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A multi-centre, open label, long-term follow-up study to evaluate the benefits of a new viscoelastic hydrogel (Hymovis®) in the treatment of knee osteoarthritis

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Abstract. – OBJECTIVE: To evaluate the long-term efficacy and safety of Hymovis® in the symptomatic treatment of knee osteoarthritis (OA).

PATIENTS AND METHODS: This is a prospective, multi-center, open label, phase III clinical study. Two intra-articular injections (3 mL) of Hymovis® (8 mg/mL HYADD® 4) were administered 1 week apart at the beginning of the study on day 0 and day 7 and after 6 months from baseline, on day 182 and 189. Follow-up assessment were conducted for 52 weeks. 50 subjects, > 40 years old, with knee OA, with clinical and radiological confirm, complain pain in the target knee were enrolled. The variables considered were: WOMAC questionnaire, Joint Space Width (JSW), OMERACT OARSI responder criteria, EQ-5D questionnaire, rescue medication consumption.

RESULTS: After the injections of Hymovis®, pain perceived by the patient when walking on a flat surface (WOMAC A1 score) significantly improves at the end of the study respect to the baseline. WOMAC stiffness, physical function and total score significantly improve during the study since 3 months after treatment, and it is maintained up to the end of the study ($p < 0.001$). By the x-ray analysis of knee, a radiological progression of OA was observed in the 26% of patients at the end of the study, while 88% of patients result to be responder to the therapy classified as per OMERACT-OARSI criteria. The EQ-5D weighted index increased significantly, against baseline, at each study time point ($p < 0.001$). Investigator's and patient's global assessment of the disease measured by the VAS both show a marked improvement in patient's health conditions.

CONCLUSIONS: Results from this study confirm that Hymovis® alleviate the knee pain since the first treatment cycle. The patients treated with two cycles of intra-articular injections of Hymovis® have a progressive pain reduction that is maintained up to one year after the treatment start with improve of all the scores considered in this study. Hymovis® is effective and safe in symptomatic treatment of painful knee OA.

Key Words:
Knee, Osteoarthritis, Hyaluronic acid, Viscosupplementation.

Introduction

Osteoarthritis (OA) is a common degenerative musculoskeletal disease, occurring in approximately 10% of people aged 55 years or older. Further, nearly one-third of all adults have radiological signs of OA[1]. The disease reduces the rheological properties of synovial fluid in the various joints affected, increasing the susceptibility of the articular cartilage to damage. Pain and functional disability caused by OA can have a major negative impact on daily living, socio-economic activity, and quality of life (QoL). OA is one of the main causes of locomotor disability and is a significant burden on healthcare services[2]. Symptomatic pharmacotherapy for OA primarily consisted of non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular injections of corticosteroid. However, the associated side effects of these agents generated interest in developing alternative treatment modalities[3,4]. One of such modality is viscosupplementation, in which intra-articular injection of hyaluronic acid (HA) is

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used to restore the viscoelastic properties of synovial fluid[5]. Hyaluronic acid (HA) plays a major role in the soft and hard-wearing nature of articular cartilage and for maintenance of the viscoelastic and lubricating properties of the synovial fluid[6,7]. Intra-articular HA is widely used in the treatment of degenerative joint diseases on the basis of its effectiveness in cartilage lubrication and protection as synovial fluid supplement. The rheological profile of intra-articular viscosupplementation is fundamental for the quality and duration of mechanical performance. In order to achieve enhanced rheological properties and a prolonged resistance to biodegradation in the articular cavity, however, chemical modification of HA structure is needed. Most of the highly viscoelastic HAbased products are obtained through cross-linking techniques, causing a strong increase of the biopolymer molecular weight but raising new issues of biocompatibility and safety in the clinical environment.

The finding that HA concentration and chain length are both reduced in patients with OA of the knee led to the hypothesis that decreased viscosity of the synovial fluid may cause the wear and pain associated with the disease. This formed the initial premise for the development of intra-articular (IA) injections of HA as a fluid replacement treatment termed ''viscosupplementation'', as therapy for the treatment of pain associated with OA[8].

The newly-developed HA of Fidia Farmaceutici S.p.A., Abano Terme, Italy, is Hymovis®, that consists of an 8 mg/mL aqueous formulation of HYADD®4 a novel, partially hydrophobic, reticulated (i.e. not chemically cross-linked) HA derivative with low modification degree[9]. Hymovis® is a viscoelastic hydrogel for intraarticular use with enhanced resistance to in vivo degradation and whose clinical safety and effectiveness has already been proven.

