SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Sodium Hyaluronate
Device Trade Name:	TRILURON™
Device Procode:	MOZ
Applicant's Name and Address:	Fidia Pharma USA Inc. 100 Campus Drive, Suite 105 Florham Park, New Jersey 07410
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P180040
Date of FDA Notice of Approval:	March 26, 2019

II. INDICATIONS FOR USE

TRILURON™ 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 simple analgesics (e.g., acetaminophen).

III. CONTRAINDICATIONS

Do not administer to patients with known hypersensitivity to hyaluronate preparations.

Intra-articular injections are contraindicated in cases of past and present infections or skin diseases in the area of the injection site.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the labeling for TRILURON™.

V. DEVICE DESCRIPTION

TRILURON™ is a sterile, non-pyrogenic, viscous solution consisting of a high molecular weight (500,000 – 730,000 daltons) fraction of purified sodium hyaluronate in phosphate buffered physiological sodium chloride, having a pH of 6.8-7.5. The sodium hyaluronate is extracted from rooster combs as described in the original PMA (P950027) approval of Hyalgan. Hyaluronic acid is a complex sugar of the glycosaminoglycan family and is a long-chain polymer containing repeating disaccharide units of Na-glucuronate-N-acetylglucosamine. TRILURON™ is supplied in colorless, borosilicate

Type I glass vials, with rubber stoppers and flip-off aluminum seals, containing 2mL of TRILURON™. It is also available in 2 mL pre-filled, sealed syringes made of colorless borosilicate Type I glass. The contents of the vials and syringes are sterile and non-pyrogenic.

Each vial and syringe, prefilled with 2.0 mL of TRILURON™ contains:

Sodium hyaluronate	20.0 mg
Sodium chloride	17.0 mg
Dibasic sodium phosphate x 12 H2O	1.2 mg
Monobasic sodium phosphate x 2H2O	0.1 mg
Water for injection	(q.s.* 2.0 mL)

*q.s. = up to

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of pain in osteoarthritis (OA) of the knee. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

For patients who have failed to respond adequately to conservative non-pharmacological therapy and simple analgesics (e.g., acetaminophen), alternative therapies and treatments to TRILURON™ include: nonsteroidal anti-inflammatory drugs (NSAIDS); intraarticular injections of corticosteroids or injections of modified hyaluronan; 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 surgery are also alternative treatments.

VII. MARKETING HISTORY

TRILURON™'s sodium hyaluronate formulation has been used clinically in Europe since 1987. An estimated 11,635,495 patients worldwide have been treated. In the US, this same formulation was approved in P950027 on May 28, 1997 for five weekly injections of 20mg of sodium hyaluronate per 2.0mL under the brand name of Hyalgan. TRILURON™ has the same chemical composition as Hyalgan, except it is administered under a weekly 3-injection regimen of 2.0 ml per injection instead of a weekly 5-injection regimen of 2.0 ml per injection. Hyalgan has been commercially distributed under different branded names (e.g. Hyalgan, Hyalart, and Polyreumin) in over 65 countries outside of the United States. Please refer to Table 1 below for a list of countries where it has been marketed.

Table 1: Marketed in These Countries

Country	Tradename	Country	Tradename	Country	Tradename
Albania	Hyalgan	Indonesia	Hyalgan	Russia	Hyalgan Fidia

