SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Hyaluronic Acid, Intra-articular

Device Trade Name: HYMOVIS®

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

Date of FDA Notice of Approval: August 28, 2015

Priority Review: N/A

II. INDICATIONS FOR USE

HYMOVIS® 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 in cases of present infections or skin diseases in the area of the injection site to reduce the potential for developing septic arthritis.

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

HYMOVIS® is a proprietary hyaluronic acid (HA) based visco-supplementation intended for the treatment of pain in patients with osteoarthritis (OA) of the knee who have failed conservative non-pharmacological therapy and simple analgesics. The device is administered by a two injection regimen under aseptic conditions.

HYMOVIS® has a nominal sodium hyaluronate concentration of 8 mg/mL, dissolved in physiologic saline. It is supplied in a 5.0 mL syringe containing 3.0 mL of HYMOVIS®. The contents of the syringe are sterile and non-pyrogenic. Hymovis is prepared by modification of hyaluronic acid with a proprietary process resulting in highly viscous and elastic hydrogel. The HA is derived from bacterial fermentation (Streptococcus equi). The HA used in HYMOVIS® is the same grade and specification that is used in HYALGAN® (P950027).

Each pre-filled syringe with 3 mL of HYMOVIS® contains the following:

Principal component:

Hyaluronan (HYADD4®)	Concentration: 8 mg/mL

Other components:

Sodium chloride	25.50 mg
Disodium hydrogen phosphate dodecahydrate	1.35 mg
Sodium dihydrogen phosphate dihydrate	0.33 mg
Water for injection	to 3 mL

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative therapies to HYMOVIS® 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® is CE-marked since 2009, and has been available in the European Union since 2011. HYMOVIS® is currently marketed globally. HYMOVIS® 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

Below is a list of the potential adverse effects (e.g., complications) associated with the use of this device and, in general, associated with intra-articular injection devices for the treatment of pain in osteoarthritis of the knee.

- 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 PRECLINICAL STUDIES

HYMOVIS® underwent extensive preclinical testing program including biocompatibility in accordance with the requirements of ISO 10993-1, Biological Evaluation of Medical Devices and was found biocompatible for its intended use.

A. Laboratory Studies

The key laboratory studies are briefly summarized in Table 1 below.

Table 1: Summary of Key Laboratory Studies

Count	Report Title	Purpose / Standard	Result
1	Determination of Rheologic Properties of Synovial Fluid in the Presence of gel	Rheological property changes after extrusion through an 18 and 21 G needle. Rheologic behavior of normal and pathological synovial fluid in the presence and absence of product.	No effect on rheological properties after extrusion through the needle. Addition of product to pathologic synovial fluid resulted in improvement of its viscoelastic properties

2	Evaluation of effects on impact induced death of chondrocytes	Ability of product to preserve cartilage cell viability in response to impact loading.	Ratio of impact induced cell degradation was shown to be the same as for healthy synovial fluid.
3	Evaluation of the lubrication of articular cartilage	Frictional coefficients under normal physiological conditions	Product provides superior boundary lubrication.
4	Study on the Effects of the product formulation on Cell Cultures	Effect on cell viability.	Increases the proliferation of cultured human chondrocytes. Data confirmed that the formulation is not toxic to chondrocytes, and that significant effect on cell survival is demonstrated.
5	Cytotoxicity Study using the ISO Elution Method	To determine the potential for cytotoxicity in HYADD4-G (8 mg/mL) in an in vitro biocompatibility study. ISO 10993: Biological Evaluation of Medical Devices, Part5: Tests for Cytotoxicity; in vitro methods	Under the conditions of this study, the 1X MEM test extract showed no evidence of causing cell lysis or toxicity.
6	Mutagenicity: AMES Test of HYADD4-G (5 mg/mL), Batch RS 073/03	To evaluate the mutagenic potential of HYADD4-G (5 mg/mL) under the bacterial reverse mutation test (Ames) ISO 10993: Biological Evaluation of Medical Devices, Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity	Under the conditions of this study, the test article was not toxic and not mutagenic in the tested species.
7	Genotoxicity: In Vitro Chromosomal Aberration Study in Mammalian Cells (Extract)	To detect chromosome structural changes using Chinese Hamster Ovary (CHO) cells.	Under the conditions of the assay the test article extract was not considered genotoxic to CHO cells in the presence or absence of S9 metabolic activation.

8	Mammalian Erythrocyte Micronucleus Test	To evaluate the clastogenic potential of the test article as measured by its ability to induce micronucleated polychromatic erythrocytes in mouse bone marrow	Under the conditions of this study a single intraperitoneal administration of the formulation did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in bone marrow. The product was concluded negative in the micronucleus test.

B. Animal Studies

The key animal studies are briefly summarized in Table 2 below.

Table 2: Summary of Key Animal Studies

Count	Report Title	Purpose / Standard	Result
1	Studies on the Effects of Two Hyaluronan Preparations (HYALGAN®) on the Progression of Gait Changes in an Animal Model of Osteoarthritis	Efficacy of HYADD4-G treatment on OA in an established sheep OA model after induced bilateral meniscetomy.	When compared to placebo treated joints, and to pre-injection values, there was an evidence of reduction in joint pain and improvement in joint movement while walking.
2	NAMSA Rabbit Antibody Responses: HYALGAN®-F, HYADD4- G, and Streptococcus Equi	To determine antibody responses for HYALGAN®-F, HYADD4-G and Streptococcus Equi (SE).	This study confirms the HYALGAN®-F and HYADD4-G ELISA data. No antibody increase against HYALGAN®-F or HYADD4-G is determined in either the test or control animals. The increase in SE antibodies titer is not different in control and test animals, demonstrating that treatment with HYADD4-G (hyaluronic acid of fermentative origin) is not responsible for antibody increase.

