FDA SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Sodium Hyaluronate for Injection
Device Trade Name:	GenVisc 850®
Device Procode:	MOZ
Applicant's Name and Address:	OrthogenRx, Inc. Pennsylvania Biotechnology Center 3805 Old Easton Road Doylestown, PA 18902-8400
Date(s) of Panel Recommendation:	Not applicable
Premarket Approval Application (PMA) Number:	P140005
Date of FDA Notice of Approval:	September 2, 2015
Priority Review:	Not applicable

II. INDICATIONS FOR USE

GenVisc 850 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 GenVisc 850 labeling.

V. DEVICE DESCRIPTION

GenVisc 850 is a sterile, viscoelastic non-pyrogenic solution of purified, high molecular weight sodium hyaluronate (average of 850,000 daltons, range of 620,000 – 1,170,000 daltons) having a pH of 6.8-7.8. The sodium hyaluronate is derived from a bacterial fermentation process. Sodium hyaluronate is a poly-saccharide containing repeating disaccharide units of glucuronic acid and N-acetylglucosamine. GenVisc 850 is supplied in a 3 ml glass syringe. The contents of the syringe are sterile and non-pyrogenic. Each 2.5 mL of GenVisc 850 contains 10 mg/mL of sodium hyaluronate dissolved in a physiological saline (1.0% solution).

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, unmodified hyaluronan injections, avoidance of activities that cause joint pain, exercise, weight loss, physical therapy, and removal of excess fluid from the knee. For those 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 has been commercially distributed in 40 countries outside of the United States (Table 1) and approved in another 23 countries. In 1995, the equivalent of GenVisc 850 was approved in Japan as a generic drug equivalent of Supartz®/Supartz FX™, another 1% hyaluronan product commercially available as Artz® in Japan since 1987.

Table 1: Countries where GenVisc 850 has been approved and launched

No.	*Launched Country*	*Region**	*No.*	*Launched Country*	*Region**
1	Spain	EU	21	Costa Rica	LA
2	Portugal	EU	22	Dominican Rep.	LA
3	Cyprus	EU	23	Ecuador	LA
4	France	EU	24	El Salvador	LA
5	Belgium	EU	25	Guatemala	LA

No.	*Launched Country*	*Region**	*No.*	*Launched Country*	*Region**
6	The Netherlands	EU	26	Honduras	LA
7	Turkey	ME	27	Mexico	LA
8	Egypt	AF	28	Nicaragua	LA
9	Georgia	NIS	29	Panama	LA
10	Kazakhstan	NIS	30	Paraguay	LA
11	Japan	AS	31	Peru	LA
12	Thailand	AS	32	Venezuela	LA
13	Indonesia	AS	33	Uruguay	LA
14	Malaysia	AS	34	Azerbaijan	NIS
15	Iran	ME	35	Vietnam	AS
16	Argentina	LA	36	Russia	EA
17	Bolivia	LA	37	China	AS
18	Brazil	LA	38	Israel	ME
19	Chile	LA	39	Ukraine	NIS
20	Colombia	LA	40	Austria	EU

* EU: European Union, LA: Latin America, ME: Middle East, AF: Africa, AS: Asia, NIS: New Independent States; EA: Eurasia

GenVisc 850 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 following adverse events related to GenVisc 850 are among those that may occur in association with intraarticular injections: arthralgia, joint stiffness, joint effusion, joint swelling, joint warmth, injection site pain, arthritis, allergic reaction, and bleeding at the injection site,.

GenVisc 850 (sold outside the U.S. as Adant®) has been on the market in Japan since 1995 and in Europe since 1996. Since the time of its first marketing through 2012, over 35 million syringes have been distributed with approximately 7 million patients receiving treatment with no major safety concerns related to the product based upon the recent Post-Marketing Surveillance Update Report[1].

According to post-marketing experience of other sodium hyaluronate preparations, anaphylactic/anaphylactoid reactions accompanied by transient

[1] Post-Marketing Surveillance Update Report (January-December 2012), filed July 2013, Notified Body, 318 (Spain), Certificate No. 97 110061 CP/97 120062; 2011 05 0762 CT/201100500763ED, Tedec-Meiji Farma, S.A.

hypotension (sudden drop in blood pressure), have been rarely reported worldwide, all of which resolved either spontaneously or after conservative treatment.

