SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Hyaluronic acid, intra-articular

Device Trade Name: DUROLANE®

Device Procode: MOZ

Applicant's Name and Address: Bioventus LLC
4721 Emperor Boulevard, Suite 100
Durham, NC 27703

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P170007

Date of FDA Notice of Approval: August 29, 2017

II. INDICATIONS FOR USE

DUROLANE® is indicated for the treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacological therapy or simple analgesics, e.g., acetaminophen.

III. CONTRAINDICATIONS

- Do not inject DUROLANE with knee joint infections, infections, or skin disease in the area of the injection site.
- Do not administer to patients with known hypersensitivity (allergy) to HA preparations.

IV. WARNINGS AND PRECAUTIONS

The warning and precautions can be found in the labeling for DUROLANE.

V. DEVICE DESCRIPTION

DUROLANE is a high molecular weight, non-animal, sodium hyaluronate, stabilized gel produced using a unique, proprietary technology, NASHA®. The device is administered as a single injection.

Each 3 mL glass syringe of DUROLANE contains 20 mg/mL of sodium hyaluronate, dissolved in phosphate buffered saline. The sodium hyaluronate is derived from bacterial fermentation (*Streptococcus equi*).

Each pre-filled syringe contains the following:

Component	Each mL contains
Stabilized Sodium Hyaluronate	20 mg
Sodium Chloride	9 mg
Potassium Dihydrogen Phosphate	0.03 mg
Disodium Hydrogen Phosphate Dihydrate	0.14 mg
Water for Injection	q.s. 1mL

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of pain in osteoarthritis (OA) of the knee. For patients who have failed to respond to conservative, non-pharmacologic therapy, alternative practices and procedures include simple analgesics, such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), intraarticular injection of corticosteroids, avoidance of activities that cause joint pain, exercise, physical therapy, and removal of excess fluid from the knee. For patients who fail to respond to these treatments, surgical interventions including arthroscopic surgery and total knee replacement are also alternatives.

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.

VII. MARKETING HISTORY

DUROLANE has been CE marked within the European Union since 2001. DUROLANE is marketed globally.

DUROLANE has not been required to be withdrawn from any market for any reason related to safety or effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- 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
- Puritis
- Tendonitis

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

IX. SUMMARY OF NONCLINICAL STUDIES

DUROLANE has undergone extensive pre-clinical testing in a variety of *in-vitro* and *in-vivo* studies. See Table 1.

The majority of the biocompatibility evaluations were performed on product formulations which are chemically equivalent to DUROLANE and which are manufactured using the same NASHA gel technology. These gels are used for different indications and fill volume. However, given the chemical equivalence, these tests are considered applicable to DUROLANE. Where there was a parameter which could impact results of the test (e.g., gel particle size), testing was done either on DUROLANE or a formulation with the same specifications. Biocompatibility tests were performed in accordance with the applicable subsection of ISO-10993, where appropriate.

Table 1: Key Pre-clinical Evaluations of DUROLANE

Study	Product Evaluated	Applicable Standard	Results
USP Rabbit Pyrogen Test	Chemically equivalent NASHA gel	USP	No pyrogens
Intra-articular injection in rabbits - acute and sub-chronic toxicity	DUROLANE	N/A – internally-developed test	No toxicity reaction after 1 and 3 weeks intra-articular injection
Repeated intra-articular injections in rabbit - chronic toxicity	DUROLANE	N/A – internally-developed test	No toxicity reaction after 1 and 13 weeks intra- articular injection
Intradermal injection in rabbits - acute, sub-chronic and chronic toxicity	Chemically equivalent NASHA gel	N/A – internally-developed test	No toxicity reaction after 1, 2, 3 or 52 weeks intradermal injection
Systemic toxicity in rats	Chemically equivalent NASHA gel	ISO 10993-11	No evidence of systemic toxicity 13 weeks post subcutaneous injection
Cytotoxicity study, ISO elution Method	Chemically equivalent NASHA gel	ISO 10993-5	Non-cytotoxic (cytotoxicity grade < 2)
Cytotoxicity test in V79 cells, colony formation test	Chemically equivalent NASHA gel	Japanese Pharmaceutical Affairs Bureau MHLW notification #99: 1995	Non-cytotoxic
Ames Test	Chemically equivalent NASHA gel	EU guidelines B14: 1992	Non-mutagenic
In vitro chromosomal aberration study in mammalian cells	Chemically equivalent NASHA gel	ISO 10993-3	Non-genotoxic
Mouse bone marrow micronucleus study	Chemically equivalent NASHA gel	ISO 10993-3	Non-genotoxic
Cancer Risk Assessment	Chemically equivalent NASHA gel	N/A – toxicological evaluation of chemical stabilizer used in NASHA process	Cancer risk from exposure minimal
ISO Maximization Sensitization study	Chemically equivalent NASHA gel	ISO 10993-10	No sensitization at injection site
ISO Intracutaneous study (solution)	Chemically equivalent NASHA gel	ISO 10993-10	Slight irritation at the injection site
Muscle implantation test in the rabbit (4 weeks)	Chemically equivalent NASHA gel	ISO 10993-6	Well tolerated by local muscle tissue
Muscle implantation test in the rabbit (90 days)	Chemically equivalent NASHA gel	ISO 10993-6	Slight general foreign body reaction
Residence time in rabbits	^{14}C-labeled DUROLANE	N/A – internally developed test	28-day half-life

