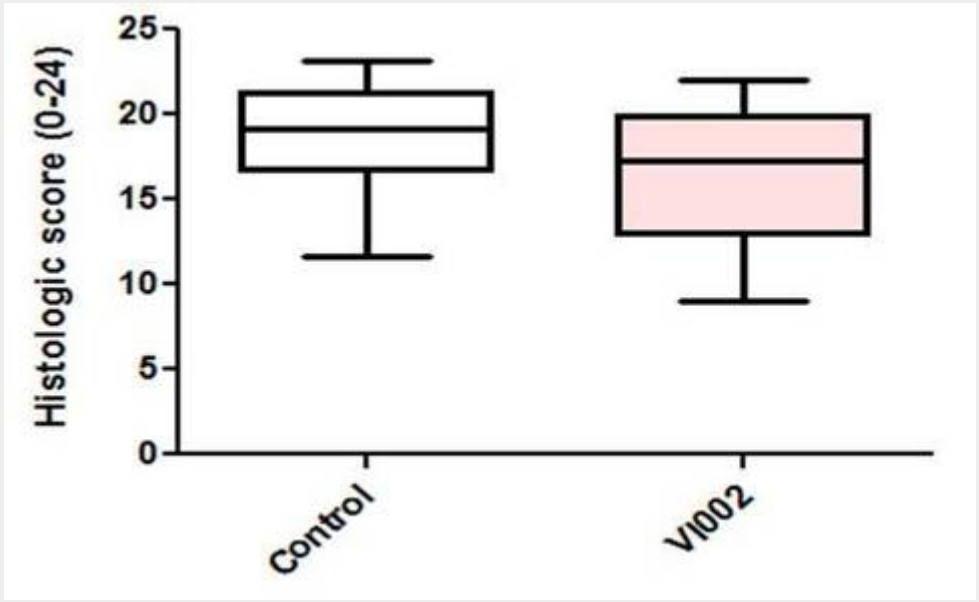

Figure 10: Global score of cartilage in Control and VI002 hydrogel groups

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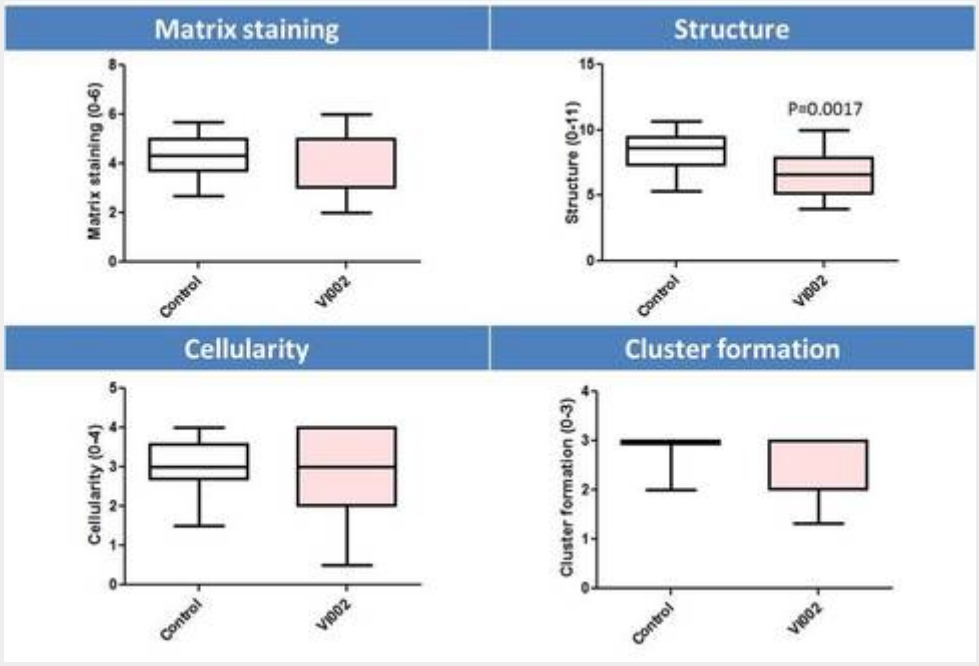

Figure 11: Detailed score of cartilage

5. Conclusion

VI002 hydrogel administered intra-articularly in rabbit after ACLT surgery was well tolerated. Altogether these results are in favor of a beneficial effect of the treatment on the development of OA. VI002 was indeed able to prevent cartilage degradation and to decrease synovitis. The results confirm the high potential of a chitosan-based hydrogel in preventing OA.

