SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Sodium Hyaluronate

Device Trade Name: TriVisc™

Device Procode: MOZ

Applicant's Name and Address: OrthogenRx, Inc.
2005 South Easton Road, Suite 207
Doylestown, Pennsylvania 18901

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P160057

Date of FDA Notice of Approval: November 13, 2017

II. INDICATIONS FOR USE

TriVisc™ 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 (allergy) to sodium hyaluronate preparations.
- Do not inject this product in the knees of patients with 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 TriVisc.

V. DEVICE DESCRIPTION

TriVisc is a sterile, viscoelastic, non-pyrogenic solution of purified, high molecular weight sodium hyaluronate, derived from a bacterial fermentation process. Sodium hyaluronate is a polysaccharide containing repeated disaccharide units of glucuronic acid and N-acetylglucosamine. TriVisc is supplied in a 3 mL glass syringe. The contents of the syringe are sterile and non-pyrogenic.

Each 3 mL syringe prefilled with 2.5 mL of TriVisc contains:

- Sodium hyaluronate (25.0 mg)
- Sodium chloride (21.3 mg)
- Disodium phosphate Dodecahydrate (1.5 mg)
- Sodium hydroxide (q.s. to adjust pH)
- Hydrochloric acid (q.s. to adjust pH)
- Water for injection (q.s. 2.5 mL)

VI. ALTERNATIVE PRACTICES AND PROCEDURES

For patients who have failed to respond adequately to conservative non-pharmacological therapy and simple analgesics (e.g., acetaminophen), alternative practices and procedures include 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 surgery are also alternative treatments.

VII. MARKETING HISTORY

GenVisc® 850, which has the same chemical composition as the subject TriVisc™ (except it is administered under a weekly 5-injection regimen of 2.5 ml per injection instead of a weekly 3-injection regimen of 2.5 ml per injection) has been commercially distributed under different branded names (e.g. ADANT) in over 40 countries outside of the United States, as shown in Table 1 below.

Table 1: Marketing History

No.	*Launched Country*	No.	*Launched Country*
1	Spain	23	Dominican Rep.
2	Portugal	24	Ecuador
3	Cyprus	25	El Salvador
4	France	26	Guatemala
5	Belgium	27	Honduras
6	The Netherlands	28	Mexico
7	Luxembourg	29	Nicaragua
8	Turkey	30	Panama
9	Egypt	31	Paraguay
10	Georgia	32	Peru
11	Kazakhstan	33	Venezuela
12	Japan	34	Uruguay
13	Thailand	35	Azerbaijan
14	Indonesia	36	Vietnam
15	Malaysia	37	Russia
16	Iran	38	China
17	Argentina	39	Israel
18	Bolivia	40	Ukraine
19	Brazil	41	Austria
20	Chile	42	United Kingdom
21	Colombia	43	Switzerland
22	Costa Rica	44	United States

TriVisc has not been withdrawn from marketing in any country for any reason related to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The adverse events that may occur with treatment with TriVisc are among those that may occur in association with intraarticular injections and include arthralgia (joint pain with no evidence of inflammation), arthropathy/arthrosis/arthritis (joint pain with evidence of inflammation), back pain, non-specific pain, injection site reaction, injection site pain, and headaches.

For the specific adverse events that occurred in the clinical studies of a sodium hyaluronate device of identical chemical formulation to TriVisc, please see Section X below. The only difference between these two devices is that GenVisc 850, approved under PMA P140005, is administered under a weekly 5-injection regimen of 2.5 ml per injection, whereas TriVisc is administered under a weekly 3-injection regimen of 2.5 ml

per injection. Thus, the clinically established safety profile of GenVisc 850 is directly applicable to TriVisc.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Nonclinical Safety Studies for TriVisc

Since TriVisc is of identical chemical formulation to GenVisc 850 (previously approved under P140005), all of the nonclinical studies used to provide evidence of the reasonable assurance of the safety of GenVisc 850 apply directly to TriVisc. These nonclinical safety studies included biocompatibility testing for acute toxicity, subacute and chronic toxicity, mutagenicity and genotoxicity, immunogenicity, irritation, and hemolysis, as well as sterility assurance testing. A summary of these nonclinical studies conducted in support of the original PMA is available in the SSED for P140005 on the CDRH website at https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140005B.pdf.

Data from accelerated and long-term stability studies were used to establish a shelf life of 48 months for TriVisc when stored at temperatures between 33.8 and 86 °F (1 and 30 °C).