For the specific adverse events that occurred in the clinical studies, please see Section X., "Summary of Clinical Studies", below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Comparison Studies

The following is an overall review of the safety and activity testing of GenVisc 850. In addition to biological bioequivalency, three main studies related to product characteristics were conducted. The first study compares Supartz®/Supartz FX (sodium hyaluronate, Seikagaku Corp.) sourced from European suppliers to GenVisc 850. It is concluded that GenVisc 850 and Supartz/Supartz FX are similar in terms of chemical attributes and compliance with proposed GenVisc 850 product specifications. The second and third evaluation compares GenVisc 850 and Supartz/Supartz FX sourced from Japanese, European and U.S. suppliers. The second study further confirmed that the two products are similar based on chemical attributes and critical analytical release characteristics of GenVisc 850. Additionally, Supartz/Supartz FX complied with GenVisc 850 product specifications.

The third study demonstrated that samples of Supartz/Supartz FX and GenVisc 850 are very similar based upon the rheological (molecular chain interactions) and molecular weight dispersion characteristics. Collectively the chemical and molecular characteristics, as well as the dosage form of GenVisc 850 (sodium hyaluronate) are similar to those of Supartz/Supartz FX.

- Analytical Chemistry and Batch Release Studies

Seven batches of GenVisc 850 and Supartz/Supartz FX were analyzed using the same analytical chemistry methods for the batch release specifications. Using currently accepted analytical methodology no significant differences were seen between all the commercial samples. The intra-product batch variability (within GenVisc 850 and within Supartz/Supartz FX) was not found to be any different than the results for the inter-product batch variability (between GenVisc 850 and Supartz/Supartz FX).

- Rheological and Molecular Weight Characteristics

Eighteen blinded commercial samples were tested for rheological and molecular weight characteristics: 5 samples of GenVisc 850, 6 samples of Supartz/Supartz FX that were U.S. commercially sourced, 5 samples of Supartz/Supartz FX that were EU and Asia commercially sourced, and two samples of two other commercially available hyaluronans (differing from Supartz/Supartz FX) used as positive controls. The high degree of similarity of GenVisc 850 to Supartz/Supartz FX in rheological and molecular weight characteristics was confirmed, and again the intra-product batch variability (within GenVisc 850 and Supartz/Supartz FX) was as great as the inter-product batch variability (between GenVisc 850 and Supartz/Supartz FX).

B. Biocompatibility

All of the components and excipients in the formulation are in full compliance with the requirements of the legally binding, current version of the declared pharmacopoeias and of the guideline ICH Q3C (R3) (CPMP/ICH/283/95 "Note for Guidance on Impurities: Residual Solvents"). The European Pharmacopoeia and the USP - NF refer to this ICH guideline. Biocompatibility characteristics of the product are classified as follow:

- Absence of phthalates - The syringe barrel is made of type I borosilicate glass, the tip cap and the plunger stopper seal are made of chlorobutyl rubber. The plunger rod and finger adapter are made of polypropylene. All of these materials are compliant with USP requirements and do not contain phthalates.
- Absences of animal derived material – The device does not contain materials of animal origin and hence it is not associated with TSE/BSE risks.
- Genetically Modified Organisms (GMOs) – Materials used in the device do not contain GMOs.
- Elastomeric materials – The plunger and syringe tip cap fully comply with USP <381> in particular biological test requirements.
- Residual Solvents / Organic Volatile Impurities complies with ICH Q3C.

- Acute Toxicity

The acute toxicity of bulk GenVisc 850 was evaluated in a single dose study at doses of 729, 1020, 1429 and 2000 mg/kg administered intraperitoneally to rats. Some males and

females administered 1020 mg/kg and 1429 mg/kg or more, respectively, died between day 1 and 12. General conditions observed in these groups included decreased spontaneous movement and respiratory rate, lacrimation, lowering of body temperature, soiled eyelids and nasal tip, lateral position and creeping, but these symptoms returned to normal by day 17 of administration in surviving animals. Except for a transient decrease in body weight in the males of the 2000 mg/kg group, the animals in the other groups mostly demonstrated a steady increase in body weight. Nothing abnormal was detected in any of the autopsied animals. Based on the above results, LD50 of GenVisc 850 bulk was assumed to be 2014 mg/kg in males and 1761 mg/kg in females.

In the absence of a trend with molecular weight, it would appear that these materials had an equal degree of acute toxicity and there is no relationship of toxicity to molecular weight of the hyaluronate.

- Subacute and Chronic Toxicity

A 28-day toxicity study of bulk GenVisc 850 by repeated intraperitoneal administration and 28 day recovery period was conducted in support of this PMA. GenVisc 850 at doses of 30, 60, 120, and 240 mg/kg/day was intraperitoneally administered for 28 days to rats, after which the recovery in the animal during the 28-day withdrawal period was observed.