6. References

1. Laverty, S., et al., The OARSI histopathology initiative - recommendations for histological assessments of osteoarthritis in the rabbit. Osteoarthritis Cartilage, 2010. **18 Suppl 3**: p. S53-65.

7. Author Information

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8. Mediafiles

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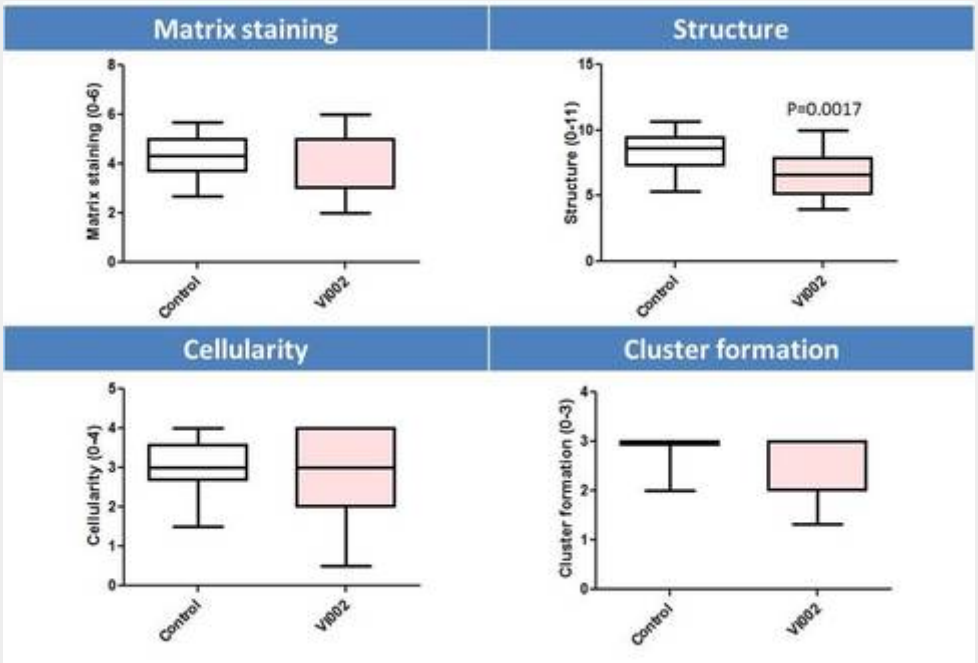

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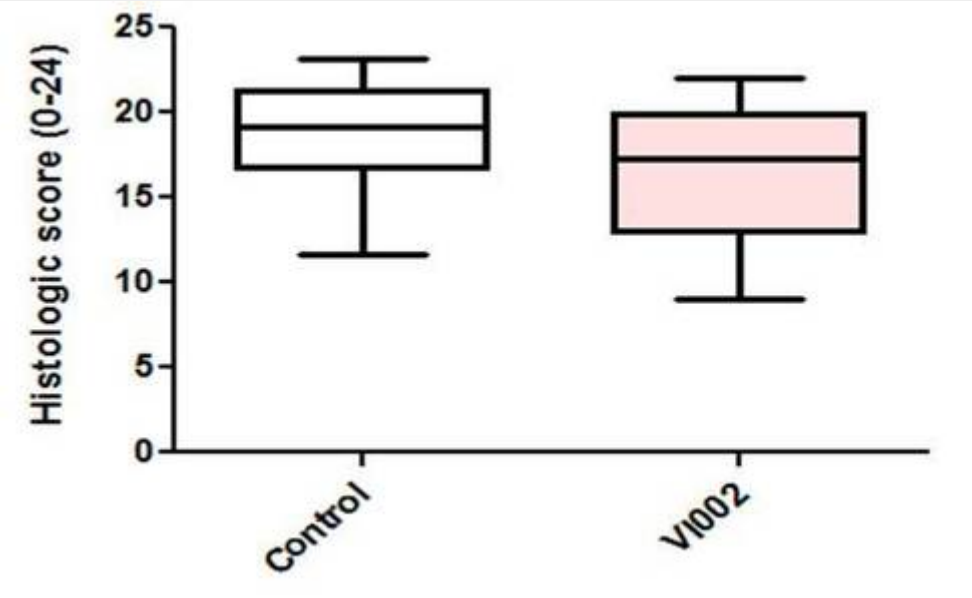