The anti-catabolic and anti-inflammatory effect of HYADD®4 on IL-1stimulated human osteoarthritic chondrocytes and synoviocytes is enhanced when compared to unmodified HA of the same MW[10]. Furthermore, the biosynthesis of HA is up-regulated by addition of HYADD®4 to synoviocytes *in vitro*, as well as with HA itself[11]. These results have been confirmed by the outcome of efficacy studies in animal models of osteoarthritis, in which Hymovis® proved to be effective in reducing the signs and symptoms of the pathology and in the protection of cartilage[11,12].

Patients and Methods

This is a prospective, multi-centre, open label, 12 months follow-up, clinical study. The clinical study was begun after approval by the Local Ethics Committee.

The study was conducted in accordance with the principles contained in the declaration of Helsinki, Appendix X of directive 93/42 EC on medical devices and GCPs defined by the following standards: ICH Topic E 6 - Guidelines for Good Clinical Practice.

EN ISO 14155-1:2011: Clinical Investigation of medical devices for human subjects.

At the Inclusion Visit (V0), prior to beginning any screening procedures, the nature, aim, procedures and possible risks of the study were explained by the clinical investigator and provided in writing to each patient.

After a screening period, patients underwent to 4 intra-articular injections of Hymovis® 3 mL syringes: two weekly injections at the inclusion (Baseline and Week 1) and two weekly injections after 6 months from the first cycle of treatment (Week 26 and Week 27).

Patients were evaluated at baseline and at Weeks 1, 13, 17, 26, 27, and 52.

Study Endpoints

The primary efficacy outcome was to evaluate the long-term benefits of 2 cycles of treatment with 3-mL intra-articular (IA) injection of 8 mg/mL of Hymovis®, on pain measured by WOMAC pain (A) subscore over 52 weeks.

Secondary outcomes included:

– Knee OA in term of pain, stiffness and physical function measured respectively by WOMAC A1 score, WOMAC stiffness (B) subscore, WOMAC physical function (C) subscore over 52 weeks;
– OA progression assessed by measures of the knee Joint Space Width (JSW) at week 52; patient's response to therapy according to OMERACT-OARSI criteria at weeks 13, 17, 26 and 52 (Table I);
– Quality of life assessed by changes from baseline in the EQ-5D Index at Week 52– Assumption of rescue medication measured as daily consumption;
– Patient's and investigator's global assessment of patient's health status assessed as changes from baseline in PTGA and COGA over 52 weeks:
– Treatment local tolerability and safety.

Table I. Objectives of the study.

Primary objective
• To evaluate the long-term benefits of 2 cycles of treatment with 2 x 3 mL intra-articular injections of 8 mg/mL of Hymovis each, on pain due to knee OA
Secondary objectives
• To evaluate the long-term benefits of 2 cycles of treatment with 2 x 3 mL intra-articular injections of 8 mg/mL of Hymovis each, on: – knee OA in term of stiffness and physical function – patient's response to therapy – Quality of Life – Assumption of rescue medication

The following variables were assessed to evaluate the performance of Hymovis® (Table II):

WOMAC questionnaire: the WOMAC pain scale (Section A) including 5 questions, the WOMAC stiffness scale (Section B) including 2 questions and the WOMAC physical function scale (Section C) including 17 questions. In this study, the Likert 3.1 of the WOMAC was used where the patient's response to each of the 24 questions is measured on a 5-point Likert scale with higher scores indicating greater symptom severity (0 = none, 1 = slight, 2 = moderate, 3 = severe and 4 = extreme).

Joint Space Width (JSW): the joint space width evaluated in mm in plain X-ray is the currently optimal recognized technique to evaluate the osteoarthritis structural progression. A X-ray according Rosenberg projection, to measure the JSW, was to be performed at inclusion (if not available within three months from inclusion) and at the final visit. The reliable measurements of JSW require that the patient is positioned as consistently as possible each time an X-ray is obtained and the central X-ray beam must be consistently oriented and centred with respect to the knee each time[13,14]. Although it is known that there are sources of error in these measurements[15] the radiographic JSW is an acceptable method for studies where any changes in cartilage degeneration must be documented. JSW measurements have the advantage that they can be analysed as continuous variables allowing for a broader range of more powerful statistical tests.