3	Thirteen (13) Week Toxicity Study in the Rat by Intraperitoneal Route	To evaluate the toxicity risk by intraperitoneal route in the Sprague-Dawley rat during a 13 week period. ISO 10993 Standard Biological Evaluation of Medical Devices, Part 11: Tests for systemic toxicity.	No signs of toxicity
4	USP and ISO Modified Systemic Toxicity Study, Solution	To evaluate HYADD4-G (8 mg/mL) for systemic toxicity. ISO 10993: Biological Evaluation of Medical Devices Part 11:	Under conditions of this study there was no mortality or evidence of systemic toxicity from the test article injected into the mice. The test article met the test requirements.
5	Evaluation of the Local Tolerance of HYADD4 Gel (Treatment for Osteo-Arthrosis) following Repeated Intra- Articular Injection in the Rabbit Knee	To evaluate local tolerance of HYADD4-G of treatment of OA following repeated intra-articular injections in the rabbit knee. ISO 10993: Biological Evaluation of Medical Devices Part 6:	No sign of pathological changes were noted in the articular cartilaginous tissue or attached bone tissue. There was no statistical difference between product and control.
6	ISO Maximization Sensitization Study - Solution	To evaluate the potential for delayed dermal contact sensitization. ISO 10993: Biological Evaluation of Medical Devices, Part 10:	Under the conditions of this study, the test solution showed no evidence of causing delayed dermal contact sensitization
7	ISO Modified Intracutaneous Study, Solution with Measurement	To evaluate local irritant effects of HYADD4-G following Intracutaneous injection in the rabbit. ISO 10993: Biological Evaluation of Medical Devices, Part 10:	Under the conditions of this study the test article met the requirements of the test since the difference between the test and corresponding control mean score was less than 1.0.
8	ISO Subcutaneous Implantation Study (2 week)	To evaluate potential of local irritant or toxic response to material implanted in direct contact with subcutaneous tissue. ISO 10993: Biological Evaluation of Medical Devices, Part 6	Under the conditions of this study, the macroscopic reaction was not significant as compared to the control material and negative control material. Microscopically, the test article was classified as a nonirritant as compared to the control and negative control material.

9	ISO Subcutaneous Implantation Study (2 week)	To evaluate subcutaneous tissue for evidence of irritation or toxicity following subcutaneous implantation the product in the rabbit. ISO 10993: Biological Evaluation of Medical Devices, Part 6	Under the conditions of this study, the macroscopic reaction was not significant as compared to the negative control. Microscopically, the test article was classified as a nonirritant as compared to the negative control article.
10	Chronic Toxicity Study in the Rabbit following Intra-Articular Injections	To evaluate the potential for chronic systemic toxicity of the product following repeated injection into the knee of the rabbit. ISO 10993: Biological Evaluation of Medical Devices, Part 11	Data revealed no evidence of systemic toxicity from the test article following repeated intra-articular injection in the knee joints of rabbits.
11	Assessment of the Tolerability and Residence Time of the product after a Single Intra-Articular Administration in Normal Rabbit Joints.	To assess residence time of the formulation in the normal rabbit knee joint at 3, 7 and 14 days after a single intra- articular injection.	The data demonstrate: no inflammation of the synovial membrane at the time-points analyzed; a progressive decrease of the product in the joint, after the intra- articular injection
12	Assessment of the Residence Time and Tolerability of the formulation after a Single Intra-Articular Administration in Normal Rabbit Joints (15, 25, 35, 45 and 55 Days Post Injection)	To assess residence time) in the normal rabbit knee joint at 15, 25, 35, 45 and 55 days after a single intra-articular injection.	This study proves that the product has a residence time of at least 25 days.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The safety and effectiveness of HYMOVIS® for the treatment of pain from osteoarthritis of the knee were evaluated in a prospective, randomized, controlled, double-blind, multicenter study, R29-09-02, to determine whether two injections of HYMOVIS® are superior to those of a saline placebo in WOMAC Pain Score (Western Ontario and McMaster Universities Osteoarthritis Index) reduction from baseline through180 days in the osteoarthritis (OA) of the knee. An open-label extension (OLE) study phase was conducted to determine whether a repeat treatment of the two-injection regimen for HYMOVIS® was safe. For the effectiveness measures, the randomized controlled (RC) R29-09-02 study was intended to demonstrate a statistically significant difference, as well as a clinically significant pain reduction difference of 6 mm on the 100 mm WOMAC A

Pain Score scale, through 180 days between the HYMOVIS® and placebo control groups. The study, however, did not show a statistically significant difference in WOMAC A Pain Score reduction at 180 days between the two groups.

As a post hoc analysis, data from the HYMOVIS® treatment arm of the RC study were compared to data from the HYALGAN® treatment arm from the clinical study that served as the basis for approval of HYALGAN® under PMA 950027. A Bayesian regression analysis was undertaken in order to determine whether the effect of two injections of HYMOVIS® was non-inferior to the effect of 5 injections of HYALGAN®, with a delta of 5mm, when WOMAC A Pain scores for HYMOVIS® and HYALGAN® from baseline up to 180 days were compared under a non-inferiority test.

The results of the post hoc Bayesian analysis showed that two injections of HYMOVIS® were non-inferior to 5 injections of HYALGAN®, with a delta of 5mm, in the reduction of WOMAC A Pain scores from baseline through Week 26 (180 day), with a posterior probability of 97%. This finding was the basis for the approval decision for this PMA, in conjunction with the review of the safety data from the HYMOVIS® clinical study.

A summary of the HYMOVIS® clinical study, comprised of the RC and OLE study phases, is presented below. Reasonable assurance of the safety of HYMOVIS® 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) was established from these study data. Reasonable assurance of the effectiveness of HYMOVIS® for this same indication was established from the post hoc Bayesian analysis described above.

A. Study Design

Eight hundred patients were studied between March 24, 2011, and January 30, 2013, at 37 investigational sites in the United States (U.S.) and one in Puerto Rico. An initial two injections of 3ml of HYMOVIS® were evaluated for safety and efficacy versus a saline placebo control over a 26-week follow-up period. Specifically, patients that satisfied the inclusion / exclusion criteria were randomized into one of two treatment arms followed by a two intra-articular 3 mL injections of HYMOVIS® (one week apart), or similarly followed by two intra-articular 3 mL injections of saline control one week apart. A repeat treatment regimen was evaluated for the safety of a second treatment of two-injections of 3ml of HYMOVIS® over a period of 90 days.

The study was a prospective, randomized, controlled, double-blind, multicenter clinical study conducted in compliance with the principles of Good Clinical Practice (GCP) guidelines established by the U.S. 21 CFR Part 312 and 812, International Conference on Harmonization (ICH) Guidelines and the Declaration of Helsinki (59th WMA General Assembly, Seoul, October, 2008).

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the randomized controlled R29-09-02 study was limited to patients who met the following inclusion criteria:

- ≥ 40 years of age;
- Diagnosis of idiopathic OA based upon clinical and/or radiographic criteria of the American College of Rheumatology;
- OA disease symptom duration of at least 3 months;
- Ability of the patient to read and understand the language and content of the study material, understanding of the requirements for follow-up visits, and willingness to provide information at the scheduled evaluations and willing and able to comply with the study requirements;
- WOMAC A1 Pain Score of < 60 mm, if a washout period was required; or 40 - 80 mm, if a washout period was not required; and
- Patient had an increase in WOMAC A1 Pain Score of at least 20 mm after completion of the washout period if the patient was on rescue medication.