A large number of males and females of the 240 mg/kg group either died or were sacrificed due to weakness between day 6 of administration and day 1 of recovery. Most of the blood chemistry tests items indicated dose-dependent change at 60 mg/kg or more. Autopsy of the dead animals or those sacrificed due to weakness in the 240 mg/kg group indicated hematoma in the ascites, brain, cecum and injected site as well as dark reddish discoloration and swelling of the lung. As to surviving animals, ascites was observed in the animals treated with 60 mg/kg or more and hematoma in the brain of females of the 240 mg/kg group.

After 28 days of withdrawal, most of the findings observed during the administration period or upon completion of administration disappeared, indicating the recovery from the treatment.

Based on the above results, the non-effect dose for GenVisc 850 in the present study was determined to be 30 mg/kg/day in both sexes. These results demonstrate an excellent safety profile at doses approximately 150 to 300 times higher than those administered to

humans and for chronic periods of daily dosing more than 28-days, compared to the once weekly dose given the humans for up to 5 injections.

No chronic toxic effects in rats or dogs following subcutaneous administration of bacteria-derived sodium hyaluronate, with the exception of tissue hardening and/or edema at the injection site (which was reversible). All organs appeared normal at termination and no tumor formations were detected in either animal species.

- Mutagenicity/Genotoxicity

Bulk GenVisc 850 was assessed for any potential to induce reverse mutation in the presence and absence of S9 Mix by preincubation method using 4 salmonellae which are histidine requiring mutants (*S. typhimurium* TA98, TA100, TA1535, TA1537) and 1 *E.coli* which is a tryptophan requiring mutant (*E.coli*, WP2 uvrA). As the stepwise doses of GenVisc 850, 62.5, 125, 250, 500, 1000 and 2000 μg/plate were established, and 2 plates per dose were used. The mean number of reverse mutant colonies in the group treated with bulk GenVisc 850 was within two times the value of negative control and did not indicate dose-dependent increase. As a result, it was determined that GenVisc 850 did not induce mutagenicity in bacteria.

In conclusion, the described study has demonstrated a very low potential for induction of mutations in bacteria and animal models. This is expected given that hyaluronates are endogenous in all mammals. Thus there is a low risk of any mutagenic or genotoxic effects of sodium hyaluronate.

- Immunogenicity and Sensitization

After intramuscular and intraarticular induction of female guinea pigs with bulk GenVisc 850, utilizing active systems for anaphylaxis (ASA) by intraarticular, intradermal, and intracorneal, evaluations by Schultz-Dale, passive cutaneous anaphylaxis (PCA), gel-diffusion and passive hemagglutination (PHA) reactions were conducted to investigate the antigenicity of GenVisc 850. In all studies for immunogenic effects and sensitization there were no effects of GenVisc 850 and no immunogenicity detected.

- Irritation

Single instillation of 0.1 ml of bulk GenVisc 850 in rabbit eyes was evaluated for signs of irritation. The left palpebral conjunctival sac of six (6) female rabbits was instilled with

0.1 ml of bulk GenVisc 850 according to the Draize method. Irritation in the cornea, iris, and conjunctiva was macroscopically observed before instillation and 0.5, 1, 3, 6, 24, 48, and 72 hours after instillation. Assessments were made according to the Draize criteria. Results showed that the instillation of 0.1 ml of bulk GenVisc 850 did not cause any irritation in the cornea, iris, and conjunctiva in all animals throughout the observation period.

- Hemolysis

As part of the quality build in the manufacturing of GenVisc 850, the bulk sodium hyaluronate used in this product requires, as part of the release methodologies, two tests for hemolysis. These two tests, *Streptococcus hemolyticus* and Hemolyzing Property, for evaluation of potential to induce hemolysis are part of the release specifications and certificate of analysis. No evidence of hemolysis has been detected in studies with Meiji sodium hyaluronate in routine testing of batches for more than 15 years.

C. Sterilization Validation

Since GenVisc 850 is a preparation for injection, the entire manufacturing process is carried out under conditions ensuring compliance with the sterility limits established by regulatory requirements and in the drug product specifications. The sterility assurance program for sodium hyaluronate solution has been designed to ensure patient safety, and has been used for the CE mark approval of this product from a manufacturing site in Japan since 1997 and at Tedec-Meiji Farma in Europe since 2011. There have been no reported safety incidents to date.

D. Shelf Life

Data from accelerated and long-term stability studies were supportive of a shelf life of 36 months for GenVisc 850 when stored at temperatures between 33.8 and 86 °F (1 and 30 °C).