Country	Tradename	Country	Tradename	Country	Tradename
Argentina	Hyalart	Ireland	Hyalgan	Saudi Arabia	Hyalgan
Austria	Hyalgan	Italy	Hyalart	Serbia	Hyalgan
Bahrain	Hyalgan	Kazakhstan	Hyalgan	Singapore	Hyalgan
Belarus	Hyalgan	Kosovo	Hyalgan	Slovak Republic	Hyalgan
Belgium	Hyalgan	Latvia	Hyalgan	Slovenia	Hyalgan
Brazil	Polyreumin	Lebanon	Hyalgan	South Korea	Hyalgan
Bulgaria	Hyalgan	Libya	Hyalgan	Spain	Hyalgan
Chile	Hyalgan	Lithuania	Hyalgan	Sweden	Hyalgan
Colombia	Hyalgan	Luxembourg	Hyalgan	Syria	Hyalgan
Croatia	Hyalgan	Malaysia	Hyalgan	Taiwan	Hyalgan
Cyprus	Hyalgan	Malta	Hyalgan	Thailand	Hyalgan
Czech Republic	Hyalgan	Mauritius	Hyalgan	Tunisia	Hyalgan
Ecuador	Hyalgan	Mexico	Hyalgane	Turkey	Hyalgan
Egypt	Hyalgan	Moldova	Hyalgan	UK	Hyalgan
Finland	Hyalgan	Morocco	Hyalgan	Ukraine	Hyalgan
France	Hyalgan	Oman	Hyalgan	UAE	Hyalgan
Georgia	Hyalgan	Panama	Hyalgan	Uzbekistan	Hyalgan
Germany	Hyalart	Perù	Hyalgan	USA	Hyalgan
Greece	Hyalart	Poland	Hyalgan	Venezuela	Hyalgan
Hong Kong	Hyalgan	Portugal	Hyalart	Vietnam	Hyalgan
Hungary	Hyalgan	Romania	Hyalgan	Yemen	Hyalgan

Hyalgan™ has not been withdrawn from any country for any reason related to its safety and effectiveness.

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 TRILURON™ are those that may occur in association with intra-articular injections of viscosupplements:

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

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

Since TRILURON™ is of identical chemical formulation to Hyalgan (previously approved under P950027), all of the clinical studies used to provide evidence of the reasonable assurance of the safety of Hyalgan apply directly to TRILURON™. Common adverse events reported for Hyalgan include gastrointestinal complaints, injection site pain, headache, local joint pain and knee swelling/effusion, rash, pruritus, and ecchymosis.

Additional supporting evidence of the safety of TRILURON™ was provided by the safety data from a prospective, randomized, controlled trial that compared TRILURON™ (investigational device, 213 treated subjects in safety analysis) to another 3-injection hyaluronic acid (control device, 223 treated subjects in safety analysis) as reported Berenbaum et al[1]. Local adverse events reported for TRILURON™ were joint effusion/swelling (4 subjects, 1.9%), joint pain (2 subjects, 0.9%), injection site hematoma (2 subjects, 0.9%) and injection site warmth (1 subject, 0.5%). The local adverse events reported for the control were joint effusion/swelling (1 subject, 0.4%) and joint pain (3 subjects, 1.4%). The local adverse events usually were transient and disappeared spontaneously within a few days of resting the affected joint and/or applying ice locally.

The 4 reports (1.9%) of adverse events in the TRILURON™ group leading to study discontinuation were worsening of knee OA, post-traumatic meniscal lesion, ischemic stroke and angiosarcoma with pleural effusion. The 2 reports in the control group of adverse events leading to study discontinuation were worsening of knee OA (2 subjects, 0.9%) and metastatic pulmonary cancer (1 subject, 0.4%).

No cases of pseudoseptic arthritis were observed. Overall, there were no new safety findings for TRILURON™. For a more detailed discussion of the adverse events that occurred in this study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

Since TRILURON™ is of identical chemical formulation to Hyalgan (previously approved under P950027), the nonclinical studies that were used to provide evidence to support the reasonable assurance of the safety of Hyalgan are directly applicable to TRILURON™ as well.

The biocompatibility testing and nonclinical test results, summarized below in Table 2, provide further evidence for the reasonable assurance of the safety of TRILURON™. Additionally, testing regarding material characterization, sterilization validation, packaging testing, and shelf life testing were conducted in support of the original PMA, and additional information is available in the SSED for P950027 on the CDRH website at http://www.accessdata.fda.gov/cdrh_docs/pdf/P950027A.pdf. Please note, some studies used Hyalectin®, or Hyalovet®, a veterinary preparation with a composition identical to Hyalgan®. Hyalectin® is the proprietary name of the sodium hyaluronate used in Hyalgan® and TRILURON™. The previously conducted shelf life testing support a shelf

life of 3 years for TRILURON™ when stored below 77°F (25°C), but not subjected to freezing.