Patients were <u>not</u> permitted to enroll in the randomized controlled R29-09-02 study if they met any of the exclusion criteria. The exclusion criteria generally included conditions or medications that could confound the assessment and conditions that could be adversely affected by an intra-articular injection.

2. <u>Follow-up Schedule</u>

All patients in the RC study phase were scheduled for follow-up examinations at Days 7, 14, 28, 60, 90, 120, and 180 following first injection in accordance with the timetable below (Table 3). Patients taking part in the subsequent OLE study phase were scheduled for follow up visits at Days 7, 14, and 90 following first injection of the retreatment cycle. Adverse events and complications were recorded at all visits.

<u>Table 3: Study Schedule of Events by Visit for Randomized Controlled (RC) Study</u>

	Visit 1 (Screening)	Visit 2 (Baseline)	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
	-21 days	Day 0	Day 7 (± 1 day)	Day 14 (± 4 days)	Day 28 (± 7 days)	Day 60 (± 7 days)	Day 90 (± 7 days)	Day 120 (± 7 days)	Day 180 (± 7 days)
Written Informed Consent	X								
Study Eligibility	X	X							X[c]
Demographics and Baseline Characteristics	X								

Height and Weight	X								
Medical History	X								
OA History	X[d]								
Physical Examination	X								X
Vital Signs	X								X
Target Knee Assessment	X	X	X	X	X	X	X	X	X
Pregnancy Test[a]	X								
Radiographs	X[b]								
Prior Treatment and Medications	X								
Prohibited Medication Washout	X	X							
Rescue Medication Monitoring	X	X[e]	X	X	X	X	X	X	X
WOMAC (Complete Assessment)		X	X	X	X	X	X	X	X
SF-36	X								X
PTGA		X			X	X	X	X	X
COGA		X			X	X	X	X	X
Randomization		X							
Dispense Patient Diary and Instructions	X	X	X	X	X	X	X	X	
AE Assessment and Recording		X	X	X	X	X	X	X	X
Concomitant Treatments and Medications[f]	X	X	X	X	X	X	X	X	X
WOMAC A1	X	X							

Injections		X	X						
Patient Contact Weekly[g]									

a. Only if female

b. X-ray taken at screening was only required if patient has not had valid X-ray taken within three months of study screening

c. For patients participating in the Open Label Repeat Treatment Phase, study eligibility was re-assessed at Week 26.

d. Radiographic confirmation of OA and Kellgren-Lawrence II-III severity for the target joint was required.

e. The usage of study rescue medication between Screening and Baseline was permitted.

f. Patients were instructed to discontinue their current pain medication (NSAIDS, COX-2 inhibitor and analgesics) before the Baseline visit. Glucosamine, and chondroitin sulphate, were permitted if the patient was on a stable dose prior to participation and the dose remained constant throughout the study.

g. The Investigators were to contact each patient at week intervals between visits to collect data on concomitant medications and the patient's well-being.

3. Clinical Endpoints

a. RC Study Phase – Safety

Safety analyses were performed for the RC Study Phase on the safety population, which was defined as all randomized and treated patients. Treatment-emergent adverse events (TEAEs) were summarized by treatment group and categorized by severity and relationship to the study procedures. Additionally, listings of serious adverse events (SAEs) and adverse events (AEs) leading to discontinuation were generated.

Concomitant medications and treatments were categorized using a standardized coding dictionary (e.g., Medical Dictionary for Regulatory Activities [MedDRA]) and analyzed.

b. RC Study Phase – Effectiveness

Primary Effectiveness Endpoint

Superiority of HYMOVIS® to a placebo control was originally to be tested for a two intra-articular injection treatment of HYMOVIS® compared with a two intra-articular injection sham treatment of 0.9 % phosphate-buffered saline (saline) by evaluating the response to HYMOVIS® and saline control treatment regimen in WOMAC A Pain Scores over 26 weeks. The study was intended to demonstrate a statistically significant difference, as well as a clinically meaningful difference of at least 6 mm, in WOMAC A Pain Scores between the two groups at six months.

Secondary Effectiveness Endpoints

The secondary effectiveness endpoints of HYMOVIS® study initially were:

i. Responder, based on OMERACT- OARSI[1], at Week 26 (Day 180).
ii. Function on WOMAC C, Change from Baseline to Week 26 (Day 180).

iii. Visual Analogue Scale (VAS) Pain on WOMAC A1, Change from Baseline to Week 26 (Day 180).
iv. WOMAC Global Score, Change from Baseline to Week 26 (Day 180).
v. Stiffness WOMAC B, Change from Baseline to Week 26 (Day 180).
vi. Rescue medication usage over the entire study, by pill count per day.
vii. Failure outcome.
viii. Clinical Observer Global Assessment (COGA) at Week 26 (Day 180).
ix. Patient Global Assessment (PTGA) at Week 26 (Day 180).
x. $SF6D^2$, Change from Baseline to Week 26 (Day 180).
xi. Area under the curve (AUC) of response over 6 months of Pain WOMAC A.

Note:
1. Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International (OMERACT-OARSI) criteria of response.
2. The SF-6D for the analyst to obtain quality adjusted life years (QALYs) from the SF-36 for use in cost utility analysis.

c. OLE Study Phase – Safety

To assess the safety of a repeat injection regimen of two 3 mL of HYMOVIS®, the compliant patients from both arms were permitted to enter a 90 days open-label repeat treatment phase after the completion of the initial study injection regimen. Safety assessment criteria corresponded to those utilized in the RC Study Phase.

d. OLE Study Phase – Effectiveness

Effectiveness was not assessed for the repeat injection regimen of two 3 mL of HYMOVIS® in the OLE Study Phase.

B. Accountability of PMA Cohort

Patient Disposition in the RC Study Phase

A total of 1321 patients were enrolled in the randomized phase of the study. (One subject was screened twice but randomized once). Of these, there were 520 screening failures, and 801patients were randomized and 800 patients were treated into the two groups, HYMOVIS® (n = 400 patients) and Placebo (n= 400 patients) groups.

As shown in Table 4 below, the distribution of patients among the three assessed study population sets were as follows: modified Full Analysis Set (mFAS) (n=786 patients), safety analysis set (n=800 patients), and modified Per Protocol (mPP) Analysis Set (n =603 patients). The mPP Analysis Set contained 312 patients (78.0%) in the HYMOVIS® group and 291 patients (72.8%) in the Placebo group. The most common reasons for exclusion of patients from the mPP Analysis Set in the overall study population were "concomitant medication not washed out prior to baseline WOMAC" (n = 42, 5.3%), and "concomitant medication not washed out prior to post-baseline WOMAC" (n= 41, 5.2%). Moreover, 14

patients did not provide post baseline primary efficacy. All other reasons for exclusion were similar between the HYMOVIS® and Placebo groups.