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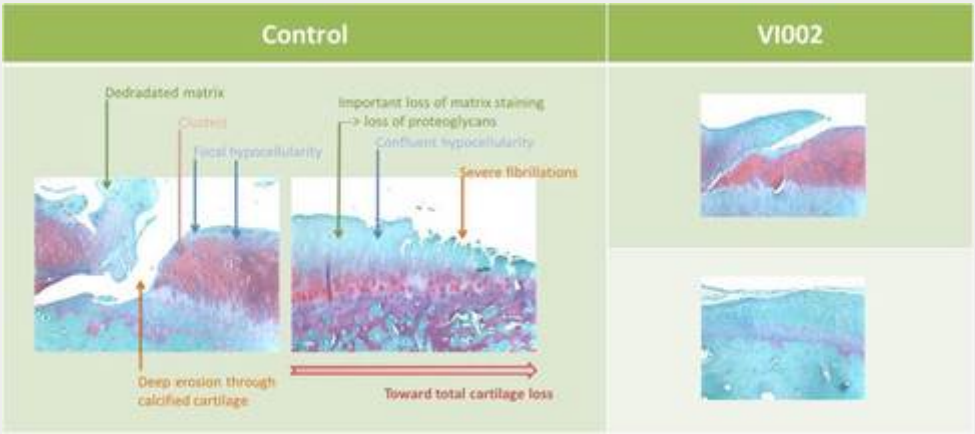

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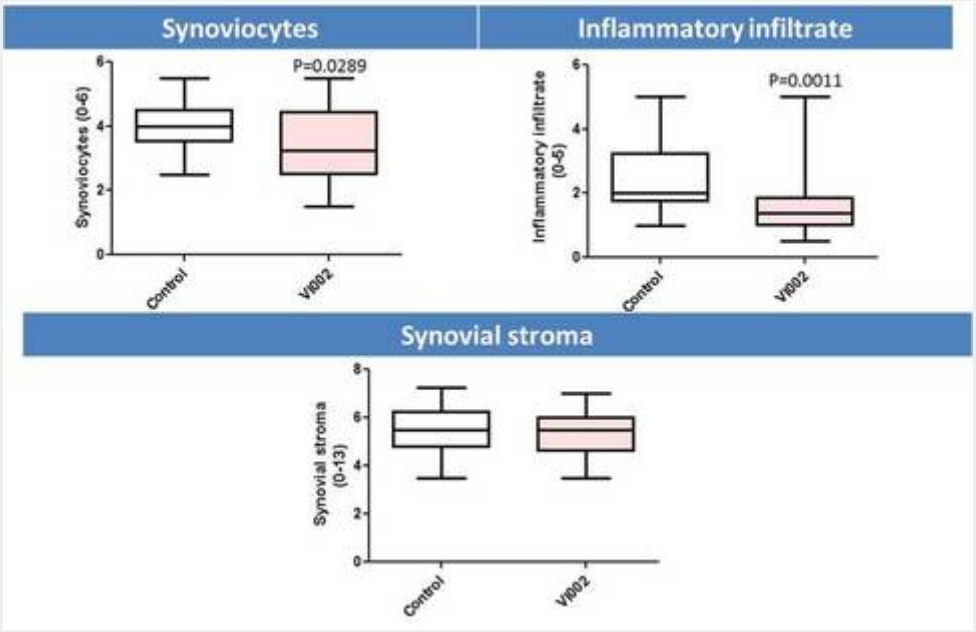