Table 2: Summary of Biocompatibility and Nonclinical Testing

Test	Test article used	Result
Biocompatibility Testing		
Cytotoxicity	Hyalgan	No cytotoxic effect on cells.
Sensitization	Hyalgan	No significant evidence of activation.
Sensitization	Hyalgan	Not a skin sensitizer in guinea pigs.
Sensitization	20 mg/2 mL of Hyalectin	No evidence of sensitization nor antigenic properties.
Irritation	Hyalgan & HA via fermentation	No evidence of any local reactions
Acute Systemic Toxicity	Hyalectin	No acute toxicity exhibited.
Subacute Toxicity	Hyalectin	No adverse reactions.
Subacute Toxicity	Hyalectin	Well tolerated and no treatment-related adverse reactions.
Subacute Toxicity	Hyalectin	No adverse reactions.
Subchronic Toxicity	Hyalectin	No adverse effects.
Subchronic Toxicity	Hyalectin	No systemic toxicity.
Genotoxicity	Hyalectin	No evidence of mutagenic potential.
Genotoxicity	Hyalectin	No evidence of mutagenic potential.
Genotoxicity	Hyalectin	No evidence of clastogenic activity.
Genotoxicity	Hyalectin	No evidence of mutagenic potential.
Genotoxicity	Hyalectin	No demonstration of mutagenic potential or bone marrow cell toxicity
Implantation	Hyalectin	No problems, signs of toxicity were noted.
Implantation	Hyalectin	No significant local or systemic toxicological effects.
Implantation	Hylovet	No evidence of local or systemic toxicity, no treatment related effects.
Nonclinical Testing		
Intra-articular injections: Pond-Nuki model in dogs	Hyalgan (weekly injections, 7mg)	Significant reduction in cartilage damage and disease progression.
Intra-articular injections: Induced OA in horses	Hyalgan (2mL (10 mg /mL))	No toxicity. No detectable differences in results noted in lameness, joint circumference, joint flexion, synovial fluid and radiographic evaluations. Consistent decrease in uptake of radionuclide in treated joints.
Intra-articular injections: Non-infectious synovitis associated with OA in horses	Hyalgan (2mL (20 mg))	No toxicity reported. Response to treatment rated as excellent or good in 90% of cases.
Evaluation in horses: compared to Hyvisc	Hyalgan (2mL (20 mg))	No adverse effects reported. Treatment response similar in both groups.

Test	Test article used	Result
Evaluation in horses: equine arthropathy	Hyalgan (2-4 mL (10 mg/mL))	No general systemic reactions noted, results judged as very good.
Dose effect in induced carpal synovitis in horses	Hyalgan (5, 20, or 40 mg)	No signs of systemic or local toxicity reported. Animals receiving 20 or 40 mg showed constant clinical improvement through duration of treatment.
Modifications in synovial fluid of horse	Hyalgan (up to 60 mg injection)	Consistent improvement observed.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

Since TRILURON™ is of identical chemical formulation to Hyalgan, previously approved under P950027, but differs from Hyalgan only in that less of the solution is injected (3 weekly injections of 2.0 ml for TRILURON™ and 5 weekly injections of 2.0 ml for Hyalgan), the clinical studies used to provide evidence of the reasonable assurance of the safety and effectiveness of Hyalgan under P950027 provide reasonable assurance of the safety of TRILURON™ as well. To support the approval of Hyalgan, a multicenter clinical investigation was performed, showing the safety and effectiveness of intra-articular injection of Hyalgan in relieving pain in patients with osteoarthritis of the knee. Additionally, forty non-U.S. clinical trials, involving a total of approximately 6,000 patients, as well as a double-blind placebo-controlled single center study provided additional support regarding the safety of Hyalgan.