B. Comparison Studies of TriVisc and VISCO-3™

In lieu of providing a clinical data set for TriVisc, the sponsor provided various nonclinical comparison studies of TriVisc and VISCO-3™, another viscosupplement device previously approved under P980044/S27 with the same indications for use as TriVisc and, similar to TriVisc, also administered under a weekly 3-injection regimen of 2.5 ml per injection. The purpose of these nonclinical comparison studies was to establish sufficient similarity of the two viscosupplement devices such that FDA could apply Section 216 of the Food and Drug Modernization Act (FDAMA), i.e., the "six-year rule", to assess the effectiveness profile of TriVisc.

According to FDA's "Guidance on Section 216 of the Food and Drug Modernization Act of 1997" available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073709.pdf , FDA may choose to utilize the publicly available detailed SSED of a previously approved device to support approval of a PMA for a

new device if the applicant provides "a detailed justification of how the information in the earlier SSED applies to the applicant's device" and if the applicant is able "to describe how the devices are similar enough to allow for the data from the earlier device to apply to the new device."

For the purpose of establishing sufficient similarity of TriVisc and VISCO-3™, the sponsor provided the following comparison of the chemical compositions of the two viscosupplement devices (Table 1).

Table 2: Comparison of TriVisc and VISCO-3™

Component	Function	VISCO-3™ * Mass / Volume	TriVisc Mass / Volume
Sodium hyaluronate	Main ingredient	25 mg	25 mg
Sodium chloride	Isotonicity	21.25 mg	21.3 mg
Disodium phosphate dodecahydrate	Buffer	1.343 mg	1.50 mg
Sodium dihydrogenphosphate dihydrate	Buffer	0.04 mg	-
Hydrochloric acid, concentrated	pH adjuster	-	q.s.**
Sodium hydroxide	pH adjuster	-	q.s.
Water	Solvent	q.s. 2.5 mL	q.s. 2.5 mL

* Chemical composition for VISCO-3™ as provided within in the SSED for P980044/S27 available on the CDRH website at https://www.accessdata.fda.gov/cdrh_docs/pdf/P980044S027B.pdf.

** *quantum satis* or "as much as is sufficient". For example, "q.s. 2.5 mL" denotes add a sufficient volume of liquid so as to produce a total volume of 2.5 mL.

The mass per unit volume concentration of 25 mg of sodium hyaluronate per injection volume of 2.5 ml is the same for both devices. While there are modest differences in other components, e.g. the concentrations of sodium chloride and buffering agents, for the two devices, none of these differences in components other than sodium hyaluronate would be expected to lead to substantial differences in the effectiveness profiles of these two viscosupplement devices.

The effectiveness profile of a sodium hyaluronate viscosupplement device is more likely associated with characteristics of the sodium hyaluronate component itself. For example, a comprehensive review by Altman et al. (Altman RD, Manjoo A, Fierlinger A, Niazi F, and Nicholls M. "The mechanism of action for hyaluronic acid

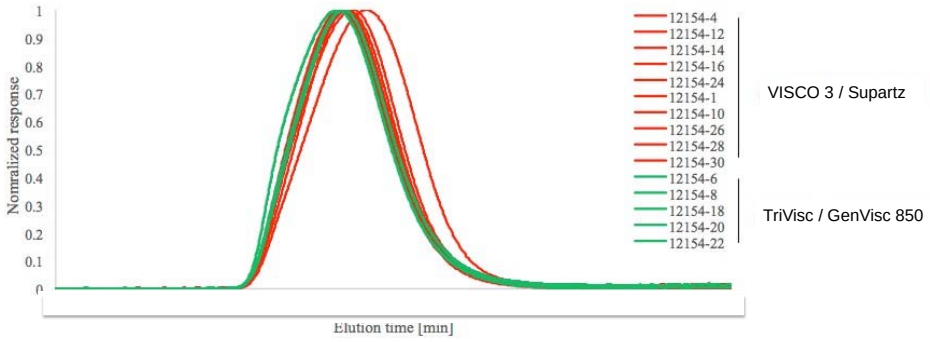
treatment in the osteoarthritic knee: a systematic review"; BMC Musculoskeletal Disorders 2015; 16: 321) of published nonclinical studies focusing on possible mechanisms of action for viscosupplement devices postulates that the molecular weight of the hyaluronic acid component appears to be the intrinsic property most responsible for the benefits of intraarticular hyaluronic acid products, with higher molecular weights inducing more pronounced effects. Altman et al. specifically stated that their review supports the premise that higher molecular weight hyaluronic acid "provides superior chondroprotective, proteoglycan and glycosaminoglycan synthesis, anti-inflammatory, mechanical, and analgesic mechanisms of actions."

