SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Hyaluronic Acid, Intra-articular

Device Trade Name: HYMOVIS® ONE

Device Procode: MOZ

Applicant's Name and Address: Fidia farmaceutici S.p.A.
Via Ponte della Fabbrica, 3/A 35031
Abano Terme Padova, Italy

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P150010/S005

Date of FDA Notice of Approval: April 9, 2025

Priority Review: Not applicable

The original PMA (P150010) for HYMOVIS® was approved on August 28, 2015, and is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and to simple analgesics, *e.g.*, acetaminophen. The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted for a new treatment regimen from the currently approved regimen of two 3mL injections given one week apart (HYMOVIS®), to a single injection regimen of 4mL (HYMOVIS® ONE). The change in injection regimen does not affect the indications for use/intended use of the device, nor the formulation or injection technique. While Fidia intends to have both products available for use, they are not intended to be used together.

II. INDICATIONS FOR USE

HYMOVIS® ONE is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and to simple analgesics (e.g., acetaminophen).

III. CONTRAINDICATIONS

- Do not administer to patients with known hypersensitivity (allergy) to hyaluronate preparations.
- Do not administer to patients with known hypersensitivity (allergy) to gram positive bacterial proteins.

- Do not administer to patients with infections or skin diseases in the area of the injection site or joint.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the HYMOVIS® ONE labeling.

V. DEVICE DESCRIPTION

HYMOVIS® ONE is a sterile, non-pyrogenic, viscoelastic hydrogel contained in a single-use syringe. HYMOVIS® ONE is based on an ultra-pure, chemically modified hyaluronan (HYADD4®), obtained using a proprietary process to increase viscosity, elasticity and residence time without chemical crosslinking. This results in a hyaluronan similar to the hyaluronan found in the synovial fluid present in the human joint. The hyaluronan in HYMOVIS® ONE is derived from bacterial fermentation.

HYMOVIS® ONE has a nominal sodium hyaluronate concentration of 8mg/ml, dissolved in physiologic saline. It is supplied in a 5.0ml syringe containing 4.0ml of HYMOVIS® ONE. The contents of the syringe are sterile and non-pyrogenic. HYMOVIS® ONE is prepared by modification of hyaluronic acid (HA) with a proprietary process resulting in a highly viscous and elastic hydrogel. The HA is derived from bacterial fermentation (*Streptococcus equi*). The HA used in HYMOVIS® ONE is the same grade and specification as that is used in HYMOVIS® (P150010). HYMOVIS® ONE has the identical formulation as HYMOVIS®, but is provided as a 4.0ml volume for one injection rather than a 3.0ml volume intended for two separate injections. The device is administered by a single injection regimen under aseptic conditions.

Each pre-filled syringe of HYMOVIS® ONE contains 32mg of the principal component, Hyaluronan (also known as HYADD4®) in a 4.0ml volume, which equals to a concentration of 8mg/ml Hyaluronan. This is the same concentration of Hyaluronan as in HYMOVIS® (P150010), which contains 24mg of Hyaluronan in a 3.0ml volume per syringe.

Each pre-filled syringe with 4.0ml of HYMOVIS® ONE contains the following amount of each component:

Principal component:	
Hyaluronan (HYADD4®)	32mg
Other components:	
Sodium chloride	34mg
Disodium hydrogen phosphate dodecahydrate	1.8mg
Sodium dihydrogen phosphate dihydrate	0.44mg
Water for injection	q.s. to 4ml

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative therapies to HYMOVIS® ONE may include conservative non-pharmacological therapy and simple analgesics (e.g., acetaminophen), nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular injection of corticosteroid, avoidance of

activities that cause joint pain, exercise, weight loss, physical therapy, and removal of excess fluid from the knee. For patients who have failed the above treatments, surgical interventions such as arthroscopic surgery and total knee replacement are also alternative treatments.

VII. MARKETING HISTORY

HYMOVIS® ONE is CE-marked and has been commercially available in Austria, Czech Republic, France, Germany, Italy, Spain, and Slovakia since September 1, 2021. HYMOVIS® ONE has not been withdrawn from marketing in any country for any reason related to safety or effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects, *e.g.*, complications, associated with the use of this type of device and, in general, associated with intra-articular injections when used for the treatment of pain in knee osteoarthritis, include:

- Infection
- Arthralgia (knee pain)
- Arthrosis
- Joint (knee) disorder
- Joint (knee) swelling
- Joint (knee) effusion
- Joint (knee) stiffness
- Pain in limb
- Tendonitis
- Paraesthesia
- Phlebitis
- Pruritus
- Injection site erythema
- Injection site edema
- Injection site pain
- Injection site reaction
- Arthropathy
- Baker's cyst
- Bursitis
- Localized osteoarthritis
- Aggravated osteoarthritis
- Immune response

Incidences of rash, headache, dizziness, chills, hives, nausea, muscle cramps, peripheral edema, and malaise have also been reported in association with intra-articular injections.

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NON-CLINICAL STUDIES

This supplement presented clinical data to support a new treatment regimen of the HYMOVIS® formulation. Because the technological characteristics and indications for use for HYMOVIS® ONE are identical to those of HYMOVIS®, no new preclinical testing was required. Data presented in the original PMA (P150010) are considered applicable to address the preclinical requirements of HYMOVIS® ONE, and a summary of the preclinical studies conducted in support of the original PMA is available in the SSED for P150010 on the CDRH website.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the use of a single 4ml injection of HYMOVIS® ONE for treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and to simple analgesics (e.g., acetaminophen) in Italy. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between September 16, 2020, and June 21, 2024. The database for this Panel Track Supplement reflected data collected through the dates listed above and included 351 patients who were enrolled and 347 who were treated. There were 18 investigational sites in Italy.