Table 4: Accountability of PMA Cohort of RC Study

	HYMOVIS® n(%)	Placebo n(%)	Overall n(%)
All Patients			1321
Screening Failures			520
Modified Full Analysis Set (mFAS or ITT)	393 (98.0)	393 (98.3)	786 (98.1)
Safety Analysis Set	400 (99.8)	400 (100.0)	800 (99.9)
Modified PP Analysis Set (mPP)	312 (78.0)	291 (72.8)	603 (75.4)
Reasons for exclusion from the mPP Analysis Set			
Patient is less than 39 years old	0	0	0
OA not confirmed at least 45 days prior to the screening visit	0	1 (0.3)	1 (0.1)
ACR clinical and radiographic criteria not met	0	0	0
Patient was pregnant	0	0	0
Target knee was ineligible	8 (2.0)	8 (2.0)	16 (2.0)
Patient was clinically obese (BMI > 42 kg/m²)	0	0	0
Concomitant treatment may affect target knee WOMAC	1 (0.3)	3 (0.8)	4 (0.5)
Concomitant Medication not washed out prior to post-baseline WOMAC	20 (5.1)	29 (7.4)	49 (6.2)
Concomitant Medication not washed out prior to baseline WOMAC	18 (4.6)	27 (6.9)	45 (5.7)
Patient took more than 32 tablets a week [pro-rata]	23 (5.9)	20 (5.1)	43 (5.5)
Patient took rescue medication >4 days in a week on >=4 weeks	7 (1.8)	10 (2.5)	17 (2.2)
Baseline WOMAC A1 not in range 40-80mm	5 (1.3)	5 (1.3)	10 (1.3)
Baseline WOMAC A1 did not increase by >=20mm after washout	5 (1.3)	5 (1.3)	10 (1.3)
Wrong target knee selected	8 (2.0)	10 (2.5)	18 (2.3)
No post-baseline Primary efficacy assessment	0	1 (0.3)	1 (0.1)
Randomized study device was not correctly received	4(1.0)	1 (0.3)	5 (0.6)

Patient Disposition in the OLE Study Phase

The OLE Study Phase consisted of 526 patients. This patient set included 256 (48.6%) patients that received HYMOVIS® in the randomized study phase [designated here as the "2nd HYMOVIS®" group for the OLE Study phase] and 270 (51.4%) patients that received Placebo in the randomized study phase [designated here as the "1st HYMOVIS®" group for the OLE Study Phase].

The number of patients in the Safety Analysis Set (SAS) of the 1st HYMOVIS® group became 272 by including 2 noneligible patients, and the number of patients in the SAS of the 2nd HYMOVIS® group became 257 patients by including an additional patient who was not eligible for treatment in the 2nd HYMOVIS® group.

Table 5: Summary of Patient Disposition of OLE Study Phase (All Patients)

	2nd HYMOVIS® n (%)	1st HYMOVIS® n (%)	Overall n (%)
All Patients			564
			32

Patients not providing continuing informed consent into the OLE Study Phase			
Eligible Patients Treated	256	270	526
Eligible Patients Not Treated	0	0	3
Non-eligible Patients Treated	1	2	3
Eligible Patients Treated	256	270	526

A total of 501 (94.7%) patients completed the open label study, which included 258 patients (94.9%) in the 1st HYMOVIS® group and 243 patients (94.6%) in the 2nd HYMOVIS® group. There were a total of 28 patients (5.3%) who discontinued the study. The same number of study discontinuations occurred in the 1st HYMOVIS® group (n = 14, 5.1%) compared to the 2nd HYMOVIS® group (n=14, 5.4%).

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a pivotal clinical study performed in the US of intra-articular hyaluronic acid devices for treatment of pain from osteoarthritis. A summary is provided below in Tables 6 and 7.

Table 6: Summary of Demographic Data of RC Study (Modified Full Analysis Set, n = 786)

	Statistic	HYMOVIS® (N=393)	Placebo (N=393)	Overall (N=786)
Age (years)	N	393	393	786
	Mean (SD)	60.9 (10.00)	60.4 (9.67)	60.7 (9.84)
Gender				
Female	n (%)	223 (56.7)	238 (60.6)	461 (58.7)
Male	n (%)	170 (43.3)	155 (39.4)	325 (41.3)

Table 7: Race and Ethnicity of Patients in RC Study

Race	American Indian/Alaskan Native	n (%)	0	2 (0.5)	2 (0.3)
	White	n (%)	342 (87.0)	329 (83.7)	671 (85.4)
	Native Hawaiian/Other Pacific Islander	n (%)	3 (0.8)	1 (0.3)	4 (0.5)
	Asian	n (%)	2 (0.5)	2 (0.5)	4 (0.5)
	Other	n (%)	5 (1.3)	3 (0.8)	8 (1.0)
Ethnicity	Hispanic or Latino	n (%)	61 (15.5)	57 (14.5)	118 (15.0)
	Not Hispanic or Latino	n (%)	332 (84.5)	336 (85.5)	668 (85.0)

The following table, Table 8, shows the baseline values for various assessment measures.

Table 8: Summary of Baseline Characteristics of RC Study (Modified Full Analysis Set)

	Statistic	HYMOVIS® (N=393)	Placebo (N=393)	Overall (N=786)
Pain WOMAC A	N	393	393	786
	Mean (SD)	57.28 (14.048)	57.18 (14.394)	57.23(14.213)
Function WOMAC C	N	390	391	781
	Mean(SD)	55.80(16.910)	56.03(16.603)	55.92(16.747)
VAS Pain WOMAC A1	N	393	393	786
	Mean(SD)	62.44(12.190)	62.30(12.200)	62.37(12.187)
Stiffness WOMAC B	N	393	392	785
	Mean(SD)	60.35(18.252)	61.36(16.902)	60.86(17.587)
WOMAC GLOBAL	N	390	390	780
	Mean(SD)	173.73(43.924)	174.58(43.063)	174.15(43.470)
SF-6D Physical Functioning (PF)	N	393	393	786
	Mean(SD)	3.4(1.21)	3.5(1.25)	3.4(1.23)

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on a randomized controlled cohort of 800 patients available for 6 months and the cohort of 529 patients evaluated through 90 days in a subsequent OLE study. The key safety outcomes and the adverse events for this study are presented below in Tables 9 to 13.

a. Safety Results of RC Study Phase

Adverse effects that occurred in the RC Study:

The overall randomized study phase Safety Analysis Set consisted of 800 patients with 400 patients in the HYMOVIS® group and 400 patients in the Placebo group. No difference was reported between the HYMOVIS® and Placebo groups with respect to patients with at least one AE, patients with at least one Treatment Emergent Adverse Event (TEAE), the number of TEAEs,

and patients with at least one Treatment Emergent Adverse Device Effect (TEADE).