In accordance with the postulation above, if two viscosupplement devices possess the same (major) chemical constituents in the same (or nearly the same) concentrations, the same (or nearly the same) solution characteristics (e.g., intrinsic viscosity, pH, etc.) the degree of similarity in molecular weight profile (i.e., molecular weight averages and molecular weight distributions) of the sodium hyaluronate component would likely be the predominant factor in any assessment of whether or not the effectiveness profile of one viscosupplement device would serve to adequately represent the anticipated effectiveness profile of a new and similar viscosupplement device in the absence of any clinical effectiveness data for the new device.

In this PMA, the sponsor provided (or referenced from its previously approved PMA, P140005, for GenVisc 850) detailed comparisons of the respective molecular weight profiles of TriVisc/GenVisc 850 and VISCO-3™/SUPARTZ FX[1]. In Figure 1 below, it can be inferred from the high degree of overlap of TriVisc™/GenVisc 850 and VISCO-3™/SUPARTZ FX samples, with respect to molecular weight distribution of the sodium hyaluronate component, that the inter-product batch variability between TriVisc and VISCO-3™ is no greater than the intra-product batch variabilities within TriVisc and VISCO-3™ themselves. Also of note is that although the sodium hyaluronate component is derived from different sources, extraction from rooster combs for VISCO-3™ and bacterial fermentation for TriVisc, the molecular weight profiles of the sodium hyaluronate component are nonetheless very similar.

[1] SUPARTZ FX, approved under P980044, is identical in chemical composition to VISCO-3™, but administered under a weekly 5-injection regimen as opposed to the 3-injection regimen for VISCO-3™. This is the same relationship as that of GenVisc 850 to TriVisc; GenVisc 850 is identical in chemical composition to TriVisc, but administered under a weekly 5-injection regimen as opposed to the 3-injection regimen for TriVisc.

Figure 1: Molecular weight distribution comparison of TriVisc/GenVisc 850 and VISCO-3™/SUPARTZ FX



The average elution profiles for 10 lots of TriVisc/GenVisc 850 and 5 lots of VISCO-3™/SUPARTZ FX confirms the conclusions. In addition, the differences in number-average (M_n), weight-average (M_w), and z-average (M_z) molecular weights and polydispersity index (PDI), defined as M_w/M_n, for a TriVisc and VISCO-3™ are much smaller in magnitude than the differences in molecular weights of viscosupplement devices cited by Altman et al. that would be expected to lead to significant differences in effectiveness profiles. Furthermore, although the assessed rheological parameters such as Crossover Frequency and Shear Viscosity provide a less sensitive means of distinguishing any significant differences in the molecular weight profiles of TriVisc and VISCO-3™ than do the parameters assessed from GPC measurements, the values of these rheological parameters do provide further evidence of the close similarity in molecular weight profiles.

In addition, the sponsor conducted comparative chemical analyses of VISCO-3™/SUPARTZ FX and TriVisc/GenVisc 850. Analytical methods included infrared (IR) spectroscopy, H^1 and C^{13} nuclear magnetic resonance (NMR) spectroscopy, circular dichroism, high pressure liquid chromatography (HPLC), electrophoresis, and ultraviolet (UV) spectroscopy. While all of these analyses provided additional confirmatory evidence of the similarity of the two viscosupplement devices, the GPC assessments discussed above provided the most sensitive means of comparing the molecular weight profiles of the sodium hyaluronate component of the two devices.

In summary, the sponsor provided adequate evidence in its PMA of the sufficient similarity of TriVisc and VISCO-3™ with regard to chemical constituents, concentrations of constituents, solution characteristics, and molecular weight

profiles of the sodium hyaluronate component. Because of this, FDA was able to apply Section 216 of the FDAMA and confirm that the evidence presented in the SSED for VISCO-3™ in support of the reasonable assurance of its effectiveness is directly applicable towards establishing reasonable assurance of the effectiveness of TriVisc.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

A. Studies Utilized to Establish Reasonable Assurance of the Safety of TriVisc

Since TriVisc is of identical chemical formulation to GenVisc 850, previously approved under P140005, but differs from GenVisc 850 only in that less of the solution is injected (3 weekly injections of 2.5 ml for TriVisc and 5 weekly injections of 2.5 ml for GenVisc 850), the clinical studies used to provide evidence of the reasonable assurance of the safety of GenVisc 850 under P140005 apply equally well to TriVisc. Two clinical studies, the AMELIA[2] and Yong Ping[3] studies, were used to establish reasonable assurance of the safety of GenVisc 850 and are summarized as follows. Additional details of these studies are provided in the SSED for P140005 that is available on the CDRH website.