The study of the safety and effectiveness of HYMOVIS® ONE for the treatment of pain from osteoarthritis of the knee was a multicenter, randomized, double-blind (patients and evaluators), active comparator-controlled, non-inferiority study to determine whether HYMOVIS® ONE was non-inferior to MONOVISC® at 12 Weeks post-treatment using a primary effectiveness performance endpoint of Change from Baseline (CFB) in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) LK3.1 A1 Pain subscale score (walking on a flat surface) at Week 12.

The control group was MONOVISC®, a marketed single injection hyaluronic acid labeled for the identical intended use and population.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the study was limited to patients who met the following inclusion criteria:

   - female and male, age ≥ 40 and ≤ 75 years
   - BMI ≥ 20 and < 35 kg/m^2
   - Tegner score ≥ 3
   - diagnosed with primary knee OA of the medial or lateral femorotibial compartment with symptoms at screening and for at least 3 months prior to screening according to American College of Rheumatology (ACR) criteria and who have not responded to conservative non-pharmacologic treatment or simple analgesic regimens

- Kellgren-Lawrence grade 2 or 3 in the target knee
- at least one X-Ray of the target knee taken at screening or within 6 months prior to the screening
- OA pain intensity at both the screening (V0) and the baseline (V1) visit pain intensity in the target knee of 2 - 3 and in the contralateral knee 0 as measured by the WOMAC LK3.1 A1 Pain subscale (walking on a flat surface)
- willingness to discontinue oral and topical analgesics, including NSAIDs, and accept "rescue" paracetamol as the only medicine for joint pain prior to the injection and throughout the study. "Rescue" medication will be discontinued 24 hours before any study visit
- willing and able to comply with study procedures
- able to provide informed consent
- if a female of childbearing potential, must have negative pregnancy test at screening and agree to use a reliable form of contraception throughout the study defined as any of the following:
  - combined hormonal contraception (containing estrogen and progestogen) associated with inhibition of ovulation (oral, intravaginal, transdermal)
  - progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
  - intrauterine device (IUD)
  - intrauterine hormone-releasing system (IUS)
  - bilateral tubal occlusion
  - vasectomized partner
  - sexual abstinence

Patients were <u>not</u> permitted to enroll in the study if they met any of the following exclusion criteria:

- inability to perform a 50-foot walk test
- secondary (post-traumatic) knee OA of the target joint
- K-L radiological grade 1 or 4 in the target knee
- known X-ray findings of acute fractures, severe loss of bone density, avascular necrosis, and /or severe bone or joint deformity in the target knee
- clinically apparent tense effusion of the target knee on examination (determined by either a positive bulge sign or ballottement of the patella (patellar tap))
- osteonecrosis of either knee
- knee joint replacement or arthroplasty of the target knee
- arthroscopy of the target knee in the past 6 months
- osteotomy or surgery of the target or contralateral knee and any other weight-bearing joint that would have interfered with knee assessment
- acute, recurrent synovitis, or any inflammatory conditions in the target knee
- any significant injury to the target knee in the last 6 months (as per Investigator judgment)
- any musculoskeletal condition affecting the target knee that would impair the proper assessment of performance in the target knee as assessed by the Investigator such as:
  - severe varus/valgus deformity (>15°)
  - predominantly patellofemoral pain syndrome
- health condition associated with pain which may interfere with study variables evaluation

- known history or present evidence of conditions which may affect the target knee assessments, *e.g.*, rheumatic disease, lupus arthropathy, infective or metabolic joint diseases; recurrent clinical chondrocalcinosis; crystal arthropathies; osteoarticular pathologies differing from arthrosis; acromegaly; haemochromatosis; Wilson's disease; primary osteochondromatosis; heritable disorders; collagen gene mutations
- gout or calcium pyrophosphate (pseudogout) diseases of the target knee with flare-ups within 6 months prior to screening
- fibromyalgia, pes anserine bursitis, lumbar radiculopathy and/or neurogenic or vascular claudication
- significant anterior knee pain due to diagnosed isolated patellofemoral syndrome or chondromalacia in the target knee
- symptomatic OA of the hips, spine or ankle that interferes with the evaluation of the target knee
- venous or lymphatic stasis in the relevant limb
- history of the following treatments:
  - intra-articular corticosteroids in any joints in the past 3 months
  - systemic (both oral and parenteral) and topical corticosteroids at the target knee in the past 30 and 90 days, respectively
  - topical anti-inflammatory agents and analgesics applied at the target knee in the past 48 hours
  - viscosupplementation with hyaluronic acid or joint-lavage in the target knee in the past 6 months
  - physical therapy started in the past 3 months in the target knee. Subjects having started a physical therapy from more than 3 months can take part in the study
  - change in the dosage of symptomatic slow-acting supplements for OA such as glucosamine, chondroitin sulfate, diacerhein, or other supplements such as avocado or soya extracts, etc. in the last month
  - chronic or recurrent use of narcotic analgesics
- chronic or recurrent use of NSAIDs/analgesics/narcotics due to diseases other than OA of the target knee
- treated with agents which alter the perception of pain such as hypnotics, muscle relaxants, anxiolytics if the intake has started less than 8 days before screening
- history of recurrent severe allergic or immune-mediated reactions or other immune disorders
- vascular insufficiency of lower limbs or peripheral neuropathy severe enough to interfere
- active liver disease
- any clinically significant laboratory values which, based on investigator judgment and subject clinical history, may affect study evaluation
- currently use heparin or anti-vitamin K (e. g. crystalline warfarin) anticoagulant therapy
- infections, wounds, bruising, disease or trauma in the area of the injection site or joint
- suspected or known history of hypersensitivity to paracetamol, lidocaine, hyaluronic acid or to hyaluronate preparations or gram-positive bacterial proteins
- any surgical procedures scheduled in the next 6 months
- have participated in a clinical study or investigation in the last 3 months

- pregnant or lactating women, and women of childbearing potential unwilling to use adequate contraception and conduct a pregnancy test at screening.