OMERACT-OARSI responder criteria: to evaluate the improvement in pain or functionality assessed by the WOMAC sub scores. A responder is defined as a patient with 50% improvement in pain or function and absolute change ³ 20 or improvement in at least 2 of the 3 following areas: pain, physical function and patient's global assessment.

Patient's and Investigator's Global Assessment: patient's and Investigator's Global assessment on how the treated knee affected the patient's status were requested at the baseline visit and at Visits 3, 4, 5 and 7. Both patient and

Table II. Criteria for evaluation.

Performance – WOMAC subscore and total score
• WOMAC A1 question score • Joint Space width • Response to therapy • EQ5D Index • NSAIDs daily intake • PTGA and COGA
Tolerability and vital signs
• Adverse Events • OA signs

investigator made their global assessment on a 0-100 mm VAS where 0 corresponds to 'Not at all and 100 to 'Extremely'.

EQ-5D (Quality of Life Measure) questionnaire: the patient was asked to indicate his/her health state by ticking in the box against the most appropriate statement in each of the 5 dimensions. This decision resulted in a one-digit number expressing the level selected for that dimension. The digits for five dimensions was combined in a five-digit number describing the respondent's health state.

Rescue medication consumption was monitored during the study by means of patient's diary where the patient was asked to record each intake (date and dosage) all over the year.

In order to evaluate the local tolerability of Hymovis® the presence of swelling, tenderness, crepitus, redness/inflammation or effusion, and adverse events have been considered

Study Population

Subjects considered eligible for this clinical trial were male and female with active life style, more than 40 years old, diagnosis of knee OA clinically and radiologically confirmed by American College of Rheumatology (ACR) diagnostic criteria for OA (based on Kellgren-Lawrence grade II-III[16] and X-rays performed according to Rosenberg view) complaining pain in the target knee, reported by a score of 2 or 3 on the first question of the A group in the WOMAC questionnaire.

Patients showing clinically apparent tense effusion of the target knee, or/and significant valgus/varus deformities, or/and ligamentous laxity or meniscal instability, or/and articular diseases of inflammatory or infective aetiology, or/and crystal arthropathy, or/and concomitant severe OA of the hip or other joints, have been excluded.

Sample Size

A sample size calculation was not conducted, as this is a non-comparative study but it was set at 50 patients as a first step investigation of the treatment effect. On the basis of statistical considerations, the sample size of 50 patients was regarded as sufficiently large to allow even small differences in the primary outcome parameter to emerge.

Statistical Analysis

To analyse data from WOMAC questionnaire, a total score was calculated for each subscale and a normalised score (0 indicating no symptoms and 100 indicating extreme symptoms) then calculated for each subscale by summing up the total score of each subscale, multiplying it by 100 and dividing by the possible maximum score for the scale. A total score has been created by combining the 3 subscales; this total score was converted into a normalized Index out of 100 as described in the WOMAC user's handbook[17]. Knee OA progression was based on the changes from baseline of the JSW: patients for whom a change in JSW > 0.5 mm was measured at final visit were considered in radiological progression for OA.

To classify patients as responder to the therapy, the OMERACT-OARSI criteria were considered. Basing on WOMAC sub scores measured at week 52, patients were classified responder if one of the following occurred:

– High improvement in pain or in function > 50% and absolute change > 20, or
– Improvement in at least 2 of the three following:
– Function > 20% and absolute change > 10
– Patient's global assessment > 20% and absolute change > 10.

The EQ-5D Index was calculated following the guidelines of each instrument.

Differences in the average daily consumption of rescue medication over 52 weeks was evaluated between period 0-3 weeks and the consecutive visits.

Number and percentages of patients reporting the event were counted and reported both for all adverse events and for adverse product reactions.

Results

Fifty (50) outpatients were enrolled into the study and entered the screening period between 31st of August 2010 and 31st of July 2012 (Table III). Patients were recruited from 3 Centres in Italy; Clinical Orthopaedics and Traumatology, S. Matteo Polyclinic Pavia; U.O. Arthroscopy and Knee Surgery II, Galeazzi Orthopaedic Institute, Milan and U.O. Orthopedics and Traumatology, Hospital of Giussano. One of the enrolled patient failed to pass the screening and 49 patients were treated.