Additional details of these studies are provided in the SSED for P950027 that is available on the CDRH website at http://www.accessdata.fda.gov/cdrh_docs/pdf/P950027A.pdf.

A. Study Design

To specifically compare the effectiveness of TRILURON™ (investigational device) to Hyalgan (control device), a retrospective comparison of data prospectively collected from two randomized, controlled trials was performed. The objective of this study was to compare the change from baseline in Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain scores after 26 weeks in subjects treated with TRILURON™ to subjects treated with Hyalgan. The study used the data on the change from baseline in WOMAC Pain after 26 weeks from the Hyalgan treatment arm in the Hyalgan PMA study as a historical control to compare to the data from the TRILURON™ treatment arm of the Berenbaum study[1]. The Berenbaum study includes data for 209 intent-to-treat (ITT) subjects that received the TRILURON™ product and 223 subjects that received another 3 injection HA device. The primary endpoint in the Berenbaum study was the change from baseline at week 26 in WOMAC Pain score, which was also collected as a secondary effectiveness endpoint in the Hyalgan PMA study with data for 105 subjects available at 26 weeks (from n=164 ITT patients). Therefore, this statistical analysis included the Hyalgan subjects from the Hyalgan PMA study as a historical control to compare to the results from the Berenbaum study.

Comparisons of study inclusion/exclusion criteria and demographic/baseline characteristics between the two groups were performed and are summarized below respectively in Table 3 and Table 4.

Table 3: Key Subject Inclusion/Exclusion Criteria

Criteria	Berenbaum Study	Hyalgan PMA Study
Age	50-80 years	40 years or older
Primary Diagnosis	Knee Osteoarthritis per American College of Rheumatology criteria	Knee Osteoarthritis per American College of Rheumatology criteria
Disease History	History of symptoms for at least 6 months and insufficient/failed response to analgesics and/or regular non-steroidal anti-inflammatory drugs (NSAID), or were intolerant to regular NSAID or weak opioids.	History of symptoms compatible with OA for at least 1 year. And failure to adequately respond to nonpharmacologic care and to simple analgesics, i.e. acetaminophen.
Current Symptoms	Global knee pain of 40 mm or greater on a 100 mm visual analogue scale (VAS), Western Ontario and McMaster Universities (WOMAC) pain subscale score of 25 or greater on the 0–100 normalized scale and Lequesne index of 4 or greater.	Knee pain on more than half of the days during the preceding month, a minimum of 20mm on at least one of the 5 items in the WOMAC pain subscale and have “moderate” or “marked” pain as assessed by the masked observer.
Contralateral Knee Symptoms	Radiological evidence of bilateral knee osteoarthritis was accepted if global pain VAS in the contralateral knee was less than 30 mm.	Bilateral OA is accepted; in the case of bilateral OA, the knee with the greater level of pain per the 50- foot walk test was identified for treatment.
Kellgren-Lawrence (KL) Grade	II or III	II or III
Exclusions	Isolated/predominantly patellofemoral symptomatic osteoarthritis, secondary knee osteoarthritis, symptomatic hip osteoarthritis homolateral to the target knee, inflammatory or other rheumatic diseases, clinical joint effusion, excessive (≥8°) varus or valgus knee deformity.	Secondary OA or other inflammatory joint disease, acute flare of pseudogout within the past 3 months, joint infection, chronic and active fibromyalgia that would interfere with the evaluation of the patient, gout, intra-articular neoplasm, axial deviation of the lower limbs > 25 degrees in valgus or varus, symptomatic OA of hip or knee that interferes with functional assessment of study knee, clinically significant ML instability, osteonecrosis of either knee that interferes with assessment of the knee.