The primary evidence of safety was provided by the comparison of GenVisc 850 to PBS in the AMELIA study. In this study, four cycles of 5 injections of GenVisc 850 or PBS were administered with an interval of 6 months for the first three cycles, and 1 year for the fourth cycle. Patients were followed for 1 year after the last injection. The population of patients evaluated for the safety of GenVisc 850 included 306 subjects (153 GenVisc 850, 153 PBS). In each treatment group, 127 subjects experienced at least one adverse event during the study, and 22 patients (11 in each treatment group) experienced at least one adverse event that was reported as possibly, probably or certainly related to the device (4). None of the related adverse events were assessed as severe. In the GenVisc 850 treatment group, the 15 adverse events reported as related adverse

[2] Navarro-Sarabia F, Coronel P, Collantes E, Navarro FJ, de la Serna AR, Naranjo A, Gimeno M, Herrero-Beaumont G; AMELIA study group. A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project. Ann Rheum Dis. 2011;70: 1957-62.

[3] Y., Jianhao, L., Tiansheng, S., Yongqiang, H., Weimin, F., Ming, C., Tiezheng, S., Jianhua, Y., Liang, X., Xiaoyuan, G., Yongping, C., 2016. The efficacy and safety of sodium hyaluronate injection (Adant(R)) in treating degenerative osteoarthritis: a multi-center, randomized, double-blind, positive-drug parallel-controlled and non-inferiority clinical study. Int J Rheum Dis 19, 271–278.

events were pain at the injection site (6), allergic reaction (3), arthralgia (2), bleeding at the injection site (2), bleeding (1), and heaviness (1). In the PBS treatment group, the 14 adverse events reported as related were bleeding at the injection site (6), allergic reaction (3), pain at the injection site (2), arthralgia (1), and arthritis (1).

Table 3: Related adverse events by severity

Related Adverse Events	GenVisc 850			PBS		
	Mild	Moderate	Total	Mild	Moderate	Total
Allergic reaction	2	1	3	3	--	3
Pain injection site	2	4	6	2	--	2
Bleeding	--	1	1	--	--	--
Bleeding at injection site	2	--	2	6	--	6
Arthralgia	--	2	2	1	1	1
Arthritis	--	--	--	--	1	1
Heaviness	1	--	1	--	--	--
Total	7	8	15	12	2	14

A total of 513 complete GenVisc 850 treatment cycles and a total of 487 complete PBS treatment cycles were administered in the study. Table 4 provides the number of related adverse events per complete treatment cycle. The rate of adverse events per treatment cycle for GenVisc 850 is 0.029, which is the same as the PBS rate. This low adverse event rate demonstrates the safety of GenVisc 850 following repeat treatments.

Table 4: Related adverse events by treatment cycles

Treatment	**No. Complete Cycles**	**No. Related Adverse Events**	**Related AEs per Complete Cycles**
GenVisc 850	513	15	0.029
PBS	487	14	0.029

Supporting evidence of safety is provided by the comparison of GenVisc 850 to SUPARTZ/SUPARTZ FX in the Yong Ping study for time periods up to 6 weeks. The population of patients evaluated to assess the safety of GenVisc 850 included 229 subjects (116 GenVisc 850, 113 SUPARTZ/SUPARTZ FX). In the Supartz/Supartz FX

group, 26 subjects (23.0%) experienced adverse events (AEs). In this group, 6 events (5.3%) were judged as possibly related to the device (4 cases of local pain and 2 cases of swelling). In the GenVisc 850 group, 21 subjects (18.1%) experienced AEs. In this group 2 events (1.7%) were judged possibly related to the device (1 case of local pain and 1 case of rash). One serious adverse event (SAE) that was unrelated to the device, prostatic hyperplasia treated with surgical excision, was reported in the Supartz/Supartz FX group. There were no statistically significant differences in the incidence rates of these adverse events between the GenVisc 850 and SUPARTZ/SUPARTZ FX groups. A summary of AEs is provided in Table 5.