Presence of knee OA was radiologically assessed in all 49 patients before the inclusion in the study and it was extended to the media tibio-fem-

Table III. Demographic and other baseline characteristics.

	Mean (±SD)
Height (cm)	168 (± 8)
Weight (kg)	76 (± 13)
BMI (kg/m^2)	26.7 (±8)
	N (%)
Sex	
Male	26 (53.1)
Female	23 (46.9)
Ethnic group	
Caucasian	48 (98.0)
Black	1 (2.0)
Smoking habit	
Never	27 (55.1)
Current	10 (20.4)
Ex-smoker	12 (24.5)

oral compartment in 96% of patients and lateral tibio-femoral compartment in 54% of cases.

A slight prevalence of Kellgren-Lawrence grade 2 was recorded (55%) against grade 3 (45%) and the joint space width presented a mean value of 4.6 mm in the treated knee against a mean value of 6.8 mm of the contra-lateral knee.

All patients complained pain due to OA, 61% morning stiffness and 57% crepitus on motion. The most frequent signs of knee OA were joint tenderness (24%) and swelling (16%). No patients presented flush or inflammation, while effusion was reported only by one patient (Table IV).

Primary Efficacy Outcome WOMAC Pain Subscore

The WOMAC pain subscore presents, at baseline, a mean value of 46.5 (range: 40-70, SD ± 7.65) that decreases to 24.7 (range: 5-45, SD = ± 11.15) 3 months after the first cycle (V3), to 20.1 (range: 0-60, SD =± 13.6) 6 months after the first cycle and reaches the value of 17.6 (range: 0-55, SD = ± 13.85) 6 months after the second cycle (V7).

Since the assumption of normal distribution of WOMAC Pain Score is not satisfied for each of the 5 WOMAC measurements, the non-parametric Friedman test has been conducted and, as significant, changes from baseline has been assessed by Wilcoxon Signed Rank test, correcting the level as per Bonferroni (a/5=0.001). A statistical significant difference against baseline was evidenced by the Wilcoxon Rank test at each time point.

Table IV. Baseline characteristics: ACR Criteria for OA at inclusion (n =49).

Pain	Yes	N	49
		%	100.0%
	No	N	0
		%	0.0%
	Total	N	49
		%	100.0%
Age <= 50 years	Yes	N	41
		%	83.7%
	No	N	8
		%	16.3%
	Total	N	49
		%	100.0%
Morning stiffness	Yes	N	30
		%	61.2%
	No	N	19
		%	38.8%
	Total	N	49
		%	100.0%
Crepitus on motion	Yes	N	28
		%	57.1%
	No	N	21
		%	42.9%
	Total	N	49
		%	100.0%
Joint tenderness	Yes	N	12
		%	24.5%
	No	N	37
		%	75.5%
	Total	N	49
		%	100.0%
Swelling	Yes	N	8
		%	16.3%
	No	N	41
		%	83.7%
	Total	N	49
		%	100.0%
Redness/inflammation	Yes	N	0
		%	.0%
	No	N	49
		%	100.0%
	Total	N	49
		%	100.0%
Presence of effusion	Yes	N	1
		%	2.0%
	No	N	48
		%	98.0
	Total	N	49
		%	100.0%
Knee arthrocentesis	Yes	N	0
		%	.0%
	No	N	1
		%	100.0%
	Total	N	1
		%	100.0%

WOMAC A1 Score

Question A1 of the WOMAC questionnaire refers to the pain perceived by the patient when walking on a flat surface. At baseline 39 patients

(80%) complained a moderate pain, 9 patients (18%) a severe pain and only one patient an extreme pain. At the end of the study 19 (39%) patients did not complain any pain when walking on a flat surface, 21 (43%) a slight pain and only 8 (18%) patients complained a moderate pain. A significant change form baseline was evidenced by the McNemar-Bowker test ($p < 0.001$). Particularly, 18 patients (37%) passes from a moderate at baseline to a slight pain at the end of the study, and 14 (29%) patients reporting a moderate pain at baseline did not complain any pain at the end of the study (Figure 1).

WOMAC, Stiffness, Physical Function Score and Total Score

Stiffness, physical function and total score present very similar trends during the study (Figure 2); mean and standard deviation of each score at 3, 6 months from baseline and 6 months at the second cycle are summarized in the Table V.