Residence time in humans	^{131}I-labeled DUROLANE	N/A – internally developed test	4-week half-life
Viscoelastic properties following free radical degradation	DUROLANE	N/A – internally developed test	More resistant to degradation effects compared to an unmodified and a cross- linked HA preparation
Viscoelastic properties under simulated osteoarthritic joint conditions	DUROLANE	N/A – internally developed test	More resistant to degradation effects when diluted as compared to a cross-linked HA preparation
Anti-nociceptive effects in rats	DUROLANE	N/A – internally developed test	High mechanical threshold required for pain induction; approximate equal weight distribution between affected and unaffected limbs
Sequestration of pain-inducing agents	DUROLANE	N/A – internally developed test	Significant absorbance of free bradykinin and PGE2 in solution.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of a single intra-articular injection of DUROLANE for the treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacological therapy or simple analgesics in the People's Republic of China. Data from this clinical study were the basis for the PMA approval decision. Summaries of this clinical study, TG1018DLN, as well as three preceding clinical development studies, 35GA0001, 35GA0301, and 35GA0608, and a repeated injection safety study, 35GA09901E, are presented below.

A. Original Clinical Development Studies 35GA0001, 35GA0301, and 35GA0608

The original clinical development of DUROLANE was founded upon three randomized, controlled trials: 35GA0001, 35GA0301, and 35GA0608. The initial two trials were superiority studies versus saline; the third was a non-inferiority trial versus the commonly used corticosteroid, methylprednisolone acetate (MPA). All trials evaluated the outcome measure associated with a pain responder rate, defined as a minimum 40% reduction from baseline in WOMAC pain scores and an absolute reduction of at least 5 points in that score.

The saline controlled trials are summarized in Table 2:

Table 2: Original Clinical Development Studies-DUROLANE vs. Saline

Clinical Study No.	n	# of Centers	Pain Responder Rate %			
			Visits	DUROLANE	SALINE	p-value
35GA0001	DUROLANE: 172 Saline: 174	7 US 6 Canada 5 Sweden	2 weeks	29.1	36.2	0.16
			6 weeks	36.6	29.9	0.18
			3 months	32.0	35.1	0.54
			6 months	29.1	32.2	0.53
35GA0301	DUROLANE: 108 Saline: 110	6 Canada 4 United Kingdom 2 Germany	2 weeks	19.4	25.5	0.29
			4 weeks	26.9	26.4	0.94
			6 weeks	30.6	26.4	0.49

Neither of these saline-controlled studies demonstrated superiority over saline. Confounding factors were identified following subgroup analyses after completion of each trial. Study 35GA001included patients with poly-articular pain, making it difficult to discriminate if pain reported was from the signal knee joint versus other joints. Study 35GA0301 identified an additional confounding factor of joint effusion. The presence of effusion may signify the presence of an active inflammatory process which can lead to degradation of HA through pro- inflammatory cytokine activity.

These two studies informed the design of the third study, 35GA0608, outside of the United States comparing DUROLANE versus MPA. Results from this study are summarized in Table 3.

Table 3: Original Clinical Development Studies-DUROLANE vs. MPA

Clinical Study No.	# of Centers	Pain Responder Rate %			
		Visits	DUROLANE n=221	MPA n=221	Difference 95% Confidence Interval*
35GA0608	15 Canada 5 Sweden 4 UK	6 weeks	47.7	50.2	(-11.9%; +6.9%)
		12 weeks	44.6	46.2	(-11.2%; +7.9%)
		18 weeks	43.0	45.2	(-11.9%; +7.4%)
		26 weeks	43.9	36.9	(-2.5%; +16.6%)

*Hypothesis testing required the lower bound to be greater than -0.15

Adverse events (AEs) from these three trials are collectively presented in Table 4.