Table 5: Adverse events reported in Yong Ping study

	Category	SUPARTZ/ SUPARTZ FX Group/N(%)	GenVisc 850 Group/N(%)	Statistics	P value	Method
AE	Yes	26 (23.0)	21 (18.1)	0.844	0.358	Chi-square
	No	87 (77.0)	95 (81.9)			
	Total	113	116			
Related AE	Yes	6 (5.3)	2 (1.7)	--	0.167	Fisher
	No	107 (94.7)	114 (98.3)			
	Total	113	116			
SAE	Yes	1 (0.9)	0 (0.0)	--	1.000	Fisher
	No	112 (99.1)	116 (100.0)			
	Total	113	116			

Note: AEs that were definitely related, probably related, and possibly related to the device and abnormal laboratory findings were judged as Related AEs.

B. Studies Utilized to Establish Reasonable Assurance of the Effectiveness of TriVisc

As discussed in Section IX, the sponsor provided comparative nonclinical test results to establish sufficient similarity of the TriVisc and VISCO-3™ (previously approved under P980044/S27) and thereby enable FDA to apply Section 216 of the FDAMA with regard to the effectiveness profile of VISCO-3™. In doing so, FDA was able to confirm that the evidence for the effectiveness of VISCO-3™ presented in the SSED for VISCO-3™ is applicable to and representative of the effectiveness profile of TriVisc.

As documented in the SSED for VISCO-3™, a pivotal, prospective, multi-center, randomized, double-blind, parallel arm, active controlled, and non-inferiority clinical study was utilized to provide reasonable assurance of the safety and

effectiveness of VISCO-3™. The active comparator arm in this study was a commercially available hyaluronan, a legally marketed alternative with identical indications for use.

The primary objective of the study was to demonstrate non-inferiority of VISCO-3™ group to the active control group for the relief of knee joint pain in subjects with OA of the knee as measured by the Western Ontario and McMaster Universities Osteoarthritis Index Visual Analog Scale (WOMAC VAS) (0-100 mm) pain subscale score change from baseline (CFB) over Week 3, Week 6, and Week 12 in the per-protocol set, using mixed model repeated measures (MMRM). The non-inferiority margin was 8% (−8 mm). The statistical test to conclude non-inferiority required the lower bound of the 2-sided 95% confidence interval (CI) of the VISCO-3™ minus the commercially available hyaluronan CFB least square means be greater than −8 mm. The control group was the commercially available hyaluronan. Additional details of this study are provided in the SSED for P980044/S27 that is available on the CDRH website.

The analysis of effectiveness was based on the 384 evaluable patients over the 12-week time point. Key effectiveness outcomes are presented in Table 6. No secondary endpoints for effectiveness were proposed.

Mean baselines of WOMAC VAS pain subscale were 57.83 mm (standard deviation [SD]: 9.654) in the VISCO-3™ group and 58.40 mm (SD: 8.977) in the active control group. The least squares mean for CFB for VISCO-3™ minus that of the active control over Week 3, Week 6, and Week 12 for WOMAC VAS pain subscale score was −3.30 mm and the 95% CI lower bound of this difference was −6.77 mm. The lower bound −6.77 mm was greater than −8 mm, leading to the conclusion that VISCO-3™ is non-inferior to the active control, as shown in Table 6.

Table 6: Primary Effectiveness Analysis: CFB on the 100 mm WOMAC VAS Pain Subscale Score over Week 3, Week 6, and Week 12 (Per-Protocol Set)

Average over Weeks 3,6, and 12	**Active Control* (N=189)**	**VISCO-3™ (N=195)**	**CFB Difference**

Baseline WOMAC VAS Pain (mm) (Mean [SD])	58.40 (8.977)	57.83 (9.654)	
LS Mean (standard error [SE]) of Change from Baseline	30.15 (1.303)	26.85 (1.270)	−3.30 (1.762)
95% CI	27.59-32.71	24.35-29.35	−6.77-0.17

*FDA-approved three-injection HA product

Results at the end of the study (i.e., at Week 12) yielded an average 52.5% reduction in pain for those patients treated with VISCO-3™ (based on a mean CFB of 30.48 mm and mean baseline pain of 57.83 mm).