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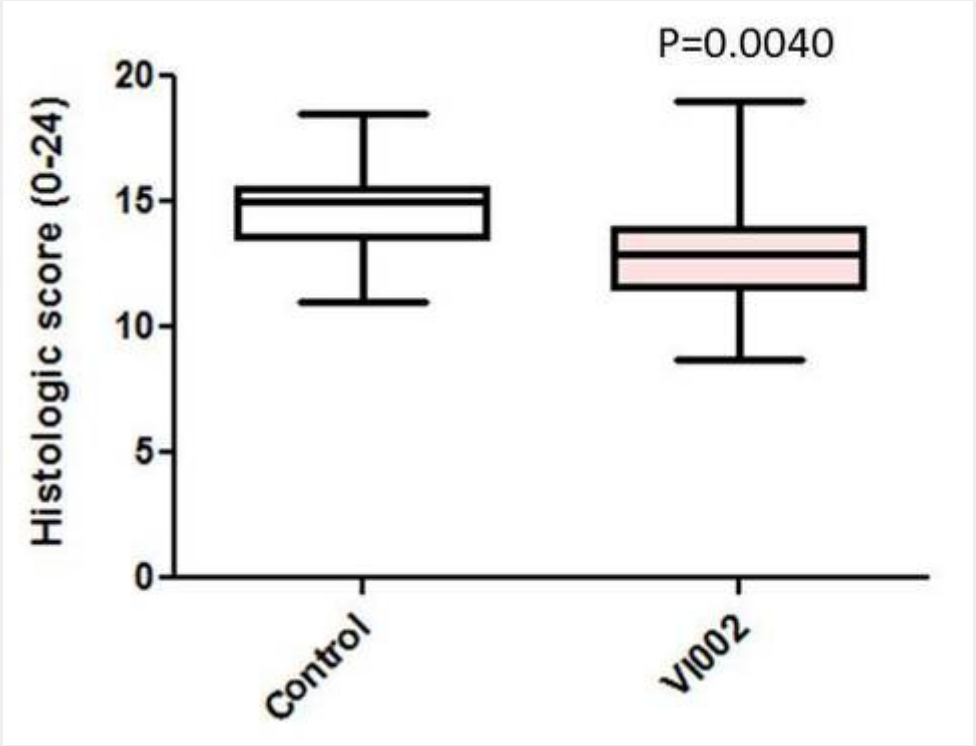

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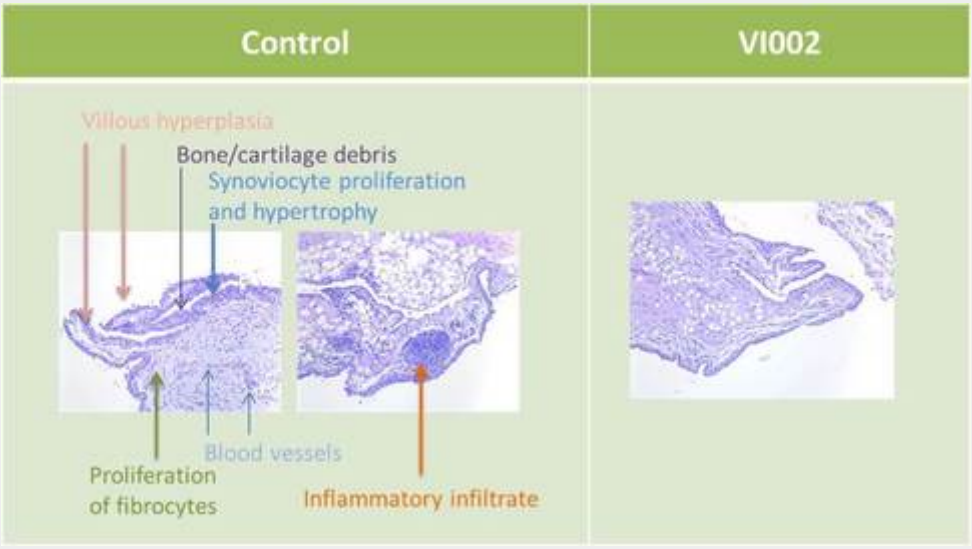

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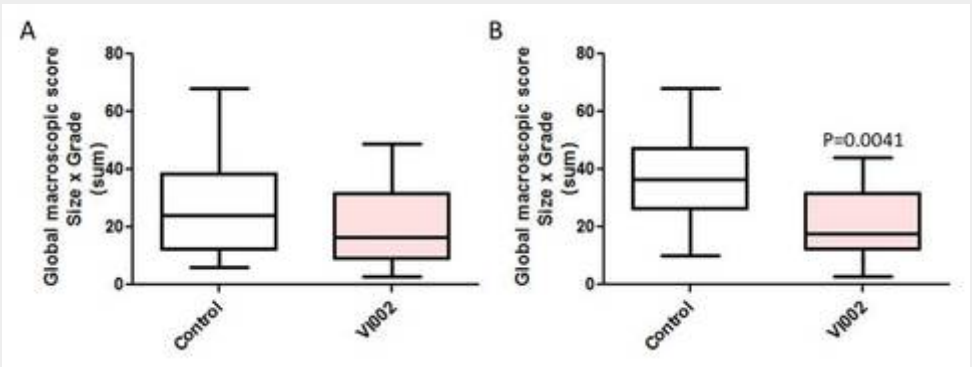