Table 4: Summary of Adverse Events Reported in Original Clinical Development Studies

Preferred Class*	DUROLANE All three studies (n=502)	MPA 35GA0608 (n=221)	Saline 35GA0001 and 35GA0301 (n=284)
Related to product or injection procedure or both			
Nausea	-	2 (0.9%)	-

Pyrexia	2 (0.4%)	-	-
Injection site haematoma	-	-	2 (0.7%)
Injection site haemmorrhage	-	-	1 (0.4%)
Injection site pain	15 (3.0%)	1 (0.5%)	2 (0.7%)
Injection site swelling	2 (0.4%)	-	-
Blood glucose increased	1 (0.2%)	-	-
Arthralgia	54 (10.8%)	7 (3.2%)	8 (2.8%)
Arthropathy	9 (1.8%)	-	5 (1.8%)
Joint crepitation	1 (0.2%)	-	-
Joint effusion	1 (0.2%)	1 (0.5%)	-
Joint lock	1 (0.2%)	-	-
Joint stiffness	4 (0.8%)	-	-
Joint swelling	5 (1.0%)	1 (0.5%)	-
Joint warmth	1 (0.2%)	-	-
Muscle spasms	1 (0.2%)	-	-
Pain in extremity	1 (0.2%)	1 (0.5%)	-
Sensation of heaviness		1 (0.5%)	
Synovitis	1 (0.2%)		1 (0.4%)
Anxiety	1 (0.2%)	-	-
Depression	1 (0.2%)	-	-
Dermatitis	-	-	1 (0.4%)
Headache	2 (0.4%)	-	-
Haemarthrosis	1 (0.2%)	-	-
Myalgia	1 (0.2%)	-	-
Oedema peripheral	-	-	1 (0.4%)
Osteoarthritis	2 (0.4%)	1 (0.5%)	-
Nervousness	1 (0.2%)	-	-

* AEs in the 35GA001 and 35GA0301 studies were classified using World Health Organisation, Adverse Reaction Terminology (WHO ART). In 35GA0608, AEs were classified using Medical Dictionary for Regulatory Activities (MedDRA).

B. Repeated Injection Safety Study, 35GA09901E, and Extension Phase of 35GA0608

The safety of repeated use of DUROLANE is supported by one open label study conducted at two centers in Sweden, 35GO9901E, and an extension phase to the non-inferiority trial versus MPA, 35GA0608. In 35GA09901E, patients were offered a second injection of DUROLANE 3 months following the initial injection at approximately 7 months from the first injection. Safety assessments were performed at 2 and 4 weeks post-injection. In 35GA0608, patients were offered an injection of DUROLANE following completion of the 26-week blinded phase of the trial.

Safety assessments were performed at 2 weeks following the second injection and at 9 and12 months post-initial injection. The adverse event rates of the three groups were comparable, and the adverse events from these studies are summarized in Table 5.

Table 5: Summary of Related Adverse Events Reported for Repeat Injections of Durolane

Preferred term*	35GA0608 1st injection: DUROLANE (n=163)	35GA0608 1st injection: MPA (n=179)	35GO9901E DUROLANE (n=53)
Related to product or injection procedure or both			
Arthralgia	30 (18.4%)	31 (17.3%)	9 (17.0%)
Arthropathy	-	-	2 (3.8%)
Joint dislocation	1 (0.6%)	-	-
Joint effusion	1 (0.6%)	-	-
Joint stiffness	1 (0.6%)	3 (1.7%)	-
Joint swelling	2 (1.2%)	1 (0.6%)	-
Joint warmth	-	1 (0.6%)	-
Musculoskeletal discomfort	3 (1.8%)	-	-
Urticaria	-	1 (0.6%)	-

* AEs in the 35GO9901E study were classified using World Health Organisation, Adverse Reaction Terminology (WHO ART) and Medical Dictionary for Regulatory Activities (MedDRA) for 35GA0308.