2. Follow-up Schedule

The patients participated in the investigation for approximately 28 Weeks (from screening to the last visit). The investigation included a two-Week screening phase (Day-14 to Day -1), a baseline/single treatment visit (Visit (V) 1, Day 0) and a 26-Week follow-up evaluation phase.

At the treatment visit (V1, Day 0), patients received a single injection of HYMOVIS® ONE or MONOVISC®. Baseline and follow-up evaluations were performed by an evaluator blinded to the treatment according to the following schedule: V1 (baseline), V2 (Week 1), V3 (Week 4), V4 (Week 12), and V5 (Week 26).

Evaluations performed at each visit are outlined in Table 1 below. Adverse events and complications were recorded at all visits.

Table 1 Follow-up schedule

Assessments				**Follow-up (26 Weeks)**							
Visits/Phone calls	**Visit 0 (Screening)**	**Phone call ***	**Visit 1 (Baseline and Injection)**	**Phone call**	**Visit 2**	**Phone call**	**Visit 3**	**Phone call**	**Visit 4**	**Phone call**	**Visit 5 End of Investigation /Early termination Visit**
Investigation Week/days/hours	D-14 (-2w) to D-1	48 h before Visit 1	0w (D0)	48 h before Visit 2	1w ± 3 days	48 h before Visit 3	4w ± 3 days	48 h before Visit 4	12w ± 5 days	48 h before Visit 5	26w ± 7 days
Informed Consent	T/E										
Demographics and medical history	T/E										
Physical examination	T/E		T/E								E
Vital signs (heart rate and blood pressure)	T/E		T/E								E
Height	T/E										
Weight	T/E		T/E				E		E		E
BMI	T/E		T/E								
Tegner score	T/E										
K-L radiographic grading[1]	T/E										
Examination of both knee	T/E										
Pregnancy test	T/E										
WOMAC[7] LK3.1 A1 Walking Pain Subscale (24-hour recall)	T/E[2]		E[3]								
Identification of the target knee	T/E										
50-foot walk test	T/E										

Assessments				Follow-up (26 Weeks)							
Visits/Phone calls	**Visit 0 (Screening)**	**Phone call ***	**Visit 1 (Baseline and Injection)**	**Phone call**	**Visit 2**	**Phone call**	**Visit 3**	**Phone call**	**Visit 4**	**Phone call**	**Visit 5 End of Investigation /Early termination Visit**
Investigation Week/days/hours	D-14 (-2w) to D-1	48 h before Visit 1	0w (D0)	48 h before Visit 2	1w ± 3 days	48 h before Visit 3	4w ± 3 days	48 h before Visit 4	12w ± 5 days	48 h before Visit 5	26w ± 7 days
Concomitant Medications/non-pharmaceutical therapies	T/E		T/E		E		E		E		E
Discontinuation of NSAIDs and analgesic	T/E		T/E								
Inclusion/Exclusion criteria	T/E		T/E								
Instruct subject on rescue medication use, dispense paracetamol and deliver subject diary	T/E		E		E		E		E		
Reminder of visit date/time		T/E		E		E		E		E	
Reminder to bring back paracetamol and diary		T/E		E		E		E		E	
Reminder of the need to abstain from paracetamol for 24h prior to the visit		T/E		E		E		E		E	
Review subject diary and reconcile paracetamol			T/E		E		E		E		E
Record use of rescue paracetamol consumption			T/E		E		E		E		E
Examination of the target knee			E		E		E		E		E
Full WOMAC LK3.1 Index (Pain, Function, Stiffness subscales) 24-hour recall			E[4]				E[4]		E[4]		E[4]
PGA			E				E		E		E
SF-12 Quality of Life			E				E		E		E
COGA			E				E		E		E
Aspiration of synovial fluid (volume; microscopic exam[5])			T								
Randomization			T								
Intra-articular Injection			T								
Vital Signs (heart rate and blood pressure) at least 30 Minutes after Injection			T								
AE assessment and recording	T/E		E[6]		E		E		E		E

Assessments				Follow-up (26 Weeks)							
Visits/Phone calls	**Visit 0 (Screening)**	**Phone call ***	**Visit 1 (Baseline and Injection)**	**Phone call**	**Visit 2**	**Phone call**	**Visit 3**	**Phone call**	**Visit 4**	**Phone call**	**Visit 5 End of Investigation /Early termination Visit**
Investigation Week/days/hours	D-14 (-2w) to D-1	48 h before Visit 1	0w (D0)	48 h before Visit 2	1w ± 3 days	48 h before Visit 3	4w ± 3 days	48 h before Visit 4	12w ± 5 days	48 h before Visit 5	26w ± 7 days

E: Evaluator, blinded to investigational treatment, performed all safety and performance assessments.
T: The Treating Physician administered the injection and did not participate in evaluations.
T/E: These tasks could be performed by either Treating Physician or Evaluator.