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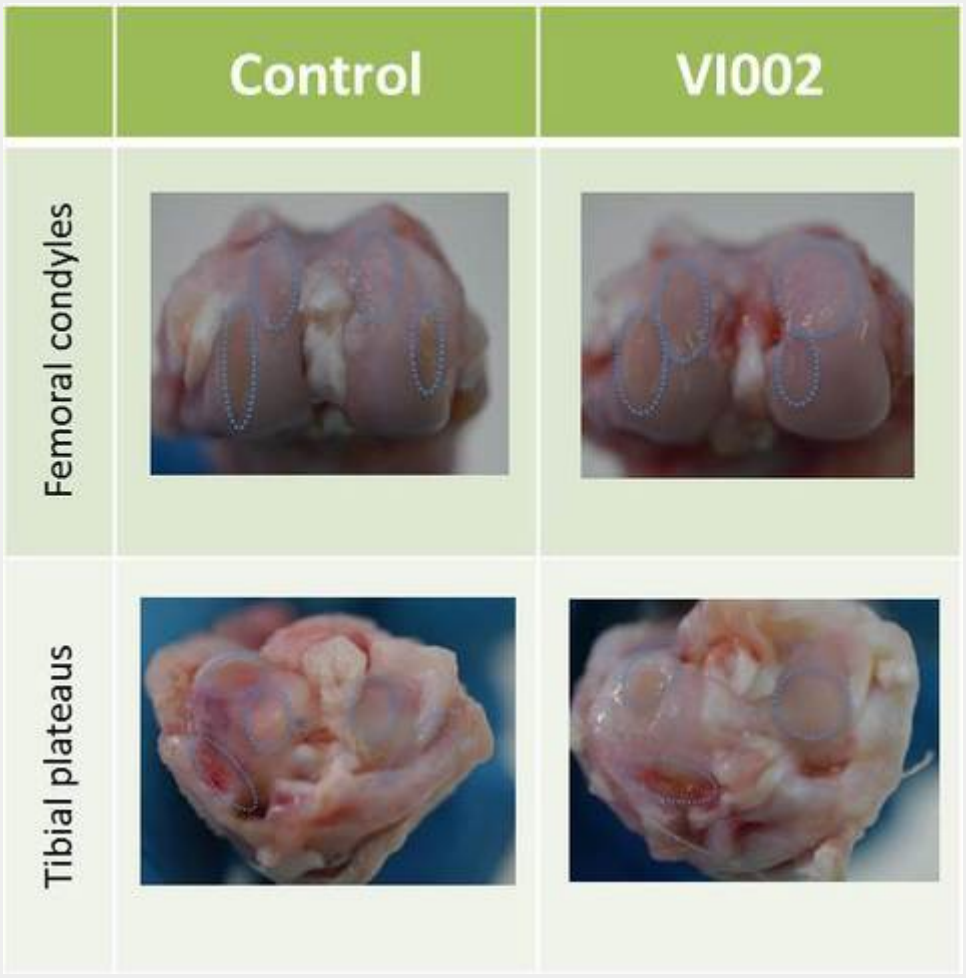

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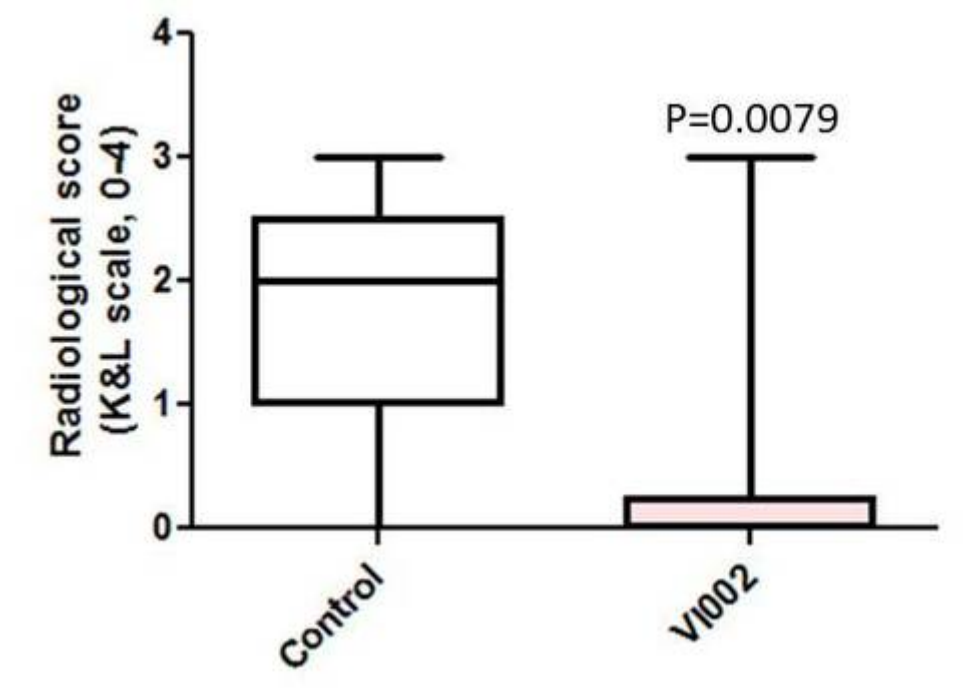