Subgroup Analyses

No subgroup analyses were performed for the pivotal clinical trial for VISCO-3™.

Pediatric Extrapolation

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

Supplemental Supportive Clinical Data

Although not utilized in the primary effectiveness evaluation, additional data supporting TriVisc effectiveness was provided. In a total of 137 patients in 3 separate studies,[4,5,6] the three-injection regimen of TriVisc was compared to three different FDA-approved intra-articular hyaluronans.

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 pivotal clinical studies for GenVisc 850 included 25 foreign investigators, and the pivotal clinical study for VISCO-3™ included 29

[4] Dıraçöglu, D. et al. *J Back and Musculo Rehab.* 2016;16: 53. Single versus multiple dose hyaluronic acid: Comparison of the results.

[5] Özgönenel, L. et al. *Istanbul Tıp Dergisi* 2008;1: 53-57. Comparison of different hyaluronates.

[6] Ulucay, I. et al. Acta Orthop Traumatol Turc 2007;41: 337-342. The use of arthroscopic debridement and viscosupplementation in knee osteoarthritis.

investigators. None of the clinical investigators in any of these clinical studies 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. 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

In this PMA the sponsor provided adequate evidence of the sufficient similarity of TriVisc and VISCO-3™ with regard to chemical constituents, concentrations of constituents, solution characteristics, and molecular weight profiles of the sodium hyaluronate component. Because of this, FDA was able to apply Section 216 of the FDAMA and confirm that the evidence presented in the SSED for VISCO-3™ in support of the reasonable assurance of its effectiveness is directly applicable towards establishing reasonable assurance of the effectiveness of TriVisc.

As detailed in the SSED for VISCO-3™, a comparative clinical trial of VISCO-3™ to a commercially available hyaluronan successfully demonstrated non-inferiority within an 8% margin as determined by comparisons of the change from baseline (CFB) of WOMAC VAS pain subscale scores over the 12 week duration of the trial. The least squares mean for CFB for VISCO-3™ minus that of the active control over Week 3, Week 6, and Week 12 for the WOMAC VAS pain subscale score was −3.30 mm and the 95% CI lower bound of this difference was −6.77 mm and thus was greater than the −8 mm margin required to demonstrate non-inferiority.

B. Safety Conclusions

Since TriVisc is of identical chemical formulation to GenVisc 850, previously approved under P140005, but differs from GenVisc 850 only in that less of the device

is injected (3 weekly injections of 2.5 ml for TriVisc and 5 weekly injections of 2.5 ml for GenVisc 850), the nonclinical and clinical studies used to provide evidence of the reasonable assurance of the safety of GenVisc 850 under P140005 apply equally well to TriVisc.

As detailed in the SSED for GenVisc 850, two clinical studies, the AMELIA and Yong Ping studies, were used to establish reasonable assurance of the safety of GenVisc 850 and are summarized as follows.

AMELIA Study[7]

In each treatment group, 127 subjects experienced at least one adverse event during the study and 22 patients (11 in each treatment group) experienced at least one adverse event that was reported as possibly, probably or certainly related to the device. None of the related adverse events were assessed as severe adverse events. In the GenVisc 850 treatment group, the 15 adverse events reported as related adverse events were pain at the injection site (6), allergic reaction (3), arthralgia (2), bleeding at the injection site (2), bleeding (1) and heaviness (1). In the PBS treatment group, the 14 adverse events reported as related adverse events were bleeding at the injection site (6), allergic reaction (3), pain at the injection site (2), arthralgia (1), and arthritis (1). There were no significant increases in adverse events in subsequent courses of GenVisc 850 administration over the first injection course.

Yong Ping Study[8]

There were no statistically significant differences ($P>0.05$), or clinically significant differences between the two groups in the rates of adverse events and related adverse events. Two (1.7%) related adverse events (1 local pain events and 1 rash event) were reported in the GenVisc 850 (Adant) group and 6 related AEs (5.3%) were reported in the SUPARTZ/SUPARTZ FX group (4 local pain events and 2 swelling events). One unrelated serious adverse event (prostatic hyperplasia) was reported in

[7] Navarro-Sarabia F, Coronel P, Collantes E, Navarro FJ, de la Serna AR, Naranjo A, Gimeno M, Herrero-Beaumont G; AMELIA study group. A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project. Ann Rheum Dis. 2011;70: 1957-62.