*Only if Visit 0 (Screening) was performed > 48 hours before Visit 1 (Baseline and Injection)

[1] An X-ray of the target knee was performed at Screening if radiographic images obtained within 6 months of screening were not available
[2] Both target and non-target knee
[3] Only for non-target knee
[4] Target knee
[5] Microscopic exam if infection was suspected (Protocol Appendix 24.7)
[6] Also Device Deficiencies (DDs) were assessed
[7] WOMAC - Western Ontario and McMaster Universities Osteoarthritis Index

3. Clinical Endpoints

a. Safety evaluation

Safety analyses were performed on the safety population, which was defined as all randomized and treated patients. Safety variables included the following:

- Treatment-Emergent Adverse Events (TEAEs).
- Physical examination findings as applicable per study schedule.
- Vital signs as applicable per study schedule.

Adverse Events (AEs) were observed for each subject from the time of informed consent until completion or withdrawal from the study. A TEAE is defined as an AE that occurs on or after the start time of the injection of study treatment through the 26-Week follow-up period. TEAEs were summarized by treatment arm and categorized by severity and relationship to the treatment. A separate analysis was conducted to summarize all serious TEAEs by system organ class (SOC) and preferred term (PT).

b. Effectiveness Evaluation

The objective of the study was to assess the effectiveness and safety of a single injection of HYMOVIS® ONE to relieve pain in the knee in patients with OA of the knee by establishing its non-inferiority to MONOVISC®. To test the non-inferiority of HYMOVIS® ONE compared to the comparator, MONOVISC®, a 95% Confidence Interval (CI) was computed on the ANCOVA-adjusted CFB mean difference at Week 12 to test the following non-inferiority hypotheses:

$H_0: \mu_T - \mu_R \geq \delta$ vs. $H_1: \mu_T - \mu_R < \delta$

where μ_T was the HYMOVIS® ONE mean, μ_R is the MONOVISC® mean, and $\delta = 0.32$ was the non-inferiority margin. If the upper limit of the 95% CI of the least squares means (LSM) difference of Test and Reference at Week 12 is lower than 0.32, then HYMOVIS® ONE is declared as non-inferior to MONOVISC®.

Primary Effectiveness Endpoint

Change From Baseline (CFB) in the WOMAC LK3.1 A1 Pain subscale score (walking on a flat surface) at Week 12.

Secondary Effectiveness Endpoints

The secondary effectiveness endpoints were defined as:

1. The proportion of "Patient Success", *i.e.*, response, in the HYMOVIS® ONE and the MONOVISC® groups, where "Patient Success" is defined by Osteoarthritis Research Society International/Outcome Measures in Rheumatology (OMERACT-OARSI) criteria at Weeks 12 and 26; Patient Success levels of 20%, 30%, 40%, and 50% were compared. The OMERACT-OARSI criteria for response are:

   (1) improvement in pain or physical function ≥ 50% and an absolute change ≥ 20; or

   (2) improvement of ≥ 20% with an absolute change of ≥ 10 in at least two of the following three categories: pain, physical function, and patient's global assessment.

   The algorithm for the definition of "Patient Success" was calculated on standardized WOMAC scores with a range of values from 0 to 100, where 0 represents the best health status and 100 the worst health status.

2. CFB in WOMAC LK3.1 Pain subscale through Week 26.

3. CFB in WOMAC LK3.1 Stiffness subscale through Week 26.

4. CFB in WOMAC LK3.1 Function subscale through Week 26.

5. Changes in Quality of Life through an SF-12 questionnaire at Weeks 4,12 and 26.

6. Patient Global Assessment (PGA) of disease activity and Clinical Observer Global Assessment (COGA) of disease severity measured using a 0-100 Visual Analogue Scale (VAS) as a CFB at Weeks 4, 12 and 26.

7. Rescue medication use (acetaminophen, also known as paracetamol in the EU)

B. Accountability of PMA Cohort

Patient disposition in the study

A total of 351 patients were enrolled in the investigation and 347 of them were randomized to the assigned treatment group: 175 were randomized to treatment with HYMOVIS® ONE and 172 were randomized to treatment with MONOVISC®. Four patients were screening failure.

Overall, 338 patients, 171 (97.7% of randomized) in the HYMOVIS® ONE group and 167 (97.1%) in the MONOVISC® group, competed the investigation, whereas 9 patients, 4 (2.3%) in the HYMOVIS® ONE group and 5 (2.9%) in the MONOVISC® group, prematurely discontinued the investigation.

The patients enrolled were female and male patients ≥ 40 and ≤ 75 years of age and diagnosed with OA of the knee based upon clinical and/or radiographic criteria of the American College of Rheumatology (Kellgren- Lawrence Score II-III) confirmed within three months prior to screening.

As reported in Table 2 below, all randomized patients in both treatment groups were treated and were included in both the SAF and the ITT population. Thirty-seven patients overall, 21 (12.0%) in the HYMOVIS® ONE group and 16 (9.3%) in the MONOVISC® group, had major protocol deviation or did not complete the follow-up at Week 12, and were excluded from the PP population, which comprised 310 patients, 154 (88.0%) in the HYMOVIS® ONE group and 156 (90.7%) in the MONOVISC® group.