C. Study Design of Pivotal Trial, TG1018DLN

The safety and effectiveness of DUROLANE was studied in pivotal trial, TG1018DLN – "Comparative Study of Safety and Efficacy of Two Hyaluronic Acids for the Treatment of Knee Osteoarthritis." The database for this PMA reflected data collected between January 10, 2011, and February 2, 2012, and 349 patients. There were 7 investigational sites in the People's Republic of China.

Study TG1018DLN was a prospective, randomized, controlled, multicenter clinical study intended to demonstrate that DUROLANE was non-inferior to a commercially-available, 5-injection regimen hyaluronic acid (HA) product in the treatment of pain associated with knee OA over 18 weeks. The primary outcome measure was based on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) 20-point Likert-scale pain score. The non-inferiority margin was established as 8% (i.e., +1.6 units of the Likert-scale). Other outcome measures collected included WOMAC subscale domains of stiffness and physical function, along with subject global assessment.

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the TG1018DLN study was limited to patients who met the following inclusion criteria:
   - Subject (female or male) with 40-80 years of age, inclusive.

- Documented diagnosis of mild to moderate OA of the studied knee and fulfilled the American College of Rheumatology (ACR) criteria*.

  *ACR criteria for diagnosis of knee OA: Knee pain plus osteophytes on radiographs and at least one of the following conditions: age > 50 years, morning stiffness < 30 minutes in duration and crepitus on motion.
- Radiographic evidence of OA in the studied knee (Kellgren-Lawrence [KL] radiographic score = 2 or 3), obtained from postero-anterior view of standing weight-bearing semi-flexed radiographs of the studied knee assessed by an assigned x-ray film reader in a study center.
- WOMAC pain score from 7 to 17 (with WOMAC Likert 3.1 A) in the studied knee at both the screening and baseline visit.
- Pain in the studied knee demonstrating a score of 2 or 3 (i.e. moderate or severe) with WOMAC Likert 3.1 A1 pain scoring.

Patients were <u>not</u> permitted to enroll in the TG1018DLN study if they met any of the following exclusion criteria:

- Clinically apparently tense effusion of the studied knee on examination determined by either a positive bulge sign or positive ballottement of the patella (patellar tap).
- Symptomatic OA of the contralateral knee or of either hip that was not responsive to acetaminophen (paracetamol) and/or required any therapies prohibited in the protocol.
- Low back pain requiring chronic ongoing analgesic therapy that confounded measurement of pain in the studied knee.
- Systemic or intra-articular injection of corticosteroids in any joint within 6 months prior to screening.
- Intra-articular HA injection in any joint including the studied knee within 9 months prior to screening.
- Treatment with glucosamine-chondroitin sulfate initiated within the past 3 months, or dosage not stable for the past 3 months.
- Serious injuries to the studied knee in the past resulting in significant restriction in ambulation.
- Arthroscopy and/or other surgical procedure in the studied knee within the past 12 months.
- Pregnant or breastfeeding women or women with potential childbearing without adequate contraception measure.

2. <u>Follow-up Schedule</u>
   Patients were followed for 26 weeks. Effectiveness was assessed at Weeks 6, 10, 14, 18, and 26. Safety was assessed at screening and at Weeks 0, 1, 2, 3, 4, 6,

10, 14, 18, and 26. To address patient blinding due to the different injection regimens for the products, the DUROLANE group was given 3 mL at Week 0 (baseline) and received subcutaneous skin punctures (i.e., the needle did not enter the joint space) with an empty syringe at Weeks 1, 2, 3, and 4. The 5-injection HA group was administered using 2.5mL injections of product at the same five time points.

Before the baseline visit, the current use of analgesics was required to have elapsed by at least 5 half-lives; within 48 hours before each visit, patients were not allowed to take any acetaminophen (paracetamol) or any other analgesic. Acetaminophen was permitted as rescue analgesia during the course of the study.

3. Clinical Endpoints

With regards to safety, safety assessments included collection of adverse events (AEs), physical examinations (including the knee), vital sign assessments, and blood and urine laboratory assessments.

With regards to effectiveness, the primary effectiveness variable was the WOMAC Likert pain subscale score Change from Baseline (CFB) over Weeks 6, 10, 14, and 18.

Secondary effectiveness variables were analyzed in a step-wise, hierarchical fashion; these variables included:

- WOMAC physical function subscale score CFB
- Subject global assessment CFB
- WOMAC stiffness subscale score CFB

Variables were tested for non-inferiority in the order as listed above. The same 8% non-inferiority margin utilized for the primary effectiveness variable was used for all secondary variables.