JSW

Joint space width was assessed to evaluate the radiological progression of the knee OA: a change in JSW (from inclusion till the end of the trial) more then 0.5 mm identifies a progression of OA. The JSW in the target knee passes form a mean value of 4.6 mm (range: 1.1-8.7, SD ± 1.61) at baseline to a mean value of 4.2 (range: 0.0-8.3, SD = ± 1.77) at the end of the study and the percentage of patients reporting a Kellgren-Lawrence grade of 2 increases to 58% at the end of the study from the 55% registered at baseline.

A radiological progression of knee OA was observed in 26% of patients. However, it should be pointed out that, as per criteria used for analyzing missing values, all patients not providing the JSW measure at the end of the study were considered in radiological progression.

EQ5D Index

A significant increase in the EQ-5D weighted index, against baseline, was observed at each study time point: the weighted Index value passes form a mean value of 0.62 (SD = ± 0.18) at baseline to a mean value of 0.73 (SD = ± 0.07) at 3 months, to a mean value of 0.75 (SD = ± 0.12) at 6 months and to a mean value of 0.79 (SD = ± 0.11) at the end of the study ($p < 0.001$ at the Wilcoxon signed ranks test).

Response to Therapy

Patient's response to therapy are assessed according to OMERACT-OARSI criteria: a responder is defined as a patient with 50% improvement in pain or function and absolute change 20 or improvement in at least 2 of the 3 following areas: pain, physical function and patient's global assessment.

The percentage of responder patients at 3 months is 80% and increases up to 86% and 88% at 6 and 12 months, respectively (Table VI).

NSAIDs Daily Intake

The average daily consumption of paracetamol (mg/day) was calculated on all patients, irrespective of their recurrence to the rescue medication.

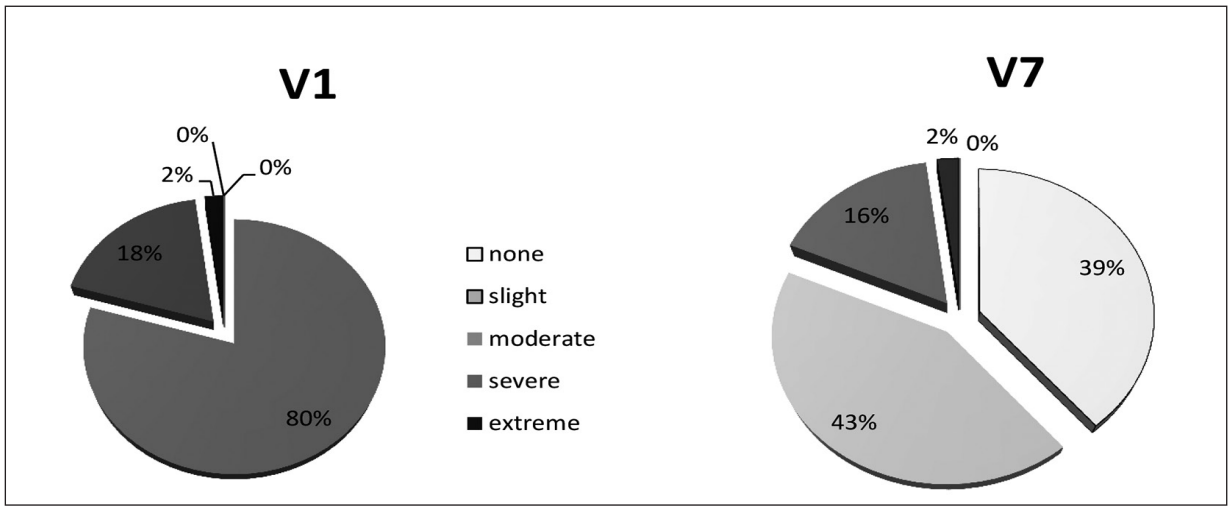

Figure 1. Pain perceived by patients (%). Changes from baseline (n = 49).