Table 2 Population Analysis (n[%])

	HYMOVIS® ONE (n = 175)	**MONOVISC® (n = 172)**	**Not Randomized (n = 4)**
Number of Enrolled Patients	175	172	4
Number of patients in the SAF	175 (100.0%)	172 (100.0%)	0 (0.0%)
Number of patients excluded from the SAF	0 (0.0%)	0 (0.0%)	4 (100.0%)
Not randomized	0 (0.0%)	0 (0.0%)	4 (100.0%)
Number of patients in the ITT population	175 (100.0%)	172 (100.0%)	
Number of patients excluded from the ITT	0 (0.0%)	0 (0.0%)	
Number of patients in the PP population	154 (88.0%)	156 (90.7%)	
Number of patients excluded from the PP	21 (12.0%)	16 (9.3%)	
Adverse Events/SAEs/DDs	0 (0.0%)	0 (0.0%)	
Deviation from protocol procedures	2 (9.5%)	0 (0.0%)	
Device (dosage, dosage regimen, etc.)	0 (0.0%)	0 (0.0%)	
I/E criteria not met	11 (52.4%)	6 (37.5%)	
Informed Consent	3 (14.3%)	0 (0.0%)	

Non permitted medication	3 (14.3%)	6 (37.5%)
Other	3 (14.3%)	3 (18.8%)
Planning/interval between visits not met	3 (14.3%)	4 (25.0%)
Rescue medication (dosage, dosage regimen, etc.)	1 (4.8%)	0 (0.0%)
Week 12 visit not performed	4 (19.0%)	4 (25.0%)

Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a pivotal clinical study of intra-articular hyaluronic acid devices for treatment of pain from osteoarthritis performed in the EU or US. A summary is provided below in Table 3.

There were no important differences between groups with respect to demographic characteristics, except for a higher proportion of females than males in the HYMOVIS® ONE group and a slightly higher proportion of males than females in the MONOVISC® group.

Table 3 Summary of Demographic Data (Safety Analysis Set)

		HYMOVIS® ONE (n = 175)	MONOVISC® (n = 172)
Age (years)	n	175	172
	Mean (SD)	59.4 (8.68)	59.3 (8.38)
	Median	59.0	60.0
	Min / Max	40.0 / 78.0	40.0 / 75.0
	Q1 / Q3	53.0 / 65.0	53.0 / 65.0
Sex			
Male	n (%)	79 (45.1%)	89 (51.7%)
Female	n (%)	96 (54.9%)	83 (48.3%)
Race			
Caucasian	n (%)	174 (99.4%)	171 (99.4%)
Asian	n (%)	0 (0.0%)	0 (0.0%)
Black	n (%)	0 (0.0%)	1 (0.6%)
Other	n (%)	1 (0.6%)	0 (0.0%)
Height (m)	n	174	172
	Mean (SD)	1.70 (0.10)	1.70 (0.09)
	Median	1.69	1.70
	Min / Max	1.48 / 1.99	1.45 / 1.91
	Q1 / Q3	1.63 / 1.76	1.65 / 1.76
Height (inches)	n	174	172
	Mean (SD)	66.80 (3.88)	67.08 (3.49)
	Median	66.34	66.93
	Min / Max	58.27 / 78.35	57.09 / 75.20
	Q1 / Q3	64.17 / 69.29	64.96 / 69.29

		HYMOVIS® ONE (n = 175)	MONOVISC® (n = 172)
BMI (kg/m^2)	n	174	172
	Mean (SD)	26.31 (3.58)	26.58 (3.69)
	Median	25.75	26.11
	Min / Max	19.03 / 34.80	20.20 / 34.96
	Q1 / Q3	23.66 / 28.57	24.06 / 29.10
KL classification			
Grade 2	n (%)	126 (72.4%)	116 (67.4%)
Grade 3	n (%)	48 (27.6%)	56 (32.6%)

Table 4 Summary of Baseline Scores of the Study (Safety Analysis Set) (mean [SD])

	HYMOVIS® ONE (n=175)	MONOVISC® (n=172)
Walking Pain WOMAC A1	2.11 (0.44)	2.16 (0.41)
Pain WOMAC A	8.45(2.83)	8.81(2.67)
Stiffness WOMAC B	3.29 (1.71)	3.53 (1.55)
Function WOMAC C	26.57(11.51)	28.30(11.10)
Tegner activity level - n (%)		
3	88 (50.3%)	85 (49.4%)
4	53 (30.3%)	58 (33.7%)
5	24 (13.7%)	18 (10.5%)

C. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on a randomized controlled cohort of 347 patients available for the 26 Weeks evaluation. The key safety outcomes and overall summary of adverse events (AEs) in the safety population are included in the tables below.

Adverse effects that occurred in the study

The overall randomized study Safety Analysis Set consisted of 347 patients with 175 patients in the HYMOVIS® ONE group and 172 patients in the MONOVISC® group. A total of 219 TEAEs were reported in 51 patients (29.1%) in the HYMOVIS® ONE group, and 348 TEAEs were reported in 58 patients (33.7%) in the MONOVISC® group. None of the TEAEs in either group were serious or led to investigation discontinuation.

TEAEs were categorized by SOC, PT and degree of severity. In the overall Safety Analysis Set, only one patient in both groups experienced TEAEs, which were considered severe - plantar fasciitis in the HYMOVIS ONE® group and influenza

in the MONOVISC® group. All the other TEAEs in both treatment groups were classified as mild or moderate. Severity describes the intensity of a specific event (as in mild, moderate or severe); however, the event itself, may be of relatively minor medical significance. This is not the same as "seriousness" which is based on the patient/event outcome usually associated with events that pose a threat to a patient's life or functioning. Accordingly, none of the reported events were categorized as "serious".