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The results of the Yong Ping study and a Bayesian longitudinal analysis that are summarized below show that the clinical performance of GenVisc 850 was superior to a

phosphate buffered saline (PBS) control and similar to that of Supartz/Supartz FX. The Yong Ping study was a randomized controlled, multicenter clinical trial that demonstrated non-inferiority of GenVisc 850 to Supartz/Supartz FX through 6 weeks. The Bayesian longitudinal analysis included data from four randomized controlled trials, two of which included comparisons of GenVisc 850 to PBS and two of which included comparisons of Supartz/Supartz FX to PBS. The results of this Bayesian longitudinal analysis show an increasing trend in superiority of GenVisc 850 to a PBS control over time, up to 30 weeks.

A. Yong Ping Study

The Yong Ping study was a parallel-controlled, randomized, multi-center clinical conducted at five hospitals.

Objective

The objective of the trial was to evaluate the efficacy and safety of GenVisc 850 sodium hyaluronate injection compared to Supartz/Supartz FX for the treatment of pain from degenerative osteoarthritis.

Methodology

Patients were to be treated once a week for 5 consecutive weeks and were followed at 1, 2, 3, 4 and 6 weeks after the last injection.

1. Main Inclusion and and Exclusion Criteria

Inclusion Criteria

(1) Aged 45 years old or above, either sex;
(2) Participating in the study voluntarily and willing to sign the informed consent;
(3) Clinically diagnosed as degenerative osteoarthritis of the knee joint (knee osteoarthritis, OA);
(4) VAS-movement score ≥ 30mm
(5) Not having a medical history of apparent injuries; and
(6) X-ray film of single-leg weight-bearing confirms knee OA, with corresponding clinical symptoms and physical signs.

Exclusion Criteria

(1) Patients with severe liver / kidney function impairment (AST > 1.5 times the normal, ALT > 1.5 times of the upper limit of normal (ULN), Cr > ULN)
(2) Patients with a history of allergies to such kind of drugs;
(3) Patients with skin disease or infection at the joint site where drug is administered;

(4) Having intra-articular blood effusion;
(5) Patients suffering severe injury to the knee joint recently, congenital abnormality, bone tuberculosis, or sequelae of pyogenic arthritis;
(6) Patients with other rheumatic diseases;
(7) Patients who used anti-inflammatory analgesics or adrenocortical hormones within 3 weeks before the treatment, or HA preparations in the past 6 months;
(8) Other patients for whom such a kind of drugs are not clinically suitable; and
(9) Women in pregnancy or lactation.

2. Evaluations

Baseline characteristics were collected prior to the first injection. Pain on movement using a visual analog scale (VAS), Lequesne index and adverse events were collected at each follow-up visit. Patients were to be treated once a week for 5 consecutive weeks and were followed at 1, 2, 3, 4 and 6 weeks after the last injection.

3. Clinical Endpoints

Primary Effectiveness: Visual Analog Scale (VAS) pain on movement at 6 weeks

4. Subject Accountability

A total of 229 subjects were enrolled with 113 subjects in the Supartz/Supartz FX treatment group and 116 subjects in the GenVisc 850 group. Of those, 92.9% and 93.1% in the Supartz/Supartz FX and GenVisc 850 groups, respectively, completed the trial.

5. Demographics and Baseline Measures

The average age was 62.3 years in the Supartz/Supartz FX group and 74% of the subjects were female. The average age was 61.9 years in the GenVisc 850 group, and 80% of the subjects were female. In both groups, the average weight was 66 kg. There were no statistically significant differences in demographic characteristics.

Analysis of the baseline individual elements of the Lequesne score (rest pain, movement pain, knee joint swelling, morning stiffness and walking ability), Lequesne total score and visual analog scale (VAS) total score showed that differences in pre-treatment symptoms between the two groups were neither statistically significant ($P>0.05$) nor clinically significant.

B. Bayesian Analaysis

Meta-Analysis of 4 Studies Using Bayesian Modeling

To further support the clinical similarities between GenVisc 850 and Supartz/Supartz FX, a Bayesian analysis was performed. This supplemental statistical analysis was intended to provide point estimates for effectiveness through Week 30 in support of GenVisc 850's superiority over PBS,) and non-inferiority relative to Supartz/Supartz FX. Previously constructed models were regenerated using only those four controlled studies collecting the WOMAC subscale (A) effectiveness endpoint with a five injection regimen. The studies analyzed included:

- For GenVisc 850, two saline-controlled studies: AMELIA (Navarro)[2] and Blanco[3]; and
- For Supartz/Supartz FX, two saline-controlled studies conducted in Australia[4] and Sweden[5].

Objectives

Primary Objectives of the Bayesian Analysis:

- Supartz/Supartz FX is superior to PBS. The null hypothesis is that PBS is superior to Supartz/Supartz FX. Rejection of the null hypothesis will in effect validate the statistical approach and modeling as it duplicates the results of the approved PMA for Supartz/Supartz FX.
- GenVisc 850 is superior to PBS. The non-inferiority margin for addressing this objective is 4 mm.