Table 4: Demographics and Baseline Characteristics

Variable		TRILURON™ (Berenbaum Study) (N=209)	Hyalgan (Hyalgan PMA Study) (N=164)
Gender N (%)	Female	134 (64.1)	99 (60.3)
	Male	75 (35.9)	65 (39.6)
Race N (%)	Caucasian	Not Available	137 (83.6)
	Black	Not Available	23 (14.0)
	Other	Not Available	4 (2.4)
Kellgren-Lawrence (KL) Grade N (%)	Grade II	113 (54.1)	56 (34.6)
	Grade III	96 (45.9)	106 (65.4)
BMI (kg/m^2)	Mean (SD) (Min, Max) N	27.7 (3.1) (--) N=209	31.42 (6.3) (18.6, 57.1) N=164
Age	Mean (SD) (Min, Max) N	66.1 (8.1) (--) N=209	63.5 (10.1) (41,90) N=164
Preoperative WOMAC Pain	Mean (SD) (Min, Max) N	48.8 (14.9) (--) N=209	48.61 (19.9) (7.8,98.4) N=164

Since the key inclusion/exclusion criteria were similar, and the demographic and baseline characteristics were comparable for the two studies, these comparisons established evidence of sufficiently comparable patient populations.

All of the patients in each study were scheduled to return for follow-up examinations. The TRILURON™ subjects were followed at 6, 14, 20 and 26 weeks. The Hyalgan subjects were followed at 9, 12, 16, 21 and 26 weeks. The follow-up intervals were similar, and the timepoint for assessment of the primary endpoint (26 weeks) was the same.

The primary effectiveness endpoint of the retrospective comparison analysis was the difference between the investigational and control groups in the mean change from baseline in WOMAC Pain scores at 26 weeks.

Secondary effectiveness evaluations for TRILURON™ include:

- WOMAC Function, Stiffness and Total scores on a 0 (best) to 100 (worst) point scale
- Global knee pain on a 0 (no pain) to 100 mm (worst pain) visual analog scale (VAS)
- Lequesne Index ranging from 0 (worst) to 24 (best);
- Intermittent and Constant Osteoarthritis Pain Index (ICOAP) on the 0–100 score
- Patient global assessment (PGA) on a 0 (best) to 100 mm (worst) VAS
- Proportion of OARSI/OMERACT responders

- Proportion of patients achieving the minimum clinically important improvement (MCII)
- Proportion of patients achieving the patient acceptable symptom state (PASS)

As the primary safety of the investigational device has been established by the safety of the Hyalgan control, the safety data on TRILURON™ in the Berenbaum study are presented as supporting safety evidence only.

B. Safety and Effectiveness Results

1. Safety Results

As TRILURON™ and Hyalgan have the identical chemical formulation and differ only in that a lower dose is injected (3 weekly injections for TRILURON™ compared to 5 weekly injections of Hyalgan), the primary evidence of safety of Hyalgan in P950027 is directly applicable to TRILURON™. Common adverse events reported for Hyalgan include gastrointestinal complaints, injection site pain, headache, local joint pain and knee swelling/effusion, rash, pruritus, and ecchymosis.

Additionally, supporting evidence of safety of TRILURON™ was provided by the safety data from a prospective, randomized, controlled trial that compared TRILURON™ (investigational device, 213 treated subjects in safety analysis) to another 3-injection hyaluronic acid (control device, 223 treated subjects in safety analysis) reported Berenbaum et al[1].

The number of subjects with any adverse events was 75 (35.2%) in the TRILURON™ group, which is very similar to the 74 (33.2%) reported in the control group. Adverse events leading to study discontinuation were reported in 4 (1.9%) in the TRILURON™ group and in 3 (1.3%) in the control group. Local adverse events were reported in 8 (3.8%) subjects in the TRILURON™ group and in 4 (1.8%) in the control group.

The 4 reports (1.9%) of adverse events in the TRILURON™ group leading to study discontinuation were worsening of knee OA, post-traumatic meniscal lesion, ischemic stroke and angiosarcoma with pleural effusion. The 2 reports in the control group of adverse events leading to study discontinuation were worsening of knee OA (2 subjects, 0.9%) and metastatic pulmonary cancer (1 subject, 0.4%).