Table 5 Summary of Adverse Events (Safety Analysis Set)

	HYMOVIS® ONE (n = 175) n (%) E	MONOVISC® (n = 172) n (%) E
Patients with at least one AE started before the date of randomization	10 (5.7%) 15	9 (5.2%) 17
Patients with at least one TEAE	51 (29.1%) 219	58 (33.7%) 348
Patients with at least one serious TEAE	0 (0.0%) 0	0 (0.0%) 0
Patients with at least one non-serious TEAE	51 (29.1%) 219	58 (33.7%) 348
Patients with at least one ADE	3 (1.7%) 4	5 (2.9%) 9
Patients with at least one serious ADE	0 (0.0%) 0	0 (0.0%) 0
Patients with at least one non-serious ADE	3 (1.7%) 4	5 (2.9%) 9
Patients with at least one TEAE leading to investigation discontinuation	0 (0.0%) 0	0 (0.0%) 0
Patients with at least one ADE leading to investigation discontinuation	0 (0.0%) 0	0 (0.0%) 0
Patients with at least one TEAEs leading to death	0 (0.0%) 0	0 (0.0%) 0
Patients with at least one ADE leading to death	0 (0.0%) 0	0 (0.0%) 0

n = number of patients, % = observed percentage, E = number of events

Four (4) adverse events relating to the study device (Adverse Device Effect or ADE) occurred in 3 patients (1.7%) in the HYMOVIS® ONE group and 9 ADEs were reported in 5 patients (2.9%) in the MONOVISC® group.

The ADEs in patients in the HYMOVIS® ONE group consisted of metatarsalgia and headache in 1 patient, joint swelling in 1 patient and neck pain in 1 patient. The ADEs in patients in the MONOVISC® group consisted of discomfort, erythema and immunization in 1 patient, 2 episodes of myalgia in 1 patient, 2 episodes of headache in 1 patient, thirst in 1 patient, and joint contracture in 1 patient.

Table 6 Summary of Treatment Emergent Adverse Effects of the Study by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	HYMOVIS® ONE (N = 175) n (%) E	MONOVISC® (N = 172) n (%) E
Patients with at least one ADE	3 (1.7%) 4	5 (2.9%) 9
General Disorders and Administration Site Conditions	0 (0.0%) 0	2 (1.2%) 2

Discomfort	0 (0.0%) 0	1 (0.6%) 1
Thirst	0 (0.0%) 0	1 (0.6%) 1
Musculoskeletal and Connective Tissue Disorders	3 (1.7%) 3	2 (1.2%) 3
Joint Contracture	0 (0.0%) 0	1 (0.6%) 1
Joint Swelling	1 (0.6%) 1	0 (0.0%) 0
Metatarsalgia	1 (0.6%) 1	0 (0.0%) 0
Myalgia	0 (0.0%) 0	1 (0.6%) 2
Neck Pain	1 (0.6%) 1	0 (0.0%) 0
Nervous System Disorders	1 (0.6%) 1	1 (0.6%) 2
Headache	1 (0.6%) 1	1 (0.6%) 2
Skin and Subcutaneous Tissue Disorders	0 (0.0%) 0	1 (0.6%) 1
Erythema	0 (0.0%) 0	1 (0.6%) 1
Surgical and Medical Procedures	0 (0.0%) 0	1 (0.6%) 1
Immunization	0 (0.0%) 0	1 (0.6%) 1

n = number of patients; % = observed percentage; E = number of events

2. Effectiveness Results

Primary Effectiveness Endpoints

The mean score of WOMAC LK3.1 A1 Walking Pain subscale decreased from baseline to Week 12 in both groups. The mean (SD) change from baseline (CFB) to Week 12 was -1.38 (0.82) (median change -2.00, range from -3.00 to 1.00) in the HYMOVIS® ONE group and -1.42 (0.81) (median change -1.00, range from -3.00 to 1.00) in the MONOVISC® group.

An inferential statistical analysis was performed on the primary effectiveness endpoint using the approach of the multiple imputation to address the missing values. The baseline WOMAC LK3.1 A1 Walking Pain, patient's age, and Kellgren-Lawrence (K-L) grade were considered as covariates.

The adjusted means (LSM) were -1.327 and -1.353 for HYMOVIS® ONE and MONOVISC®, respectively. The adjusted means difference was 0.026 [95% CI: -0.1334 to 0.1849]. The difference between the two groups was not statistically significant (p = 0.7486). As the upper limit of the 95% CI of the difference of LSM of Test and Reference at Week 12 was lower than the non-inferiority margin of 0.32, HYMOVIS® ONE resulted to be non-inferior to MONOVISC® (p = 0.0003 in the test for non-inferiority).

At the investigational site level, no statistically significant treatment-site effect was observed (p=0.5669).

The same findings were observed in the analysis performed using roll back and last observation carried forward (LOCF) imputation for missing values, as well as in the PP population: all analyses did not show statistically significant differences between groups and confirmed that HYMOVIS® ONE was non-

inferior to MONOVISC® in the primary effectiveness endpoint. See Tables 8 and 9 below for a summary of the WOMAC LK3.1 A1 Walking Pain subscale from baseline to Week 26. The results of CFB to Week 12 of WOMAC LK3.1 A1 Walking Pain subscale in the PP population were consistent with those observed in the ITT population.