In the overall RC Safety Analysis Set, one patient from saline placebo groups had an AE of mild severity that led to discontinuation of participation in the study (0.3% of saline placebo group, n=400).

TEAEs were categorized by degree of severity. In the overall Safety Analysis Set, the most commonly assessed degree of severity of a TEAE was 'mild' (n = 178, 22.3%), followed by 'moderate' (n =147, 18.4%), and then 'severe' (n = 39, 4.9%). A similar number of patients with mild, moderate and severe TEAEs occurred in both the Placebo and HYMOVIS® groups (Table 9).

Table 9: Summary of Adverse Events of RC Study (Safety Analysis Set)

	HYMOVIS® (N=400) n (%)	Placebo (N=400) n (%)	Overall (N=800) n (%)
Patients with at least one Adverse Event	187 (46.8)	182 (45.5)	369 (46.1)
Patients with at least one Treatment Emergent Adverse Event	184 (46.0)	180 (45.0)	364 (45.5)
Treatment Emergent Adverse Events	358	353	711
Patients with at least one Treatment Emergent Adverse Device Effect	17 (4.3)	19 (4.8)	36 (4.5)
Patients with AEs that led to discontinuation of Study Device	0	1 (0.3)	1 (0.1)
Patients with Treatment Emergent Adverse Events by Degree of Severity			
Mild	88 (22.0)	90 (22.5)	178 (22.3)
Moderate	78 (19.5)	69 (17.3)	147 (18.4)
Severe	18 (4.5)	21 (5.3)	39 (4.9)

Adverse events relating to the study device occurring in 5% or more patients in the Safety Analysis Set (Table 10) were all recorded in one MedDRA coding system organ class (SOC), namely, 'musculoskeletal and connective tissue disorders'. The MedDRA coding preferred term (PT) was arthralgia.

In the overall RC study phase Safety Analysis Set, 176 patients (22.0%) with TEAEs were categorized by MedDRA coding to 'musculoskeletal and connective tissue disorders' (SOC). There were similar numbers of patients with TEAEs for musculoskeletal and connective tissue disorders in the HYMOVIS® and Placebo groups.

In the overall RC study phase Safety Analysis Set, 92 patients (11.5%) with TEAEs were categorized by MedDRA coding for arthralgia. There were

similar numbers of patients with TEAEs categorized as arthralgia in the HYMOVIS® and Placebo groups.

Table10: Summary of Adverse Events Related to RC Study Device Occurring in 5% or More Patients (Safety Analysis Set)

	HYMOVIS® (N=400) n (%)	Placebo (N=400) n (%)	Overall (N=800) n (%)
Number of Patients with at Least One TEAE	184 (46.0)	180 (45.0)	364 (45.5)
System Organ Class Preferred Term			
Musculoskeletal and connective tissue disorders	93 (23.3)	83 (20.8)	176 (22.0)
Arthralgia	47 (11.8)	45 (11.3)	92 (11.5)

As shown below in Table 11, among the overall Safety Analysis Set, 36 patients had at least one TEADE (4.5%). A similar number of patients with at least one TEADE occurred in the Placebo group (n = 19, 4.8%) and the HYMOVIS® group (n = 17, 4.3%). Among the overall population, TEADEs were identified within five SOCs, namely, 'musculoskeletal and connective tissue disorders' (n = 27, 3.4%), 'general disorders and administration site conditions' (n = 7, 0.9%), 'injury, poisoning and procedural complications' (n = 1, 0.1%), 'nervous system disorders' (n = 1, 0.1%), and 'skin and subcutaneous tissue disorders' (n=1, 0.1%). The HYMOVIS® and Placebo group profiles were approximately similar among SOCs and PTs.

Table 11: Summary of Treatment-Emergent Adverse Device Effects of RC Study Phase by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	HYMOVIS® (N=400) n (%)	Placebo (N=400) n (%)	Overall (N=800) n (%)
Number of Patients With At Least One TEADE	17 (4.3)	19 (4.8)	36 (4.5)
General disorders and administration site conditions	2 (0.5)	5 (1.3)	7 (0.9)
Injection site discomfort	0	1 (0.3)	1 (0.1)
Injection site erythema	1 (0.3)	2 (0.5)	3 (0.4)
Injection site pain	1 (0.3)	3 (0.8)	4 (0.5)
Injection site pruritus	1 (0.3)	1 (0.3)	2 (0.3)
Injury, poisoning and procedural complications	0	1 (0.3)	1 (0.1)

Contusion	0	1 (0.3)	1 (0.1)
Musculoskeletal and connective tissue disorders	15 (3.8)	12 (3.0)	27 (3.4)
Arthralgia	7 (1.8)	7 (1.8)	14 (1.8)
Haemarthrosis	0	1 (0.3)	1 (0.1)
Joint crepitation	0	1 (0.3)	1 (0.1)
Joint effusion	0	2 (0.5)	2 (0.3)
Joint instability	0	1 (0.3)	1 (0.1)
Joint lock	1 (0.3)	1 (0.3)	2 (0.3)
Joint stiffness	4 (1.0)	1 (0.3)	5 (0.6)
Joint swelling	4 (1.0)	3 (0.8)	7 (0.9)
Pain in extremity	1 (0.3)	0	1 (0.1)
Sensation of heaviness	1 (0.3)	0	1 (0.1)
Nervous system disorders	1 (0.3)	0	1 (0.1)
Sensory disturbance	1 (0.3)	0	1 (0.1)
Skin and subcutaneous tissue disorders	0	1 (0.3)	1 (0.1)
Pruritus	0	1 (0.3)	1 (0.1)

b. Safety Results of OLE Study Phase

The OLE Study was designed only to determine whether the repeat treatment of two HYMOVIS® injections was safe. The number of patients in the Safety Analysis Set (SAS) of the 1st HYMOVIS® group became 272 by including 2 noneligible patients, and the number of patients in the SAS of the 2nd HYMOVIS® group became 257 by including an additional patient who was not eligible for treatment in the 2nd HYMOVIS® group. The overall OLE Safety Analysis Set contained 529 patients.

There were a total of 28 patients (5.3% of the total of 529) who discontinued participation in the study. The same number of study discontinuations were recorded for the 1st HYMOVIS® group (n = 14, 5.1%) as compared to the 2nd HYMOVIS® group (n=14, 5.4%).