Testing was first conducted over Weeks 6, 10, 14, and 18 for a given variable; contingent upon a determination of non-inferiority, testing was extended out through Week 26. Each variable tested over these two timeframes required a conclusion of non-inferiority in order to continue hierarchical non-inferiority testing.

With regards to success/failure criteria, the primary effectiveness analysis involved a non-inferiority test of the WOMAC pain subscale variable using a Mixed Model for Repeated Measures (MMRM) over 18 weeks. The non-inferiority margin was established as +1.6 units of the Likert 20-point scale, corresponding to 8 units on a 100-point scale (i.e., 8%).

D. Accountability of PMA Cohort

At the time of database lock, a total of 404 subjects were screened at seven (7) sites. There were 349 (86.4%) subjects (175 DUROLANE and 174 5-injection HA) who received the study treatment after randomization.

Among subjects treated, there were about 5% of subjects who did not complete the 18-week primary analysis period. For the 17 subjects who did not complete Visit 10 (Week 18), five refused to participate; five were due to protocol violations; three were due to adverse events (none of which were device-related); three were due to other reasons; and one subject was lost to follow-up.

A total of 331 (94.8%) subjects (168 DUROLANE and 163 5-injection HA) received all five HA injections or a single injection of DUROLANE and four needle-sticks; had at least one effectiveness assessment; and met all inclusion/exclusion criteria, therein forming the Full Analysis Set (FAS) population.

A total of 319 (91.4%) subjects (161 DUROLANE and 158 5-injection HA) were included in the Per Protocol Set (PPS) population. Twelve (12) subjects from the FAS were excluded from the PPS due to various protocol deviations.

E. Study Population Demographics and Baseline Parameters

The study was conducted in the People's Republic of China, and all patients were of Chinese ethnicity. Demographic and baseline characteristics were balanced between the two groups; see Table 6.

Table 6: Demographic Data and Baseline Characteristics

Variable	Measure	DUROLANE (N=161)	5-injection HA (N=158)	TOTAL (N=319)
Age (years)	Mean (SD)	60.2 (8.1)	60.4 (7.8)	60.3 (7.9)
	Median	60	59	59
	Min; Max	40; 78	42; 78	40; 78
Sex [n (%)]	Female	119 (73.9)	127 (80.4)	246 (77.1)
	Male	42 (26.1)	31 (19.6)	73 (22.9)
	Total	161 (100.0)	158 (100.0)	319 (100.0)
Nationality [n (%)]	Han	155 (96.3)	157 (99.4)	312 (97.8)
	Other	6 (3.7)	1 (0.6)	7 (2.2)
	Total	161 (100.0)	158 (100.0)	319 (100.0)
Weight (kg)	n	161	158	319
	Mean (SD)	66.5 (10.2)	66.8 (10.8)	66.6 (10.5)
	Median	65.0	67.0	65.0

	Min; Max	44.0; 100.0	44.5; 106.0	44.0; 106.0
Height (cm)	n	161	158	319
	Mean (SD)	162.5 (6.7)	162.4 (7.7)	162.4 (7.2)
	Median	162	160	162.0
	Min; Max	147; 183	145; 190	145; 190
BMI (kg/m^2)	n	161	158	319
	Mean (SD)	25.1 (3.2)	25.3 (3.2)	25.2 (3.2)
	Median	24.8	25.1	25.0
	Min; Max	18.4; 33.9	19.0; 35.0	18.4; 35.0
BMI classification	Underweight	1 (0.6)	0 (0.0)	1 (0.3)
	Normal range	81 (50.3)	76 (48.1)	157 (49.2)
	Overweight	65 (40.4)	69 (43.7)	134 (42.0)
	Obese	14 (8.7)	13 (8.2)	27 (8.5)
	Total	161 (100.0)	158 (100.0)	319 (100.0)

The basic demographics and baseline characteristics of the Chinese population studied in TG1018DLN were also found to be reasonably similar to other non-inferiority HA studies conducted in both China and the United States.

F. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the prospective and randomized cohort of 349 patients available for the 18-week evaluation. The key safety outcomes for this study are presented below in Tables 7 and 8. There were three subjects (1 DUROLANE; 2 5-injection HA) who discontinued the study due to an AE; none of these were considered device-related.

Adverse Effects that occurred in the PMA clinical study:

Subjects with device-related AEs were 13.1% and 9.8% in the DUROLANE and 5-injection HA groups, respectively. The most common device-related AE was arthralgia for both groups (DUROLANE: 8.6%; 5-injection HA: 7.5%).