Table 7 Summary of results of WOMAC LK3.1 A1 Walking Pain subscale using multiple imputation (ITT population)

	HYMOVIS® ONE (n = 175)	MONOVISC® (n = 172)
Baseline	2.11 ± 0.44 (N=175)	2.16 ± 0.41 (N=172)
Changes from baseline		
Week 4	-1.19 ± 0.78 (N=175)	-1.19 ± 0.83 (N=172)
Week 12	-1.38 ± 0.82 (N=175)	-1.42 ± 0.81 (N=172)
Week 26	-1.54 ± 0.82 (N=175)	-1.49 ± 0.86 (N=172)

Values are mean ± SD; n = number of patients

Table 8 Summary of results of WOMAC LK3.1 A1 Walking Pain subscale (PP population)

	HYMOVIS® ONE (n = 154)	MONOVISC® (n = 156)
Baseline	2.10 ± 0.31 (N=154)	2.17 ± 0.38 (N=156)
Changes from baseline		
Week 4	-1.20 ± 0.74 (N=154)	-1.21 ± 0.81 (N=156)
Week 12	-1.38 ± 0.78 (N=154)	-1.46 ± 0.77 (N=156)
Week 26	-1.57 ± 0.74 (N=154)	-1.53 ± 0.84 (N=156)

Values are mean ± SD; n = number of patients

Secondary Effectiveness Endpoints

Patient success (OMERACT-OARSI)
Patient success was achieved at Week 12 in 152 HYMOVIS® ONE patients (86.9%; 95% CI, 80.9-91.5%) and in 140 MONOVISC® patients (81.4%; 95% CI, 74.8-86.9%) and at Week 26 in 151 HYMOVIS® ONE patients (86.3%; 95% CI, 80.3- 91.0%) and in 147 MONOVISC® patients (85.5%; 95% CI, 79.3-90.4%). The difference between groups was not statistically significant.

CFB in WOMAC LK3.1 pain subscale
The mean score of WOMAC LK3.1 Pain subscale decreased from baseline to any post-treatment timepoint in both groups. The mean (SD) change from baseline to Week 4 was -4.16 (2.91) in the HYMOVIS® ONE group and -4.28 (3.28) in the MONOVISC® group; the mean (SD) change from baseline to Week 12 was -5.16 (3.34) in the HYMOVIS® ONE group and -5.13 (3.60) in the MONOVISC® group; and the mean (SD) change from baseline to Week 26 was -5.54 (3.61) in the HYMOVIS® ONE group and -5.30 (3.88) in the MONOVISC® group. The

comparison between groups showed that the adjusted mean difference between the HYMOVIS® ONE group and the MONOVISC® group was -0.091 (95% CI: -0.7228 to 0.5407) at Week 4, 0.262 (95% CI: -0.8977 to 0.3735) at Week 12, -0.508 (95% CI: -1.1395 to 0.1243) at Week 26, and -0.287 (95% CI: - 0.6534 to 0.0795) in the overall investigation period. The comparison between groups did not show statistically significant differences at any post-baseline time point and in the overall investigation period.

CFB in WOMAC LK3.1 stiffness subscale

The mean score of WOMAC LK3.1 Stiffness subscale decreased from baseline to any post-treatment time point in both treatment groups. The comparison between groups did not show statistically significant differences at any post-baseline time point and in the overall investigation period, and the same was true for the extent of the mean decrease from baseline to any post-baseline time point of WOMAC LK3.1.

CFB in WOMAC LK3.1 function subscale

The mean score of WOMAC LK3.1 Function subscale progressively decreased from baseline to any post-treatment timepoint in both treatment groups. The comparison between groups did not show statistically significant differences at 4 and 12 Weeks post-treatment. At Week 26 the mean (SD) change from baseline was -16.26 (12.03) in the HYMOVIS® ONE group and -15.24 (13.68) in the MONOVISC® group with an adjusted means difference between the HYMOVIS® ONE group and the MONOVISC® group of -2.244 (95% CI: -4.3487 to -0.1384). The comparison between groups showed a statistically significant difference between groups was observed at 26 Weeks post-treatment ($p = 0.0367$) in favor of the HYMOVIS® ONE group.

Short-Form (SF)-12 questionnaire

physical component summary (PCS)

The mean score of PCS progressively improved from baseline to any post-treatment timepoint for both groups. There were no statistical differences between the groups at any post-treatment timepoint. The mean change from baseline

- to Week 4 was 3.83 (7.20) in HYMOVIS® ONE patients and 4.58 (7.25) in MONOVISC® patients
- to Week 12 was 4.77 (7.77) in HYMOVIS® ONE patients and 5.29 (8.04) in MONOVISC® patients
- to Week 26 was 6.29 (7.79) in HYMOVIS® ONE patients and 5.76 (8.54) in MONOVISC® patients

mental component summary (MCS)

The mean score of MCS improved from baseline to any post-treatment timepoint for both groups. There were no statistical differences between the groups at any post-treatment timepoint. The mean (SD) change from baseline

- to Week 4 was 1.52 (7.50) in HYMOVIS® ONE patients and 1.60 (7.85) in MONOVISC® patients
- to Week 12 was 1.92 (8.98) in HYMOVIS® ONE group and 2.47 (8.19) in MONOVISC® patients
- to week 26 was 1.76 (8.78) in HYMOVIS® ONE group and 2.07 (9.12) in MONOVISC® patients.

Patient Global Assessment (PGA) of disease activity and of Clinical Observed Global Assessment (COGA) of disease severity

The mean score of PGA of disease activity and of COGA of disease severity progressively improved from baseline to any post-treatment timepoint for both groups, with similar improvements observed in both groups. The comparison between groups did not show statistically significant differences at any post-treatment timepoint and in the overall investigation period for both endpoints. Similar results were also observed for the two groups at any post-treatment timepoint with respect to in improvements ≥ 30%, ≥ 40% and ≥ 50% from baseline.

Use of rescue medication (acetaminophen)

The number of patients that used rescue medication was 134 (76.6%) in the HYMOVIS® ONE group and 136 (79.1%) in the MONOVISC® group. The comparison between groups of total amounts of rescue medication used was not statistically significant. A similar proportion of patients in the two groups used rescue medication.