No difference was reported between the 1st HYMOVIS® and 2nd HYMOVIS® groups with respect to patients with at least one AE, patients with at least one Treatment Emergent Adverse Event (TEAE), the number of TEAEs, and patients with at least one Treatment Emergent Adverse Device Effect (TEADE).

In the overall OLE Safety Analysis Set, three patients had AEs that led to discontinuation of participation in the study (0.6%). All three of these patients were in the 2nd HYMOVIS® group (1.2%).

Patients with occurrence of TEAEs were categorized by degree of severity. In the overall OLE Safety Analysis Set, the most common TEAE was 'moderate'

(n = 79, 14.9%), followed by 'mild' (n = 51, 9.6%) and then 'severe' (n = 8, 1.5%).

A lower percentage of patients experiencing a 'mild' TEAE occurred in the 2nd HYMOVIS® group (n= 20, 7.8%) as compared to the 1st HYMOVIS® group (n =31, 11.4%). A higher percentage of patients experiencing a 'moderate' TEAE occurred in the 2nd HYMOVIS® group (n=47, 18.3%) as compared to the 1st HYMOVIS® group (n =32, 11.8%). An equal number of patients with severe TEAEs were recorded in the 2nd HYMOVIS® group (n= 4, 1.6%) compared to the 1st HYMOVIS® group (n=4, 1.5%). However, there were significantly smaller percentages of patients with AE's observed in the 90-day OLE study phase as compared to the180 day RC study phase.

Table 12: Summary of Adverse Events of OLE Study (Safety Analysis Set)

	2nd HYMOVIS® (N=257) n (%)	1st HYMOVIS® (N=272) n (%)	Overall (N=529) n (%)
Patients with at least one Adverse Event	71 (27.6)	67 (24.6)	138 (26.1)
Patients with at least one Treatment Emergent Adverse Event	71 (27.6)	67 (24.6)	138 (26.1)
Treatment Emergent Adverse Events	97	109	206
Patients with at least one Treatment Emergent Adverse Device Effect	18 (7.0)	12 (4.4)	30 (5.7)
Patients with AEs that led to discontinuation of the Study Device	3 (1.2)	0	3 (0.6)
Patients with Treatment Emergent Adverse Events by Degree of Severity			
Mild	20 (7.8)	31 (11.4)	51 (9.6)
Moderate	47 (18.3)	32 (11.8)	79 (14.9)
Severe	4 (1.6)	4 (1.5)	8 (1.5)

Among the overall OLE Safety Analysis Set, 30 patients had at least one TEADE (5.7%). A similar number of patients with at least one TEADE was recorded in the 2nd HYMOVIS® group (n= 18, 7.0%) as compared to the 1st

HYMOVIS® group (n = 12, 4.4%). Among the overall OLE Safety Analysis Set, TEADEs were identified within five SOCs, namely, 'musculoskeletal and connective tissue disorders' (n = 26, 4.9%), 'general disorders and administration site conditions' (n = 2, 0.4%), 'immune system disorders' (n = 1, 0.2%), 'infections and infestations' (n = 1, 0.2%) and 'injury, poisoning and procedural complications' (n = 1, 0.2%). The 1st and 2nd HYMOVIS® group profiles were broadly similar among all SOCs and PTs.

Table 13: Summary of Treatment-Emergent Adverse Device Effects of OLE Study Phase by System Organ Class and Preferred Term (Safety Analysis Set)

	2nd HYMOVIS® (N=257) n (%)	1st HYMOVIS® (N=272) n (%)	Overall (N=529) n (%)
Number of Patients With At Least One TEADE	18 (7.0)	12 (4.4)	30 (5.7)
System Organ Class Preferred Term			
General disorders and administration site conditions	1 (0.4)	1 (0.4)	2 (0.4)
Inflammation	0	1 (0.4)	1 (0.2)
Injection site pain	1 (0.4)	0	1 (0.2)
Immune system disorders	1 (0.4)	0	1 (0.2)
Hypersensitivity	1 (0.4)	0	1 (0.2)
Infections and infestations	1 (0.4)	0	1 (0.2)
Arthritis bacterial	1 (0.4)	0	1 (0.2)
Injury, poisoning and procedural complications	0	1 (0.4)	1 (0.2)
Contusion	0	1 (0.4)	1 (0.2)
Musculoskeletal and connective tissue disorders	15 (5.8)	11 (4.0)	26 (4.9)
Arthralgia	13 (5.1)	9 (3.3)	22 (4.2)
Arthritis	1 (0.4)	0	1 (0.2)
Joint effusion	2 (0.8)	1 (0.4)	3 (0.6)
Joint stiffness	1 (0.4)	1 (0.4)	2 (0.4)
Joint swelling	1 (0.4)	2 (0.7)	3 (0.6)
Osteoarthritis	0	1 (0.4)	1 (0.2)

Adverse events relating to the study device occurring in 5% or more patients in the OLE Safety Analysis Set were all identified in one MedDRA coding system organ class (SOC), namely, 'musculoskeletal and connective tissue disorders'. The MedDRA coding preferred term (PT) was arthralgia.

In the overall OLE Safety Analysis Set, 65 patients (12.3%) with at least one TEAE were categorized by MedDRA coding to 'musculoskeletal and connective tissue disorders' (SOC). There was a similar percentage of patients with TEAEs for 'musculoskeletal and connective tissue disorders' in the 2nd HYMOVIS® group as compared to the 1st HYMOVIS® group.

In the overall OLE Safety Analysis Set, 46 patients (8.7%) with TEAEs were categorized by MedDRA coding for arthralgia (PT). There were similar percentages of patients with TEAEs categorized as arthralgia in the 2nd HYMOVIS® and 1st HYMOVIS® groups.

2. Effectiveness Results

a. Effectiveness Results of RC Study Phase

Primary Effectiveness Endpoint

The analysis of the effectiveness of HYMOVIS® was based on the mFAS (n=786 patients) evaluable at the 6-month time point. The pain reduction from baseline for HYMOVIS® was -19.47 mm on the whole 100 mm WOMAC A Pain scale and that of saline placebo was -18.13 mm. The primary effectiveness endpoint was not met in this study. As shown below in Table 14, the study did not demonstrate a statistically significant difference, as well as a clinically meaningful difference of at least 6 mm, between the two groups in WOMAC A Pain Scores at six months.