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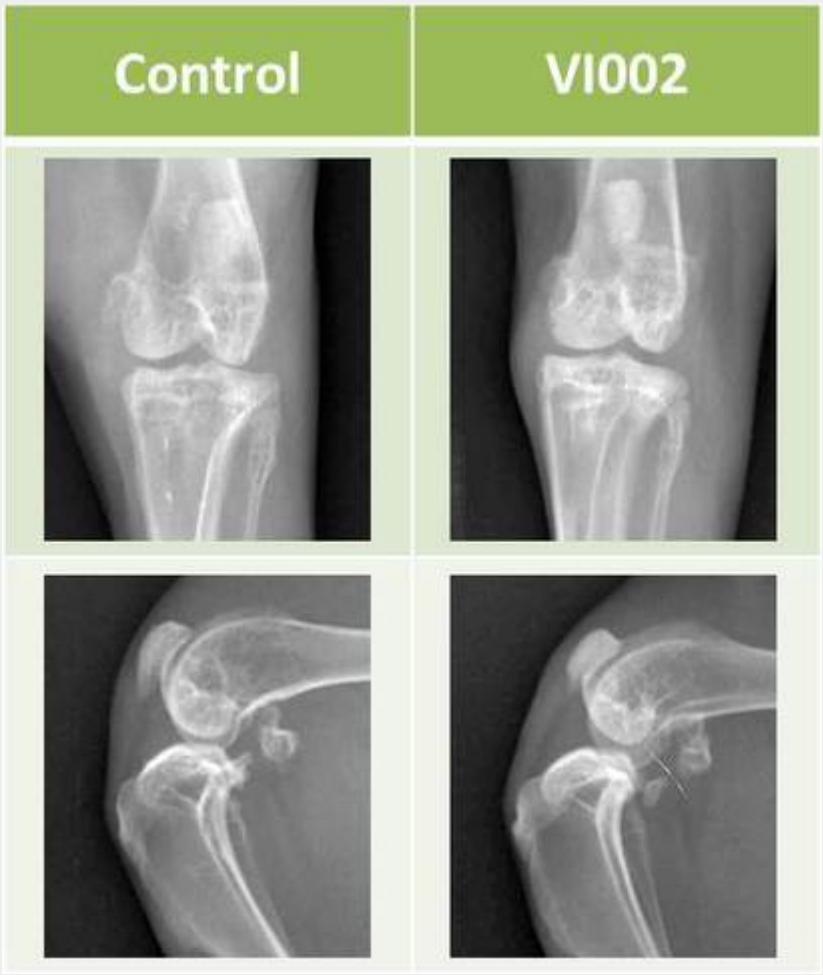

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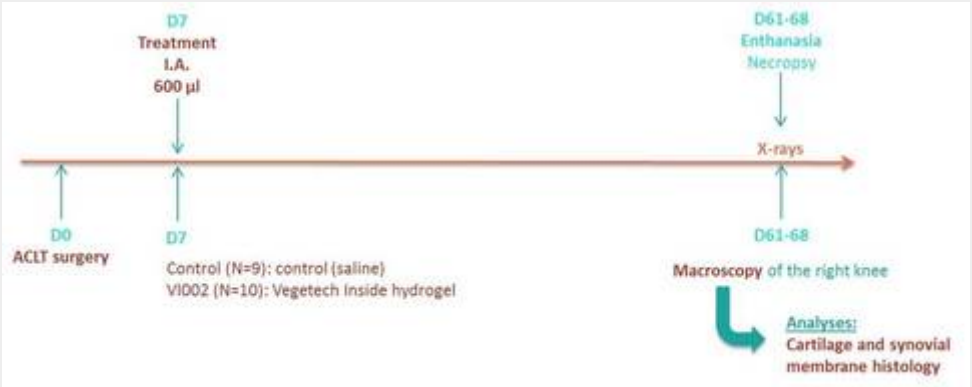

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