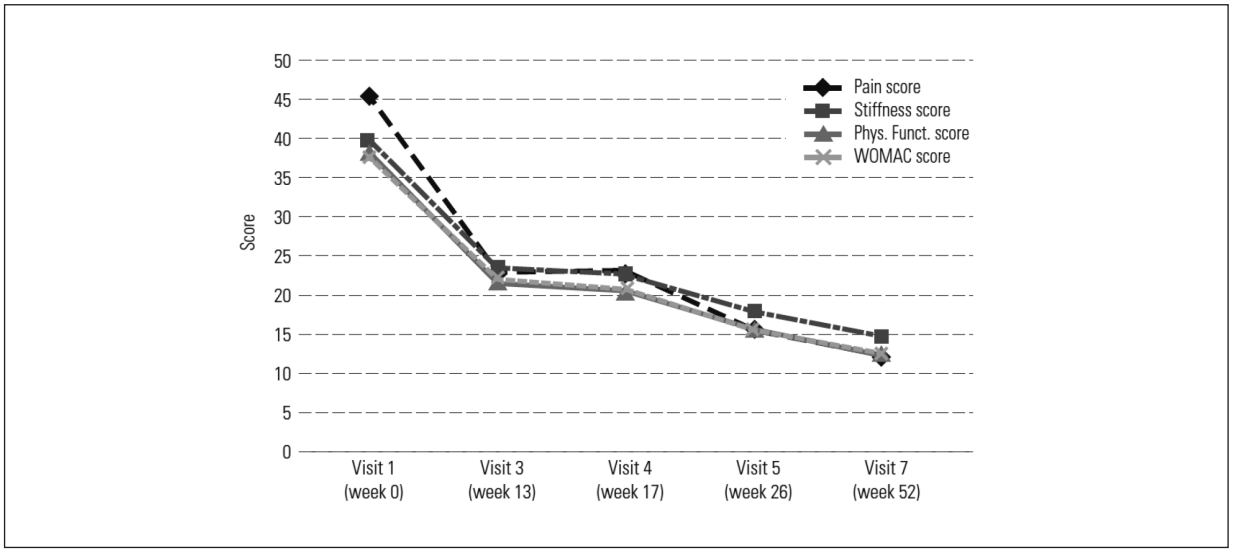

Figure 2. WOMAC normalized score at study visits.

The 0-13, 14-17, 18-26 and 27-52 weeks period was calculated starting from the date of V1 (first injection).

Data on NSAIDs daily intake did not allow to evidence any significant difference among study periods ($p > 0.05$ at the Wilcoxon Signed Ranks test) as too few patients recurred to the rescue medication.

PTGA and COGA

Investigator's and patient's global assessment of the disease measured by the VAS both show a marked improvement in patient's health conditions. Since the assumption of normal distribution of PTGA VAS and COGA VAS is satisfied, the parametric test MANOVA has been used to analyze the changes from baseline. For both parameters a statistical significant difference resulted at each study time point against baseline ($p < 0.001$). Furthermore, the multiple comparisons analysis evidences that an increasing overall improvement of the disease was perceived by the patient at each study point ($p < 0.001$) with the exception of V4 (at 4 months) that did not result to be different from the V3 (at 3 months).

Safety Analysis

A total of 76 adverse events were reported during the study on 28 patients (57%). 4 events were considered related to the product and consisted in an increase of knee pain all were of mild intensity. The most frequent adverse events were mild or moderate headache (14% of events) mild flu (12%) and mild or moderate back pain (6%).

During the course of the study 7 serious adverse events were reported. The causality with Hymovis was excluded in all cases.

Discussion

Osteoarthritis (OA) of the knee joint, that causes pain to the patient, is the most common reason

Table V. Stiffness, physical function score and total score at baseline and after 3, 6, 12 months.

	V1 (mean ± SD)	V3 (mean ± SD)	V5 (mean ± SD)	V7 (mean ± SD)
Stiffness	41.1 ± 19.09	26.0 ± 14.62	23.0 ± 17.92	17.6 ± 16.72
Physical function	40.4 ± 12.63	23.2 ± 10.56	20.1 ± 12.25	17.9 ± 12.51
Total function	41.2 ± 10.9	23.8 ± 10.27	20.3 ± 12.46	17.8 ± 12.45
Total	41.2 ± 10.9	23.8 ± 10.27	20.3 ± 12.46	17.8 ± 12.45

Table VI. Patients response to therapy as per OMERACT-OARSI criteria (n=49).