The severities of device-related AEs in both groups were mainly mild and moderate; only one injection site pain in the DUROLANE group and two cases of arthralgia and one case of joint swelling in the 5- INJECTION HA group were classified as severe.

The proportion of subjects with Serious Adverse Events (SAEs) was 1.7% (3/175) and 3.4% (6/174) in the DUROLANE and 5-injection HA groups,

respectively. No SAEs were considered related to the investigational products. No deaths occurred in this study.

The adverse events of the two groups were comparable.

Table 7: Summary of Adverse Events – safety set (SS)

	DUROLANE	**5-injection HA**
	(N=175)	(N=174)
	n (%)	n (%)
Subjects with at least one treatment emergent AE	83 (47.4)	74 (42.5)
Subjects with device-related AEs	23 (13.1)	17 (9.8)
Subjects with a severe AE	6 (3.4)	8 (4.6)
Subjects with a SAEs	3 (1.7)	6 (3.4)
Subjects with a device-related SAE	-	-
Death	-	-

Table 8: Subjects with Device Related AEs

Primary System Organ Classification (SOC) **Preferred term**	**DUROLANE**	**5-injection HA**
	(N=175)	(N=174)
	n (%)	*n (%)*
General disorders and administration site conditions	4 (2.3)	2 (1.1)
Injection site pain	4 (2.3)	2 (1.1)
Musculoskeletal and connective tissue disorders	18 (10.3)	16 (9.2)
Arthralgia	15 (8.6)	13 (7.5)
Joint swelling	3 (1.7)	3 (1.7)
Arthropathy	1 (0.6)	-
Epicondylitis	-	1 (0.6)
Joint effusion	1 (0.6)	-
Limb discomfort	-	1 (0.6)
Muscular weakness	1 (0.6)	-
Musculoskeletal discomfort	1 (0.6)	-
Myalgia	-	1 (0.6)
Pain in extremity	1 (0.6)	-
Skin and subcutaneous tissue disorders	1 (0.6)	-
Erythema	1 (0.6)	-

2. Effectiveness Results

The analysis of effectiveness was based on the 319 evaluable patients at the 26-week time point. Key effectiveness outcomes are presented in Table 9.

Primary Effectiveness Endpoint

The analysis of the effectiveness of DUROLANE was based on the PPS (n=319). The results demonstrated that DUROLANE was non-inferior to the 5-injection HA. The Least Square Mean (LSM) WOMAC pain subscale score change from baseline (CFB) over 18 weeks was -5.97 for DUROLANE and -5.87 for the 5-injection HA, with a difference (DUROLANE - 5-injection HA) of -0.09 (95% CI:-0.58, 0.39). See Table 9 for a tabular summary of the results of the primary endpoint by visit.

Table 9: Mixed Model Repeated Measures (MMRM) Analysis of WOMAC Pain Subscale Score CFB by Visit -PPS

Visit (week)	Measure	Actual Result		Change from Baseline		Baseline Change Difference (95%CI)[a]
		DUROLANE (N=161)	5-injection HA (N=158)	DUROLANE (N=161)	5-injection HA (N=158)	DUROLANE - 5-injection HA
Baseline (Week 0)	Mean(SD)[b]	9.4 (1.98)	9.5 (1.80)			
Visit 7 (Week 6)	Mean(SD)	4.6 (3.32)	4.6 (2.93)	-4.9 (3.16)	-5.0 (2.68)	
	LSM[c] (95% CI)			-5.02 (-5.46; -4.58)	-5.06 (-5.50; -4.61)	0.04 (-0.58; 0.65)
	p-value			<0.0001	<0.0001	0.91
Visit 8 (Week 10)	Mean(SD)	3.7 (3.19)	3.7 (2.81)	-5.7 (3.03)	-5.8 (2.65)	
	LSM (95% CI)			-5.45 (-5.85; -5.05)	-5.49 (-5.89; -5.09)	0.04 (-0.51; 0.59)
	p-value			<0.0001	<0.0001	0.89
Visit 9 (Week 14)	Mean(SD)	3.2 (2.90)	3.4 (2.69)	-6.2 (2.87)	-6.1 (2.59)	
	LSM (95% CI)			-5.76 (-6.14; -5.39)	-5.73 (-6.11; -5.36)	-0.03 (-0.54; 0.48)
	p-value			<0.0001	<0.0001	0.91
Visit 10 (Week 18)	Mean(SD)	3.0 (2.88)	3.3 (2.75)	-6.5 (2.79)	-6.2 (2.75)	
	LSM (95% CI)			-5.97 (-6.32; -5.61)	-5.87 (-6.23; -5.52)	-0.09 (-0.58; 0.39)
	p-value			<0.0001	<0.0001	0.70
Visit 11 (Week 26)	Mean(SD)	2.8 (2.73)	2.9 (2.68)	-6.6 (2.67)	-6.6 (2.58)	
	LSM (95% CI)			-6.15 (-6.49; -5.81)	-6.05 (-6.39; -5.71)	-0.10 (-0.56; 0.37)
	p-value			<0.0001	<0.0001	0.68