Local adverse events reported for TRILURON™ were joint effusion/swelling (4 subjects, 1.9%), joint pain (2 subjects, 0.9%), injection site hematoma (2 subjects, 0.9%) and injection site warmth (1 subject, 0.5%). The local adverse events reported for control were joint effusion/swelling (1 subject, 0.4%) and joint pain (3 subjects, 1.4%). Usually, local adverse events are transient and disappear spontaneously within a few days of resting the affected joint and/or applying ice locally.

The number of subjects with any adverse events and adverse events leading to study discontinuation were similar in both the TRILURON™ and Hyalgan groups. A slightly higher number of transient, local adverse events were reported in the TRILURON™ group. No cases of pseudoseptic arthritis were observed. Overall, there were no new safety findings for TRILURON™.

2. Effectiveness Results

The study used to establish reasonable assurance of the effectiveness of TRILURON™ compared prospectively collected data from the Hyalgan treatment arm in the Hyalgan PMA study to prospectively collected data from the TRILURON™ treatment arm of a study (Berenbaum study) summarized in an article by Berenbaum et al.[1]

The primary evidence of effectiveness was the difference between the mean WOMAC Pain change from baseline at 6 months in the ITT population. Missing data were replaced using the baseline observation carried forward imputation method. This "worst case" method imputes a WOMAC Pain change of 0 at 6 months for each subject with missing data. As shown in Table 5, the mean WOMAC Pain from baseline at 6 months post-injections were -18.4 and -14.9 in the TRILURON™ and Hyalgan, respectively. The difference between the means was -3.545 and the upper limit of the one-sided 95% CI (0.2403) was less than the upper limit of 9. Thus, TRILURON™ is non-inferior to Hyalgan.

Table 5: WOMAC Pain Primary Effectiveness Evaluation (Baseline Observation Carried Forward)

Device	N	Mean	Std Dev.	Diff btw Means (TRILURON - Hyalgan)	Upper Limit of one-sided 95% CI	Non-inferiority (i.e., upper limit <=9)?
TRILURON™	209	-18.4	21.54	-3.545	0.2403	Yes
Hyalgan	164	-14.9	22.56			

For the primary endpoint analysis, 59 subjects in the Hyalgan group and 37 in the TRILURON™ group were missing data. As patient level data for the TRILURON™ group were not available, it was not possible to perform analyses using other missing data imputation methods. However, last observation carried forward, completers, multiple imputation and tipping point analyses were performed to assess the effect of missing data in the Hyalgan group on the primary endpoint. These results were compared against the "worst case" baseline-carried-forward imputation for TRILURON™. The sensitivity analyses support the robustness of the non-inferiority finding of the primary endpoint.

Secondary effectiveness evaluations of TRILURON™ are provided in Table 6. Improvement over baseline at 26 weeks was demonstrated in the WOMAC Function, Stiffness and Total scores, VAS Pain, Lequesne Index, ICOAP Total,

Constant and Intermittent scores, and VAS Patient Global. Additional secondary endpoints assessed the number and proportion of subjects achieving a prespecified minimum value for the endpoint (responders). More than 50% of the TRILURON™ subjects met the minimum OARSI/OMERACT responders criteria and achieved the minimum clinically important improvement (MCII) Pain and Function. More than 40% achieved the minimum patient acceptable symptom state (PASS) for Pain, Function and Patient Global, and for the MCII Patient Global.

Table 6: Secondary Effectiveness Evaluations of TRILURON™

Evaluation	Results
	Change from Baseline at 26 weeks
WOMAC Function	-15.4 (-18.2 to -12.7)
WOMAC Stiffness	-15.7 (-19.0 to -12.4)
WOMAC Total	-16.1 (-18.8 to -13.4)
VAS Pain	-26.7 (-30.0 to -23.4)
Lequesne Index	-3.0 (-3.5 to -2.5)
ICOAP Total	-17.9 (-20.8 to -15.1)
ICOAP Constant	-16.9 (-19.8 to -14.0)
ICOAP Intermittent	-18.8 (-21.9 to -15.8)
VAS Patient Global	14.3 (10.6 to 17.9)
	Responders at 26 weeks n (%)
OARSI/OMERACT Responders	122 (58.4%)
MCII Pain	122 (58.4%)
PASS Pain	102 (48.8%)
MCII Function	117 (56.0%)
PASS Function	97 (46.4%)
MCII Patient Global	92 (44.0%)
PASS Patient Global	90 (43.1%)

3. Subgroup Analyses

   No subgroup analyses were performed.