V3 *vs.* V1	Not responder	N (%)	10 (20.4)
	Responder	N (%)	39 (79.6)
	Total	N (%)	49 (100)
V4 *vs.* V5	Not responder	N (%)	9 (18.4)
	Responder	N (%)	40 (81.6)
	Total	N (%)	49 (100)
V5 *vs.* V1	Not responder	N (%)	7 (14.3)
	Responder	N (%)	42 (85.7)
	Total	N (%)	49 (100)
V7 *vs.* V1	Not responder	N (%)	6 (12.2)
	Responder	N (%)	43 (87.8)
	Total	N (%)	49 (100)

Included 8 responder patients prematurely discontinued.

behind functional disability that leads to lower the quality of life in old age people. Age is the strongest predictor of knee OA and, therefore, increasing age and extended life expectancy will result in a greater occurrence of the disease. Genetic predisposition, inflammation, and immune system activity can also play a role in abnormal cartilage changes[18]. The management of knee OA is broadly divided into non-pharmacological, pharmacological, and surgical treatments. Pharmacological management includes control of pain and improvement in function and quality of life. However, pharmacological agents used to treat the symptoms of knee OA are associated with various side effects. A good alternative to the pharmacological therapy is the intra-articular injection of hyaluronic acid[19]. Injecting HA into the joint aimed not only to restore the mechanical properties of the cartilage and synovial fluid, but also to achieve certain biological effects. Administration of intra-articular HA leads to anti-inflammatory, anabolic, and analgesic activity within synovial joints. Documented anti-inflammatory properties include inhibition of phagocytosis[20], mitogen-induced stimulation, and adherence[21].

There are several HAs with different molecular weight (MW) available on the market. Recent data suggests that clinical effectiveness of HA is MW-dependent. In particular, has been showed that HA preparations with a MW of 500-730 kDa penetrate better the synovial membrane and stimulate the synthesis of higher level of endogenous HA in the synovial fluid compared with HA products with a larger MW.

The viscoelasticity and intraarticular residence time of Hymovis® are greatly increased compared to that of native HA solutions and are equivalent to that of the main cross-linked HA-based products, though not being a cross-linked derivative. Moreover, when the mechanical performance is measured in stress conditions (e.g. after repeated mechanical shocks), Hymovis® hydrogel shows a self-healing behavior. This feature is closely related to the 3dimensional arrangement of HYADD®4 in the hydrogel system[9] and is one of the main claims of the technological innovation for the new product (MO.RE.® Technology).

The aim of this study was to investigate the performance of Hymovis®, a CE class III medical device consisting of Hyaluronic Acid, on knee OA. Furthermore, following the recommendations of European Commission (EC) post-marketing guidance for medical devices, the study aims to provide evidence of long-term benefit in patients with knee OA, especially regarding tolerability and improvement of the quality of life.

Results from this research involving 49 patients confirm that Hymovis® alleviate the knee pain since the first treatment cycle. The patients treated with two cycles of intra-articular injections of Hymovis® have a progressive pain reduction that is maintained up to one year after the treatment start. Similarly, patient's health status as well as the quality of life significantly ameliorate after the first treatment cycle and up to one year after, as evidenced by the variation in WOMAC stiffness, the physical function, the total score and the EQ5-D indices. The improvement against baseline is perceived both by the patient and by the physician as resulting from the analysis of the measures of the global assessment of the disease.

The good performance of Hymovis® is also confirmed by the OMERACT OARSI responder criteria that evidences a total of 88% of responder patients at 12 months from treatment start and by the significant increase of the joint space width

registered at 12 months, considering that a reduction of the joint space width greater than 0.5 mm in long-term trials reflected a clinical relevant change in the OA progression[22,23], and that in this study over a 1-year period the joint space width was reduced of 0.2 mm.

The adverse events considered related to the study product were few and all consisted in an increase of the knee pain. All serious adverse events reported during the 12 months study were unrelated to the received treatment.

The limit of our trial is the small cohort of patients. Double blind randomized controlled trial on bigger cohort of patients would be useful to improve the evidence of effectiveness of this treatment.

Conclusions

The good clinical performance and safety of Hymovis® in the treatment of pain due to knee OA, proven by past studies, is confirmed by the results of this study. The new hydrogel has proven to be effective also in ameliorating the stiffness, physical functioning, joint space width and patient's quality of life, producing long-term benefits.

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Conflict of Interests

The Authors declare that they have no conflict of interests

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