Supporting Objective of the Bayesian Analysis:

- GenVisc 850's advantage over PBS is non-inferior to Supartz/Supartz FX's advantage over PBS. The non-inferiority margin for addressing this objective is 4 mm.

---

[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] Blanco FJ, Fernández-Sueiro JL, Pinto-Tasende JA, Fernández-López JC, Ramallal M, Freire A et al. Intra-articular hyaluronan treatment of patients with knee osteoarthritis waiting for replacement surgery. The Open Arthritis Journal 2008;1: 1-7.

[4] Day, R. et al. A double blind, randomized, multicenter, parallel group study of the effectiveness and tolerance of intraarticular hyaluronan on osteoarthritis of the knee. J Rheumatol 2004;31: 755-782,.

[5] Lohmander LS, Dalén N, Englund G, Hämäläinen M, Jensen EM, Karlsson K, Odensten M, Ryd L, Sernbo I, Suomalainen O, Tegnander A. Intra-articular hyaluronan injections in the treatment of osteoarthritis of the knee: a randomised, double blind, placebo controlled multicentre trial. Hyaluronan Multicentre Trial Group. Ann Rheum Dis. 1996;55: 424-31.

Endpoints

The effectiveness measure is the WOMAC A subscale (pain),

Evaluation

Statistical Model

A longitudinal model (linear) described in the previous section was employed. Visit data from 44 studies that reported WOMAC A as their outcome were included, as shown in Tables 2 and 3.

Table 2: Studies included in the analysis

Study (# pts.)	Treatments compared	Time Window
AMELIA (n=301)	GenVisc 850 vs. PBS	30 weeks
Australia (n=223)	Supartz/Supartz FX vs. PBS	18 weeks
Sweden (n=240)	Supartz/Supartz FX vs. PBS	20 weeks
Spain (n=42)	GenVisc 850 vs. PBS	26 weeks

The data from Table 3 below were included in the Bayesian longitudinal analysis, using each time point of various times, 5, 6, 10, 13, 14, 17, 18, 20, 26, and 30 weeks from Amelia, Australia, Sweden and Spain studies.

Table 3: Effectiveness endpoint sample sizes, means and standard deviations for each on-study visit for each treatment in 4 studies who used WOMAC A as an outcome

Study	Treatment	Endpoint	Time	N	Mean	SD
AMELIA	PBS	WOMAC A	Baseline	151	56.668	15.37
		0-100	Week 6	149	-21.558	20.226
			Week 17	143	-21.514	21.404
			Week 30	135	-20.354	21.87
	GenVisc 850	WOMAC A	Baseline	149	55.97	16.78
		0-100	Week 6	148	-21.69	20.24
			Week 17	145	-24.28	22.05
			Week 30	141	-24.08	21.45
Australia	PBS	WOMAC A	Baseline	115	68.0	27.4
		0-100	Week 6	115	-21	24
			Week 10	115	-23	24
			Week 14	115	-21	24
			Week 18	115	-20	24

Study	Treatment	Endpoint	Time	N	Mean	SD
	Supartz/ Supartz FX	WOMAC A	Baseline	108	66.0	22.8
		0-100	Week 6	108	-26	24
			Week 10	108	-27	24
			Week 14	108	-30	24
			Week 18	108	-28	24
Sweden	PBS	WOMAC A	Baseline	120	62.2	24.84
		0-100	Week 5	120	-22.1	24
			Week 13	120	-17.6	24
			Week 20	120	-17.6	24
	Supartz/ Supartz FX	WOMAC A	Baseline	119	65.3	25.25
		0-100	Week 5	119	-19.1	24
			Week 13	119	-20.6	24
			Week 20	119	-22.1	24
Blanco	PBS	WOMAC A	Baseline	20	67.6	15.28
		0-100	Week 13	20	-9.64	18.96
			Week 26	20	-11.16	28.16
	GenVisc 850		Baseline	22	62.66	14.18
			Week 13	22	-12.34	13.12
			Week 26	26	-21.72	25.86

C. Safety and Effectiveness Results

1. Safety Results

Two of the three GenVisc 850 studies included in the effectiveness analyses, the AMELIA and Yong Ping studies, had safety data available for analysis.

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 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 4: 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 5 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 5: 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 6.

Table 6: 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.