3. Subgroup Analyses

   The following baseline characteristics were evaluated for potential association with safety and effectiveness outcomes: sex, age (by decade), and site. In both treatment groups, no important differences by sex and age class were observed in primary and secondary endpoints and in all subscales. This suggests that elderly patients had similar benefit from treatment to those observed in younger patients. There was also no evidence of important differences between sites in mean decrease from baseline to Week 12 of WOMAC LK3.1 A1 Pain subscale. The distribution of TEAEs by age range did not show an increase of risk of TEAEs in patients aged 70-80 years compared to the other age classes.

4. Pediatric Extrapolation

   In this premarket application, existing clinical data were not leveraged to support approval of a pediatric patient population.

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included eighteen principal investigators. One of the eighteen clinical investigators had disclosable financial interests/arrangements (significant payment of other sorts) as defined in sections 54.2(a), (b), (c), and (f). The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. The information provided does not raise any questions about the reliability of the data.

XII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

No supplemental clinical information was used to support the determination of safety and effectiveness.

XIII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Orthopedic and Rehabilitation Devices Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The analysis of effectiveness showed the following:

- The mean score of WOMAC LK3.1 A1 Walking Pain subscale (primary effectiveness endpoint) decreased from baseline to Week 12 to a similar extent for both treatment groups. HYMOVIS® ONE was non-inferior to MONOVISC® at Week 12 in all methods of analysis (multiple imputation, roll back and Last Observation Carried Forward (LOCF) imputation, and Mixed Model for Repeated Measures (MMRM)), and in both the ITT and the PP population.

- The comparison between the two treatment groups for changes from baseline to Week 26 of WOMAC LK3.1 A1 Walking Pain subscale based on the ANCOVA model showed that HYMOVIS® ONE was non-inferior to MONOVISC® also at Week 26.

- The results of WOMAC Pain, Stiffness and Function showed improvements from baseline to any post-baseline time point (as well as in the overall investigation period) in both treatment groups for all subscales. The comparison between the two treatment groups did not show statistically significant differences, except for a difference between the two treatment groups at Week 26 in the Function subscale, due to a greater improvement in the HYMOVIS® ONE group compared to the MONOVISC® group. The proportion of patients with a percent reduction from baseline ≥30%, ≥40% and ≥50% was comparable in the two treatment groups at any post-baseline time point for all subscales.

- A similarly high proportion of patients in both treatment groups achieved success (based on OMERACT-OARSI first and second criterion) at Week 12 and at Week 26.

- The results of quality of life assessed by means of SF-12 version 2 questionnaire showed improvement of both Physical Component Summary (PCS) and Mental Component Summary (MCS) from baseline to any post-baseline time point in both treatment groups, with no statistically significant differences between groups.

- The mean score of PGA of disease activity and of COGA of disease severity

progressively improved from baseline to any post-baseline time point in both treatment groups, with no significant differences between groups.

- A similar proportion of patients in the two treatment groups used rescue medication during the investigation, and the mean total amount of rescue medication used during the investigation was also similar between the two groups.

- No important differences by gender or by age range were observed at the primary and secondary endpoint, or in rate of TEAEs, thus suggesting that elderly patients and younger patients had similar benefit from treatment and similar low risk of adverse effects.

B. Safety Conclusions

The risks of the device are based on the nonclinical laboratory studies, animal studies and clinical studies conducted to support PMA approval as described above. Treatment with both HYMOVIS® ONE and MONOVISC® were well tolerated. The rate of patients with TEAEs was similar between the two groups (29.1% in the HYMOVIS® ONE group and 33.7% in the MONOVISC® group). None of the TEAEs in either group were serious or led to investigation discontinuation. All patients with TEAEs completed the entire post-treatment observational period. The safety data provides reasonable assurance of the safety of HYMOVIS® ONE for the treatment of knee pain due to OA in patients who have failed to respond adequately to conservative non-pharmacological therapy and simple analgesics (e.g., acetaminophen).

C. Benefit-Risk Determination

The probable benefits of the device are based on the data collected in a clinical study as described above to support PMA approval. The data support that one injection of HYMOVIS® ONE provides clinically meaningful benefits for reducing pain and improving the joint function for patients with osteoarthritis of the knee. The probable risks of the device are low based on the low adverse event rate as discussed in Section X.D.1 Safety Results above. The safety data demonstrated minimal or negligible risks and therefore provided reasonable assurance of safety for the product to support the conclusion that the benefits outweigh the risks of possible adverse events relating to the study device.

Patient Perspectives

While the clinical study summarized above included patient reported outcome assessments, e.g., WOMAC Pain scores, WOMAC Stiffness scores, WOMAC Function subscale scores, no patient perspective information was included as part of the demonstration of safety and effectiveness. The lack of this information would not alter the outcomes from the study or the proposed recommendation that HYMOVIS® ONE was found to be non-inferior to MONOVISC® in the treatment of knee pain due to osteoarthritis in patients who have failed to adequately respond to conservative non-pharmacological therapy and simple analgesics (e.g., acetaminophen).

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this product when used in accordance with the indications for use. The clinical data support the safety and effectiveness of a single injection regimen of 4ml of HYMOVIS® ONE. Results from this noninferiority comparison of HYMOVIS® ONE and MONOVISC® provide valid scientific evidence of reasonable assurance of the safety and effectiveness of HYMOVIS® ONE for the treatment of knee pain due to osteoarthritis in patients who have failed to adequately respond to conservative non-pharmacological therapy and simple analgesics (e.g., acetaminophen).

XV. CDRH DECISION

CDRH issued an approval order on April 9, 2025.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XVI. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVII. REFERENCES

Not applicable