Table 14: WOMAC VAS Pain Improvement from Baseline of RC Study – mFAS Population

Treatment	Baseline	Changes from Baseline WOMAC Score	Model-Estimated Advantage (HYMOVIS® - PBS)	95% CI Lower and Upper Bound (mm)	P-value
HYMOVIS® (n=393)	57.28	-19.47	-1.39	(-3.74, 0.96)	0.25
Saline placebo (n=393)	57.18	-18.13			

The analysis was based on a two sided t-test at 180 days for the primary endpoint.

Secondary Effectiveness Endpoints

None of the secondary endpoints below were statistically different between HYMOVIS® and the Saline Placebo groups at 180 days:

Function measured by Section C of WOMAC VAS pain measured by Section A1 of WOMAC A
WOMAC Global Score
Stiffness measured by Section B of WOMAC B
Responder Analysis by OMERACT-OARSI Criteria*
*Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International
(OMERACT-OARSI) criteria of response

b. Effectiveness Results of OLE Study Phase

The OLE study was designed only for the assessment of the safety of a repeated cycle treatment of two injections of HYMOVIS®. The effectiveness of a repeated cycle treatment of two injections of HYMOVIS® was not intended to be assessed in the OLE Study.

E. 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 356 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. POST HOC NON-INFERIORITY ANALYSIS OF HYMOVIS® VS. HYALGAN® (SODIUM HYALURONATE)

The primary effectiveness endpoint for the HYMOVIS® pivotal RC study (R29-09-02), comparison of the reductions in the WOMAC Pain Score (WOMAC A) from baseline through 180 days, was used for a post-hoc non-inferiority comparison of HYMOVIS® to HYALGAN®, previously approved under P950027 for an identical indication for use. WOMAC A Pain Scores were utilized to determine the non-inferiority of HYMOVIS® to HYALGAN® using Bayesian regression analysis. Under this Bayesian analysis, a two-injection treatment regimen of HYMOVIS® was assessed for its ability to provide pain relief non-inferior to that of a 5-injection treatment regimen of HYALGAN® as determined through comparison of the reduction in WOMAC A Pain Scores from baseline through 180 days utilizing a non-inferiority margin of 5 mm on the 100mm WOMAC A Pain Scale.

The primary effectiveness endpoint for this non-inferiority analysis was met as calculated using a Bayesian regression analysis with posterior probability of 97%. Details of this analysis are provided as follows:

Treatment group labels
1 = Active (HYMOVIS®)
2 = Control (HYMOVIS®)
3 = Active (HYALGAN®)
4 = Control (HYALGAN®)

Populations considered are the modified Per Protocol (mPP) Analysis Sets. The numbers of patients per treatment group are shown in Table 15 below.

Table 15: Number of Patients Per Treatment Group

Population/Group	1	2	3	4
Modified PP	312	291	152	157

A set of three hypotheses (defined below as H1, H2, and H3) were postulated in order to assess whether HYMOVIS®' benefit over Placebo was non-inferior to HYALGAN®'s benefit over Placebo. The non-inferiority margin was set at 5 mm (on a 100mm WOMAC VAS Scale) to be consistent with the non-inferiority margin utilized for a similar analysis used to support the recent approval of another intra-articular hyaluronic acid device.

The hypotheses were tested by calculating the posterior probability of each of the three claims in the following manner:

Let:
δ_1 be the mean WOMAC A baseline change through 180 days in the HYMOVIS® arm,
δ_2 be the mean WOMAC A baseline change through 180 days in the placebo arm of the HYMOVIS® study,
δ_3 be the mean WOMAC A baseline change through 180 days in the HYALGAN® arm, and
δ_4 be the mean WOMAC A baseline change through 180 days in the placebo arm of the HYALGAN® study,

The criteria for evaluating the three hypotheses were based on the following posterior probabilities:

H1 is true if
$\pi_1 = P\left((\delta_1 - \delta_2) - (\delta_3 - \delta_4) < 5 \middle| Data\right) > \pi_1^*$

H2 is true if
$\pi_2 = P\left((\delta_3 - \delta_4) < 0 \middle| Data\right) > \pi_2^*$

H3 is true if
$\pi_3 = P\left((\delta_1 - \delta_2) < 0 \middle| Data\right) > \pi_3^*$

where and π_1^* π_2^* and π_3^* are values close to 1.

The resulting estimates of the means, or differences of means between groups, and standard deviations (sd) are shown below in Table 16.

Table 16: Analysis of Average Changes from Baseline Through 180 Days for the Modified PP Population

	mean	sd
beta[1]	-20.81	1.83
beta[2]	-20.15	1.85

beta[3]	-16.57	2.11
beta[4]	-15.33	2.15
diff12	-0.66	1.41
diff34	-1.24	1.97

beta[1]=mean of WOMAC A Pain Change from baseline through 180 days for HYMOVIS® from baseline
beta[2]=mean of WOMAC A Pain Change from baseline through 180 days for saline placebo control of HYMOVIS®
beta[3]=mean of WOMAC A Pain Change from baseline through 180 days for HYALGAN® from baseline
beta[4]=mean of WOMAC A Pain Change from baseline through180 days for saline placebo control of HYALGAN®
diff12 $=\delta_1-\delta_2$
diff34 $=\delta_3-\delta_4$

The posterior probabilities of hypotheses H1, H2, and H3 are presented below in Table 17.

Table 17: Posterior Probability for Per Protocol Population (PP) Bayesian Model

	Modified PP (mPP)
π_1	97%
π_2	74%
π_3	68%

Population = mPP
Outcome = Change in baseline through 180 days
Adjustment variables: Baseline WOMAC A, Age > 50, and Male.

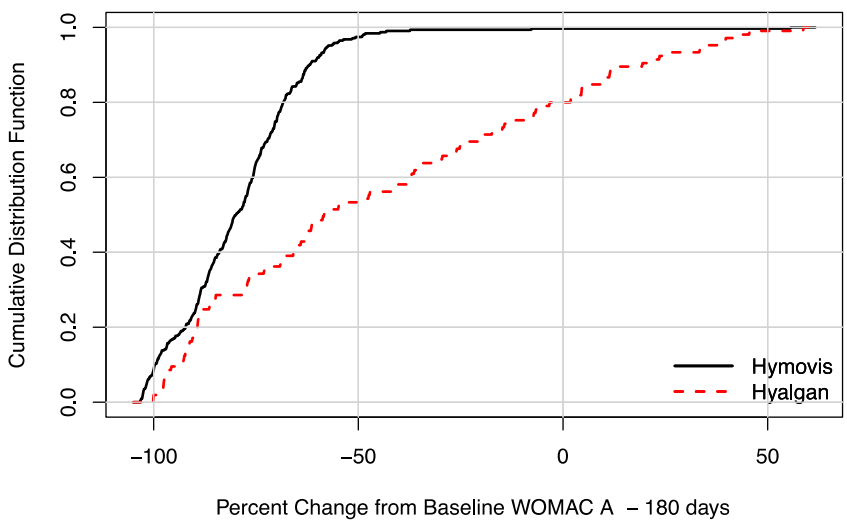
These posterior probabilities are in accordance with the data indicating that 2 injections of HYMOVIS® are non-inferior to 5 injections of HYAGAN®.