Supporting evidence of safety is also provided by post-marketing reports for GenVisc 850 that has been commercially distributed in 40 countries outside of the United States. GenVisc 850 is also approved in 23 other countries, but is not presently distributed in these countries. GenVisc 850 (sold outside the U.S. as Adant) has been on the market in Japan since 1995 and in Europe since 1996. Since the time of its first marketing through 2012, over 35 million syringes have been distributed and approximately 7 million patients have received treatment without any major safety concerns related to the product based upon the recent Post-Marketing Surveillance Update Report.[1]

2. Effectiveness Results

a) Results of Yong Ping Study

Primary effectiveness

In the full analysis set (FAS) population, VAS pain on movement of the Supartz/Supartz FX group at week 6 decreased by 48.0±23.39 mm compared to baseline, and VAS pain in the GenVisc 850 group decreased by 49.2±21.50 mm. The difference between the two groups was neither statistically nor clinically significant (P>0.05). These analyses are shown in Table 7.

Table 7: VAS pain on movement (mm) and baseline variations (Week 6 - Baseline) (FAS)

	Supartz/Supartz FX Group	**GenVisc 850 Group**	**Statistics**	**P value**	**Method**
N	113	116	0.403	0.688	t test
Mean±SD	−48.0 ± 23.39	−49.2 ± 21.50			
95%CI(L-H)	−52.33 - −43.61	−53.12 - −45.21			
Min-Max	−95.0 - 1.00	−90.0 - 17.00			
Median	−50.00	−50.25			

b) Results of Meta-Analysis of 4 Studies Using Bayesian Modeling

Primary Analysis-Methodology: For the primary analysis which pools all data from post-baseline visits for all treatments in all studies analyzed, the estimated between-study variability (T) was examined and found to be acceptable for the superiority and non-inferiority assessments. The Gelman-Rubin convergence statistic was very close to 1, thus indicating convergence of the sampler. Overall the model fits the data well.

Primary Analysis

For the primary analysis, the difference in mean change from baseline between GenVisc 850 and PBS was examined. The mean advantage of GenVisc 850 vs. PBS at Week 30 is 6.88 mm (on the 100 mm normalized WOMAC A scale) and the posterior probability of superiority of GenVisc 850 vs. PBS is 79% by 30 weeks.

Secondary Analysis

For the secondary analyses, treatment effects of GenVisc 850 and PBS were examined. For GenVisc 850, towards the end of the time interval, a paucity of data causes an increase in variance, and therefore the posterior probability of non-inferiority does not increase. However, the mean difference between the treatment effect of GenVisc 850 and Supartz/Supartz FX was always below the non-inferiority margin with a posterior probability of 50%.

Further details of the primary and secondary analysis assessments are provided below in Tables 8 and 9.

Table 8: Posterior mean estimates of the treatment effect in each treatment arm across time using a linear trend longitudinal model

Arm	Week	Mean Baseline Difference	Lower 95% CI	Upper 95% CI
PBS	5	-19.99	-29.62	-8.66
PBS	6	-19.85	-29.35	-8.64
PBS	10	-19.27	-28.78	-8.23
PBS	13	-18.85	-28.77	-7.63
PBS	14	-18.70	-28.82	-7.43
PBS	17	-18.27	-28.99	-6.61
PBS	18	-18.13	-29.07	-6.30
PBS	20	-17.85	-29.28	-5.65
PBS	26	-16.99	-29.95	-3.46
PBS	30	-16.42	-30.48	-1.79
GenVisc 850	5	-18.96	-37.35	1.20
GenVisc 850	6	-19.14	-36.07	-0.53
GenVisc 850	10	-19.83	-36.81	-1.74
GenVisc 850	13	-20.35	-41.84	2.22
GenVisc 850	14	-20.53	-43.63	3.58
GenVisc 850	17	-21.05	-49.53	8.00
GenVisc 850	18	-21.22	-51.53	9.55
GenVisc 850	20	-21.57	-55.90	12.93
GenVisc 850	26	-22.61	-69.73	23.72
GenVisc 850	30	-23.30	-79.40	31.35
Supartz/Supartz FX	5	-21.28	-41.09	-0.28
Supartz/Supartz FX	6	-21.51	-40.07	-1.62
Supartz/Supartz FX	10	-22.42	-40.82	-2.50
Supartz/Supartz FX	13	-23.11	-44.91	0.21

Supartz/Supartz FX	14	-23.34	-46.33	1.20
Supartz/Supartz FX	17	-24.02	-51.14	4.45
Supartz/Supartz FX	18	-24.25	-52.72	5.50
Supartz/Supartz FX	20	-24.70	-56.16	7.81
Supartz/Supartz FX	26	-26.07	-67.02	15.41
Supartz/Supartz FX	30	-26.98	-74.72	20.93