[8] Y., Jianhao, L., Tiansheng, S., Yongqiang, H., Weimin, F., Ming, C., Tiezheng, S., Jianhua, Y., Liang, X., Xiaoyuan, G., Yongping, C., 2016. The efficacy and safety of sodium hyaluronate injection (Adant(R)) in treating degenerative osteoarthritis: a multi-center, randomized, double-blind, positive-drug parallel-controlled and non-inferiority clinical study. Int J Rheum Dis 19, 271–278.

the SUPARTZ/SUPARTZ FX group and no serious adverse events were reported in the GenVisc 850 group.

C. Benefit-Risk Determination

The probable benefits of TriVisc are based on data collected in the clinical study conducted to support PMA approval of VISCO-3™. As described above, results of comparative nonclinical testing provided evidence of the sufficient similarity of TriVisc and VISCO-3™ such that FDA could then apply Section 216 of the FDAMA and cite effectiveness data presented in the SSED for VISCO-3™ in support of a determination of reasonable assurance of the effectiveness of TriVisc.

As documented in the SSED for VISCO-3™, evaluation of the primary effectiveness endpoint for the clinical study showed a difference of –3.30 mm (on the whole 100mm WOMAC VAS pain scale) in mean reductions from baseline pain scores for VISCO-3™ versus a commercially available hyaluronan used as an active control, thus demonstrating that the effectiveness of three injections of VISCO-3™ to be non-inferior to that of three injections of the commercially available hyaluronan at 12 weeks. The mean pain reduction from baseline for three injections of VISCO-3™ was 26.85mm at 12 weeks on a whole 100mm VAS pain scale, whereas the mean pain reduction for three injections of the control was 30.15 mm. Thus, this non-inferiority study served to demonstrate that the magnitude of the treatment effect for VISCO-3™ was statistically and clinically comparable to that of the commercially available hyaluronan approved for the same indication for use.

The probable risks and safety profile of TriVisc are identical to those of GenVisc 850, a viscosupplement device previously approved under P140005 and of identical chemical formulation to GenVisc 850. TriVisc differs from GenVisc 850 only in that less of the device is injected (3 weekly injections of 2.5 ml for TriVisc and 5 weekly injections of 2.5 ml for GenVisc 850); therefore, the nonclinical and clinical studies used to provide evidence of the reasonable assurance of the safety of GenVisc 850 under P140005 apply equally well to TriVisc.

As documented in the SSED for GenVisc 850, the probable risks consisted of various transitory, non-serious adverse events that were observed in the clinical trials. These included pain at the injection site, allergic reaction, arthralgia, bleeding at the injection site, bleeding, and heaviness. In both the Amelia and Yong Ping clinical

studies, adverse event rates were similar for GenVisc 850 and the controls utilized in the studies.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information identified above and its applicability to TriVisc, 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 TriVisc outweigh its probable risks.

D. Overall Conclusions

The data in this application and its applicability to TriVisc support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

With regard to reasonable assurance of the effectiveness of TriVisc, the sponsor provided adequate evidence of the sufficient similarity of TriVisc and VISCO-3™ with regard to chemical constituents, concentrations of constituents, solution characteristics, and molecular weight profiles of the sodium hyaluronate component (as primarily confirmed by GPC assessments). Because of this, FDA was able to apply Section 216 of the FDAMA and confirm that the evidence presented in the SSED for VISCO-3™ in support of the reasonable assurance of its effectiveness is directly applicable towards establishing reasonable assurance of the effectiveness of TriVisc.

With regard to reasonable assurance of safety, TriVisc is of identical chemical formulation to GenVisc 850, for which reasonable assurance of safety (and effectiveness) had already been established through its prior approval under P140005. TriVisc differs from GenVisc 850 only in that less of the device is injected (3 weekly injections of 2.5 ml for TriVisc and 5 weekly injections of 2.5 ml for GenVisc 850); therefore, the nonclinical and clinical studies used to provide evidence of the

reasonable assurance of the safety of GenVisc 850 under P140005 apply equally well to TriVisc.

The probable benefits of TriVisc, reflected in the effectiveness results of the clinical study used to support approval of VISCO-3™, were determined to outweigh the probable risks of TriVisc, reflected in the safety results and adverse events observed in two clinical studies used to support approval of GenVisc 850. Accordingly, this PMA provided valid scientific evidence for reasonable assurance of the safety and effectiveness of TriVisc 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).

XIII. CDRH DECISION

CDRH issued an approval order on November 13, 2017.

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.