4. Pediatric Extrapolation

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

C. 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 clinical study of P950027 (that was utilized for the control arm in the submitted non-inferiority analysis) included 15 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). No information was available regarding the number of investigators in the published Berenbaum study (that was utilized for the investigative arm in the submitted non-inferiority analysis), and this study was funded by a sponsor other than the submitter of this PMA. Therefore, the information provided does not raise any questions about the reliability of the data.

XI. 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 Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary endpoint analysis was mean change in WOMAC Pain from baseline and used baseline observation carried forward to replace missing data. The mean change in WOMAC Pain from baseline at 6 months post-injections were -18.4 and -14.9 in the TRILURON™ and Hyalgan, respectively. The difference between the means was -3.545 and the upper limit of the one-sided 95% CI (0.2403), which was less than the upper limit of 9. Thus, the primary effectiveness evaluation demonstrates that TRILURON™ is non-inferior to Hyalgan.

Despite the sensitivity analyses' bias in favor of Hyalgan, TRILURON™ met the non-inferiority requirements in two of the three analyses. Likewise, the tipping point was 17 (29%) and 35 (59%) subjects when the imputed value for Hyalgan was higher than that of TRILURON™ by -83 and -38.4, respectively. When the imputed value for Hyalgan was -23.2 higher than that of TRILURON™, the results did not change from non-inferiority even after 100% of missing data was imputed. Thus, the sensitivity analyses support the non-inferiority finding of the primary endpoint and confirm its robustness.

All secondary effectiveness evaluations of continuous and categorical variables showed improvement over baseline at 26 weeks. More than 50% of the TRILURON™ subjects were OARSI/OMERACT responders and achieved the minimum clinically important

improvement (MCII) Pain and Function, and more than 40% achieved the patient acceptable symptom state (PASS) Pain, Function and Patient Global, and the MCII Patient Global.

B. Safety Conclusions

As TRILURON™ and Hyalgan have the identical chemical formulation and differ only in that a lower dose is injected (3 weekly injections for TRILURON™ compared to 5 weekly injections of Hyalgan), the primary evidence of safety of Hyalgan in P950027 is directly applicable to TRILURON™. Thus, the safety of TRILURON™ has already been established.

As described in Section IX, preclinical data from PMA P950027 for Hyalgan are applicable for this current submission for TRILURON™ because the technological characteristics and indications for use for TRILURON™ are identical to those of Hyalgan, and the preclinical data from the original application are incorporated by reference here. The nonclinical studies, including biocompatibility testing, nonclinical effectiveness tests, material characterization testing, sterilization validation, packaging testing, and shelf life testing, which were conducted in support of the original PMA P950027, provide reasonable assurance of the safety and effectiveness of Hyalgan for treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy, and simple analgesics.

The safety data from the Berenbaum et al study, discussed in Section 2.10.1, provide supporting evidence of the safety of the TRILURON™ device. The number of subjects with any adverse events was 75 (35.2%) in the TRILURON™ group, which is very similar to the 74 (33.2%) reported in the control group for this study. Local adverse events were reported in 8 (3.8%) subjects in the TRILURON™ group and in 4 (1.8%) in the control group. The difference in local adverse events was not statistically significant. Adverse events leading to study discontinuation were reported in 4 (1.9%) instances in the TRILURON™ group and in 3 (1.3%) instances in the control group. There were no new safety findings for TRILURON™.