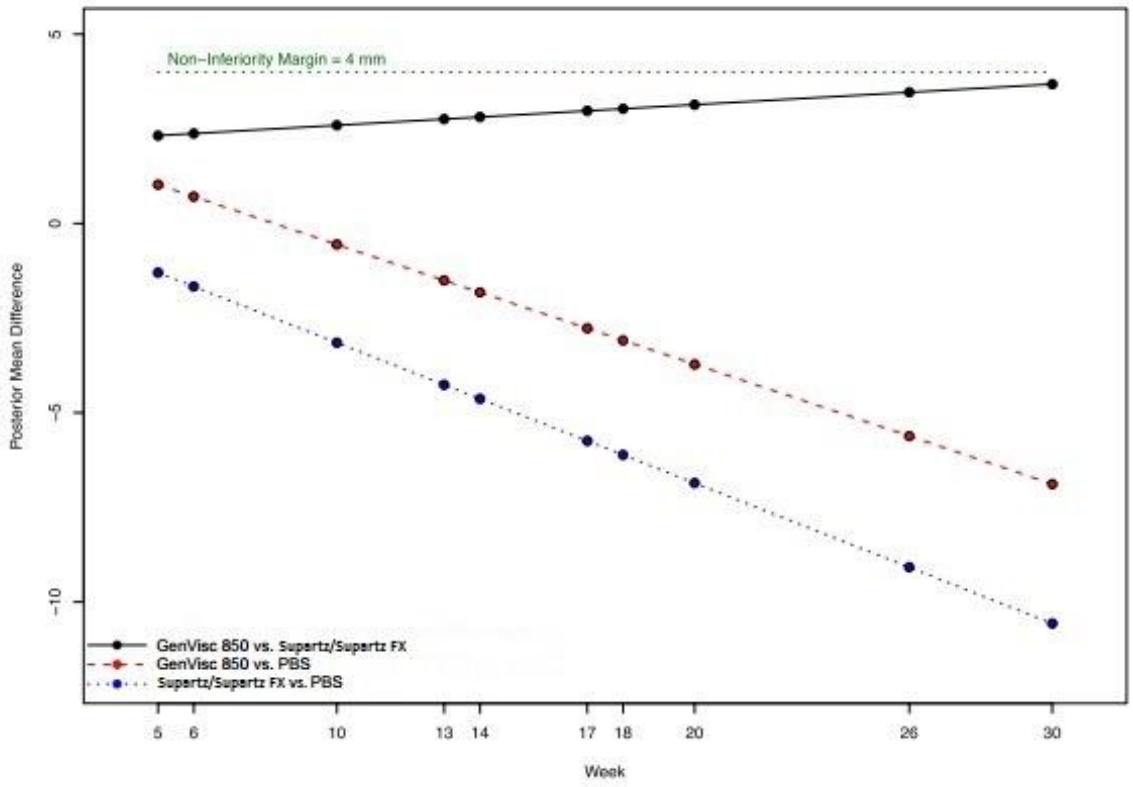
Table 9: Treatment difference estimates along with posterior probability of the objectives using a linear trend longitudinal model

Comparison	**Week**	**Mean Difference**	**Lower 95% CI**	**Upper 95% CI**	**Posterior Probability**
GenVisc 850 vs PBS	5	1.03	-13.02	17.14	42%
GenVisc 850 vs PBS	6	0.71	-11.61	15.11	44%
GenVisc 850 vs PBS	10	-0.56	-12.75	13.28	60%
GenVisc 850 vs PBS	13	-1.51	-19.11	16.90	69%
GenVisc 850 vs PBS	14	-1.82	-21.34	18.21	71%
GenVisc 850 vs PBS	17	-2.77	-28.00	22.65	75%
GenVisc 850 vs PBS	18	-3.09	-30.30	24.22	75%
GenVisc 850 vs PBS	20	-3.72	-35.02	27.37	76%
GenVisc 850 vs PBS	26	-5.62	-49.79	37.29	78%
GenVisc 850 vs PBS	30	-6.88	-59.91	44.45	79%
GenVisc 850 vs. Supartz/Supartz FX	5	2.32	-21.60	26.67	62%
GenVisc 850 vs. Supartz/Supartz FX	6	2.38	-19.10	24.26	63%
GenVisc 850 vs. Supartz/Supartz FX	10	2.59	-18.91	24.01	62%
GenVisc 850 vs. Supartz/Supartz FX	13	2.76	-26.30	31.37	58%
GenVisc 850 vs. Supartz/Supartz FX	14	2.81	-28.87	34.28	57%
GenVisc 850 vs. Supartz/Supartz FX	17	2.98	-37.61	43.34	55%
GenVisc 850 vs. Supartz/Supartz FX	18	3.03	-40.76	46.54	54%
GenVisc 850 vs. Supartz/Supartz FX	20	3.14	-47.21	53.00	53%
GenVisc 850 vs. Supartz/Supartz FX	26	3.47	-68.22	74.59	51%
GenVisc 850 vs. Supartz/Supartz FX	30	3.68	-82.95	89.63	50%