[a] CI = confidence interval
[b] SD = standard deviation [Note: SD are descriptive statistics using at visit observations.]
[c] LSM = Least Square Mean [Note: LSM (95% CI) and p-values are repeated measure statistics using at visit and all preceding visit observations.]

As the upper bound of the confidence interval did not exceed the pre-specified non-inferiority margin of +1.6, non-inferiority was established. See Figure 1.

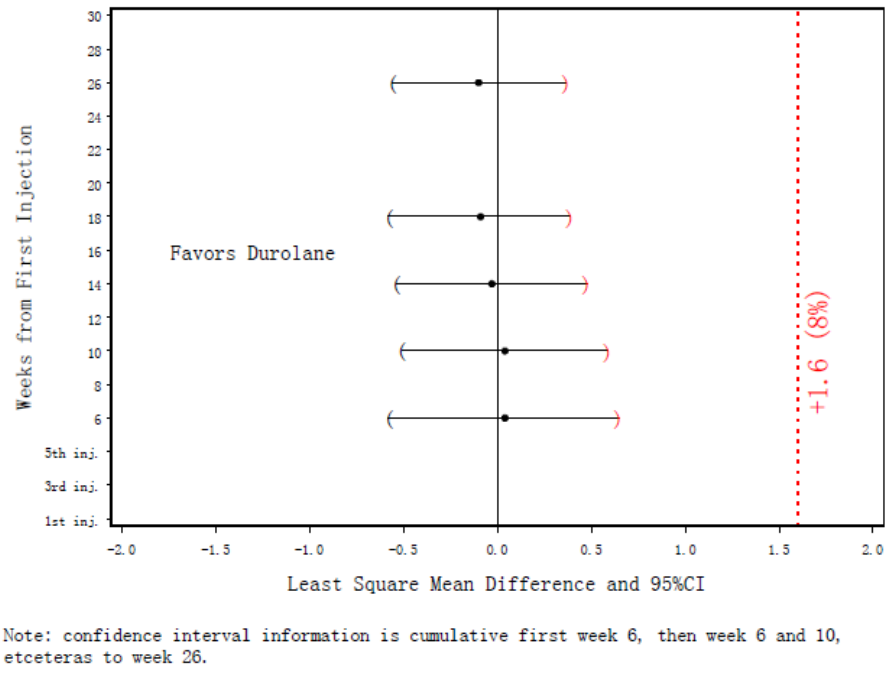

Figure 1: MMRM 95% CI Plot
MMRM 95% CI Plot of DUROLANE-5-injection HA Likert-type WOMAC Pain Subscale Score-PPS

Secondary Effectiveness Endpoints
The same 8% non-inferiority margin utilized for the primary effectiveness variable was used for all secondary variables. Results through 26 weeks for the WOMAC pain subscale score CFB are included in Table 9 above.

The remaining secondary variables were tested for non-inferiority in a stepwise order as outlined in Table 10 below.

Table 10: Results of Stepwise Non-inferiority Analyses of Other Secondary Effectiveness Variables