Clinical Significance Demonstration

To demonstrate clinical significance a cumulative distribution method for determining of the change from baseline for each of the endpoints was employed. Cumulative Distribution Function (CDF) plots comparing the HYMOVIS® two injection regimen to the HYALGAN® five-injection regimen effectiveness were conducted and provided for primary and secondary endpoints. At -6.0 mm on a 100mm WOMAC VAS scale, which is considered by Agency a valid clinically important difference, the CDF plots demonstrate that HYMOVIS® demonstrates a higher degree of clinical improvement than HYALGAN® for all significant test endpoints.

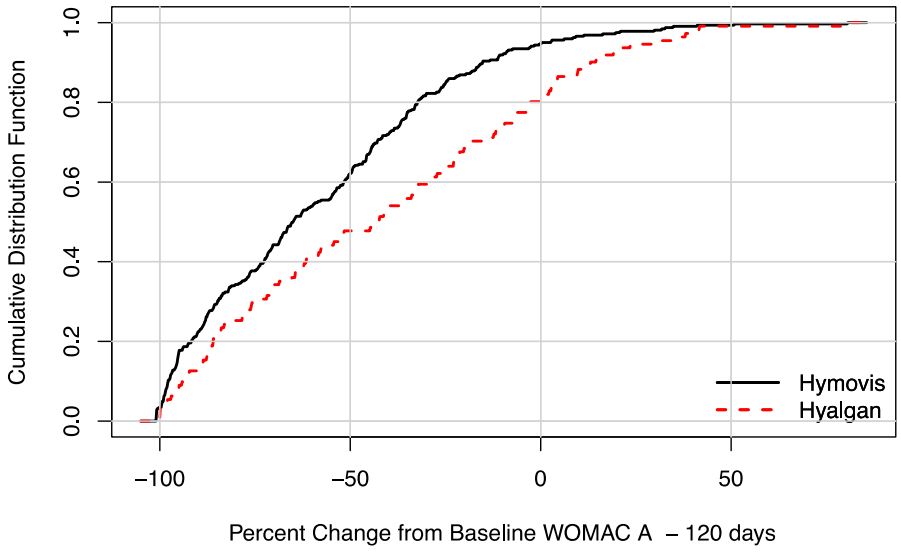
Figures 1 and 2 below show the Cumulative Distribution Plot for Change in WOMAC A Pain Score from Baseline to Day 120 and Day 180.

Figure 1 Cumulative Distribution Function for Percent Change in WOMAC A at Day 180



The CDF curves for the endpoints (WOMAC Pain Score at day 180) show that the HYMOVIS® mPP population demonstrates a higher degree of clinical improvement at day 180 to HYALGAN®.

Figure 1 Cumulative Distribution Function for Percent Change in WOMAC A at Day 120



The CDF curves for the endpoints (WOMAC Pain Score at day 120) show that the HYMOVIS® population demonstrates a higher degree of clinical improvement at day 120.

XII. 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.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The original study (RC) did not meet its primary endpoint, WOMAC A Pain reduction at 180 days. The analysis of the effectiveness of HYMOVIS® was based on the mFAS (n=786 patients) evaluable at the 6-month time point. The mean difference between the HYMOVIS® and placebo saline (HYMOVIS® - saline placebo) was -1.39, with p=0.25 (two sided t- test). The pain reduction from baseline for HYMOVIS® was -19.47 mm on the whole 100 mm WOMAC A Pain scale and that of saline placebo was -18.13 mm.

To demonstrate clinical benefit, a comparison was made, using Bayesian regression analysis, of the reduction in WOMAC A Pain Scores from baseline through 180 days for HYMOVIS® and HYALGAN® utilizing a non-inferiority margin of 5 mm on the 100mm WOMAC A Pain Scale. It was demonstrated that a two-injection treatment regimen of HYMOVIS® was non inferior to a 5-injection treatment regimen of HYALGAN® with a posterior probability of 97%. The difference in pain reduction between HYMOVIS® and a saline placebo was 0.66 on the whole 100mm WOMAC A Pain Scale at 180 days, whereas the difference between HYALGAN® and its saline placebo was 1.24.

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. There were observed rare instances of injection site pain, swelling and discomfort (<1%). The safety data from the RC and OLE studies provide reasonable assurance of the safety of treatment and repeat treatment of 2 injections of HYMOVIS® 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 Conclusions

The probable benefits of the device are also based on analyses performed on data collected in a clinical study conducted to support PMA approval as described above. The primary endpoint was improvement in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) A Pain subscore from baseline to 26 weeks. The study was intended to demonstrate a statistically significant difference, as well as a clinically meaningful difference of at least 6 mm, in WOMAC A Pain Scores between the HYMOVIS® active treatment and saline placebo (sham) treatment groups at six months. This primary effectiveness endpoint was not met, but the safety data for this study and the subsequent open label extension study demonstrated minimal or negligible risks and therefore provided reasonable assurance of safety for the product.

In order to demonstrate the effectiveness of HYMOVIS®, the sponsor performed a post hoc non-inferiority analysis utilizing data from the HYMOVIS® treatment arm of the study compared to data from the HYALGAN® treatment arm from the clinical study that served as the basis for approval of HYALGAN® under PMA 950027 for an identical indication for use. The primary effectiveness endpoint for this non-inferiority analysis was met as calculated using a Bayesian regression analysis with posterior probability of 97%. This analysis indicates that HYMOVIS® will provide comparable or better relief of pain due to OA of the knee than the previously approved product, HYALGAN®. In addition, HYMOVIS® offers additional advantage and convenience over that of HYALGAN® to the user in that HYMOVIS® is administered by only 2 injections as opposed to the 5 injections required for HYALGAN®.

In conclusion, given the available information above, the data and analyses support that for the indication for use 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 probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The primary preclinical and clinical data support the safety and effectiveness, and safety of a repeat treatment, of 2 injections of HYMOVIS®. Results from non-inferiority comparison of HYMOVIS® and HYALGAN®, utilizing a Bayesian regression analysis and longitudinal modeling of data from clinical studies for the two devices, provide valid scientific evidence of reasonable assurance of the safety and effectiveness of HYMOVIS® 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).

XIV. CDRH DECISION

CDRH issued an approval order on August 28, 2015.

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

XV. 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.