Comparison	Week	Mean Difference	Lower 95% CI	Upper 95% CI	Posterior Probability
Supartz/Supartz FX vs PBS	5	-1.30	-17.46	15.60	65%
Supartz/Supartz FX vs PBS	6	-1.67	-16.54	13.90	70%
Supartz/Supartz FX vs PBS	10	-3.15	-17.80	12.51	83%
Supartz/Supartz FX vs PBS	13	-4.26	-22.55	15.28	84%
Supartz/Supartz FX vs PBS	14	-4.63	-24.33	16.16	85%
Supartz/Supartz FX vs PBS	17	-5.75	-29.52	18.97	85%
Supartz/Supartz FX vs PBS	18	-6.12	-31.35	20.04	85%
Supartz/Supartz FX vs PBS	20	-6.86	-34.97	21.92	86%
Supartz/Supartz FX vs PBS	26	-9.08	-46.70	28.97	86%
Supartz/Supartz FX vs PBS	30	-10.57	-54.82	33.96	86%

The results of the longitudinal analyses are presented in support of the observation that GenVisc 850 is superior to PBS across time. There is a good linear fit of the data to the model demonstrating increasing mean differences between GenVisc 850 and PBS through 30 weeks, Figure 1.

Figure 1: Treatment Difference Estimates Across Time Using a Linear Trend Longitudinal Model.



D. 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 25 foreign 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. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Orthopedic and Rehabilitation Advisory Panel or 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 Yong Ping study and a meta-analysis of 4 other studies using Bayesian and longitudinal modeling provide reasonable assurance of the effectiveness of GenVisc 850 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).

Yong Ping Study

There were no detectable differences between the Supartz/Supartz FX and GenVisc 850 groups in the FAS or PPS populations for the primary endpoint of Week 6 VAS pain on movement. Additionally, a statistically significant decrease was observed in both groups in VAS pain on movement at Week 6 compared to baseline. A non-inferiority test analysis of both the PPS and FAS populations demonstrated that the Week 6 VAS pain on movement decrease of the GenVisc 850 group is non-inferior to that of the Supartz/Supartz FX group.

Meta-Analysis of 4 Studies Using Bayesian Longitudinal Modeling

The posterior probability that GenVisc 850 is superior over PBS is 79% at time periods up to 30 weeks, while the posterior probability of the Supartz/Supartz FX being superior over PBS is 86%. Using a non-inferiority margin of 4 mm, the posterior probability of GenVisc 850 being non-inferior to Supartz/Supartz FX is 50% at time periods up to 30 weeks. The results of the Bayesian longitudinal analysis support the claim that GenVisc 850 is superior to PBS for a time period up to 30 weeks.

B. Safety Conclusions

The AMELIA (Navarro) and Yong Ping studies, coupled with the post-marketing data, provide reasonable assurance of the safety of GenVisc 850 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).

AMELIA Study

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

There were no statistically significant differences ($P>0.05$), or clinically significant differences between the two groups in the rates of AEs and related AEs. Two (1.7%) related AEs (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 SAE (prostatic hyperplasia) was reported in the Supartz/Supartz FX group and no SAEs were reported in the GenVisc 850 group.

C. Benefit-Risk Conclusions

A series of 5 weekly injections of GenVisc 850 provides the potential benefit for pain reduction in a proportion of patients with osteoarthritis in the knee. The difference between GenVisc 850 and PBS injections at 30 weeks was 6.88 mm on the 100 mm scale for the WOMAC A Pain Subscore, thus exceeding a difference of 6 mm that was defined as clinically meaningful. The data support the conclusion that the probable benefits outweigh the probable risks of transitory adverse events such as pain and swelling in the treatment of knee pain due to osteoarthritis in patients who have failed to adequately respond to conservative non-pharmacological therapy and simple analgesics (e.g., acetaminophen).

D. Overall Conclusions

The primary preclinical and clinical data support the safety and effectiveness of GenVisc 850. Results from the Yong Ping study (head-to-head) and the meta-analysis using a Bayesian and longitudinal modeling of GenVisc 850 studies provide valid scientific evidence of reasonable assurance of the safety and effectiveness of GenVisc 850 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 September 2, 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).

XIV. APPROVAL SPECIFICATIONS

Directions for Use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.