C. Benefit-Risk Determination

The probable benefits of TRILURON™ are based on the results of a retrospective non-inferiority analysis comparing TRILURON™ (from Berenbaum study) to Hyalgan (P950027).

The primary evidence of effectiveness was the demonstration of non-inferiority of TRILURON™ to Hyalgan with respect to the difference between the mean WOMAC Pain changes from baseline at 6 months in the ITT populations for the respective studies. Missing data were replaced using the baseline observation carried forward imputation method. The mean WOMAC Pain change from baseline at 26 weeks post-first injection were -18.4 and -14.9 in the TRILURON™ and Hyalgan groups,

respectively. The difference between the means was -3.545 and the upper limit of the one-sided 95% CI (0.2403) was less than the upper limit of 9. Thus, TRILURON™ is non-inferior to Hyalgan.

The change from baseline in WOMAC Pain at 26 weeks for TRILURON™ was non-inferior to Hyalgan. Improvement over baseline at 26 weeks was demonstrated in the WOMAC Function, Stiffness and Total scores, VAS Pain, Lequesne Index, ICOAP Total, Constant and Intermittent scores, and VAS Patient Global. More than 50% of the TRILURON™ subjects met the minimum OARSI/OMERACT responders criteria and achieved the minimum clinically important improvement (MCII) Pain and Function. More than 40% achieved the minimum patient acceptable symptom state (PASS) for Pain, Function and Patient Global, and for the MCII Patient Global.

The probable risks and safety profile of TRILURON™ are identical to those of Hyalgan, a viscosupplement previously approved under P950027 and of identical chemical formulation to Hyalgan. TRILURON™ differs from Hyalgan only in that less of the product is injected (3 weekly injections of 2.0 ml for TRILURON™ and 5 weekly injections of 2.0 ml for Hyalgan); therefore, the nonclinical and clinical studies used to provide evidence of the reasonable assurance of the safety of Hyalgan under P950027 apply equally well to TRILURON™.
As reported in the Hyalgan SSED, common adverse events reported for Hyalgan include gastrointestinal complaints, injection site pain, headache, local joint pain and knee swelling/effusion, rash, pruritus, and ecchymosis. In the Berenbaum study, adverse event rates for TRILURON™ were similar to those for Hyalgan and the controls used in the study.

Patient Perspectives

Patient perspectives considered during the review included patient-reported assessments consisting of WOMAC Pain scores, WOMAC Function, WOMAC Stiffness and WOMAC Total scores, VAS Pain, Lequesne Index, ICOAP Total, Constant and Intermittent scores, and VAS Patient Global. These assessments provided the basis for evaluation of the primary and secondary effectiveness endpoints of the retrospective non-inferiority analysis used to support the PMA approval of TRILURON™.

In conclusion, given the available information identified above and its applicability to TRILURON™, the data support that for the treatment of knee pain due to osteoarthritis in patients who have failed to adequately respond to conservative nonpharmacological therapy and simple analgesics (e.g., acetaminophen) the probable benefits for TRILURON™ outweigh its probable risks.

D. Overall Conclusions

The data in this application and its applicability to TRILURON™ provide reasonable assurance of the safety and effectiveness of TRILURON™ when used in accordance

with the indications for use. Reasonable assurance of the safety of TRILURON™ was established through reference to the approved PMA (P950027) for Hyalgan, which is identical in composition to TRILURON™. Reasonable assurance of effectiveness was demonstrated from the results of a retrospective non-inferiority analysis of data obtained from randomized, controlled trials for TRILURON™ (published study by Berenbaum et al.[1]) and Hyalgan (P950027).

XIII. CDRH DECISION

CDRH issued an approval order on March 26, 2019.

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

XIV. 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.

XV. REFERENCES

1. Berenbaum, F. et al. (2012). A randomized, double-blind, controlled trial comparing two intra-articular hyaluronic acid preparations differing by their molecular weight in symptomatic knee osteoarthritis. Annals of the rheumatic diseases. 71(9), 1454-1460.