Secondary Variable (order of importance)	Baseline Change Mean (SD)		(DUROLANE-5-injection HA) LSM[a] (95%CI[b])	Non-Inferiority 8% Margins	Conclusion
	DUROLANE	5-injection HA			
WOMAC Physical Function CFB (over 18 weeks)	-12.75 (-13.60; -11.91)	-12.10 (-12.95; -11.26)	-0.65 (-1.81,**0.51**)	+5.44	Non-inferior
WOMAC Physical Function CFB (over 26 weeks)	-12.58 (-13.39; -11.77)	-13.16 (-13.97; -12.35)	-0.58 (-1.69,**0.53**)	+5.44	Non-inferior
Subject Global Assessment CFB (over 18 weeks)	2.70 (2.48; 2.92)	2.55 (2.33; 2.77)	0.15 (-**0.15**,0.45)	-0.8	Non-inferior
Subject Global Assessment CFB (over 26 weeks)	2.81 (2.59; 3.02)	2.67 (2.45; 2.88)	0.14 (-**0.16**,0.43)	-0.8	Non-inferior
WOMAC Knee Stiffness CFB (over 18 weeks)	-1.87 (-2.00; -1.73)	-1.73 (-1.87; -1.59)	-0.14 (-0.33,**0.05**)	+0.64	Non-inferior
WOMAC Knee Stiffness CFB (over 26 weeks)	-1.95 (-2.08; -1.82)	-1.80 (-1.93; -1.67)	-0.15 (-0.33,**0.03**)	+0.64	Non-inferior

[a]LSM = Least Square Mean [b]CI = confidence interval

3. Subgroup Analyses

   Subgroup analyses were conducted on the PPS and included subjects with different age, gender, and osteoarthritis condition (e.g. joint fluid removal and KL grade). Results showed that at Weeks 18 and 26, the DUROLANE WOMAC pain subscale scores in all subgroup populations were non-inferiority to the 5-injection HA group. The only exception involved subjects who had joint fluid aspirated at baseline. However, the results were not superior for the 5-injection HA group and the number of subjects in this subgroup were too small to draw any conclusions based on these findings. Additionally, there was no statistically significant difference between DUROLANE and the 5-injection HA group in the corresponding WOMAC pain responder rate at Weeks 18 and 26 in all subgroup populations, inclusive of the joint aspirated subgroup.

4. Pediatric Extrapolation

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

G. 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 was conducted in the People's Republic of China and included 7 investigators. Financial disclosure was not conducted before or during the study, and there were no responses from the investigators during attempts to collect these disclosures retrospectively. However, 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 Orthopaedic 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 clinical evidence for reasonable assurance of the effectiveness of DUROLANE was the results from a 26-week randomized controlled clinical non-inferiority trial comparing DUROLANE to a commercially available HA with 319 evaluable patients. The results demonstrated that DUROLANE was non-inferior to the 5-injection HA. The LSM WOMAC pain subscale score CFB over 18 weeks was -5.97 for DUROLANE and -5.87 for the 5-injection HA, with a difference (DUROLANE – 5-injection HA) of -0.09 (95% CI:-0.58, 0.39). See Table 9 for a tabular summary of the results of the primary endpoint by visit.

B. Safety Conclusions

The risks of the device are based on the pre-clinical laboratory studies, animal studies, and clinical studies conducted to support PMA approval as have been described in the preceding sections. Pre-clinical studies have shown that DUROLANE is biocompatible. Results from the pivotal clinical trial showed comparable adverse events rates between DUROLANE and a multi-injection commercially available HA product. The most common side effects include transient pain and swelling, which are common types of reactions for any type of intra-articular therapy.

Additional clinical studies have not shown any safety concerns related to its use, including its use in patients receiving a repeated course of therapy.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in clinical studies conducted to support PMA approval as described above. A single injection of DUROLANE provides probable benefit for pain reduction in patients with osteoarthritis in the knee. An additional benefit of DUROLANE is the ability for patients to be treated with a single injection versus a series of injections required of multi-injection HA formulations. The data support the conclusion that the benefits outweigh the risks of transitory adverse events such as pain and swelling in treatment of pain associated with osteoarthritis of the knee.

1. Patient Perspectives

   Patient perspectives considered during the review included patient-reported global assessments of pain that were collected in the pivotal trial as a secondary endpoint. Mean reductions from baseline in these reported pain assessments are summarized in Table 10.

In conclusion, given the available information above, the data support that for the treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacological therapy or simple analgesics the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data contained within the PMA support the reasonable assurance of safety and effectiveness of DUROLANE when used in accordance with its labeled indications. Pre-clinical and clinical data support the safety and effectiveness of a single injection of DUROLANE. Results from a randomized, controlled non-inferiority pivotal study demonstrated that DUROLANE was non-inferior to a commercially available 5-injection HA for the treatment of pain in OA of the knee. Results from this pivotal study also showed the adverse event rates and safety profiles of DUROLANE and the 5-injection HA to be comparable. Clinical data in the PMA also supported the safe, repeated use of the product.

XIII. CDRH DECISION

CDRH issued an approval order on August 29, 2017.

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.