MONOVISC™

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Hyaluronic Acid, Intra-articular
Device Trade Name: MONOVISC™
Applicant's Name and Address: Anika Therapeutics, Inc.
32 Wiggins Ave
Bedford, MA 01730

Premarket Approval (PMA) Application Number: P090031
Date of Panel Recommendation: None
Date of Notice of Approval to the Applicant: February 25, 2014

II. INDICATIONS FOR USE

MONOVISC™ is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and to simple analgesics (e.g., acetaminophen).

III. CONTRAINDICATIONS

- Do not administer to patients with known hypersensitivity (allergy) to hyaluronate preparations.
- Do not administer to patients with known hypersensitivity (allergy) to gram positive bacterial proteins.
- Do not inject MONOVISC™ in the knees of patients with infections or skin diseases in the area of the injection site or joint.
- Do not administer to patients with known systemic bleeding disorders.

IV. WARNINGS AND PRECAUTIONS

Warnings and precautions can be found in the labeling for MONOVISC™.

V. DEVICE DESCRIPTION

The MONOVISC™ device is a proprietary high molecular weight hyaluronic acid (HA) visco-supplementation intended for the treatment of pain in patients with moderate osteoarthritis (OA) of the knee who have failed conservative non-pharmacological therapy and simple analgesics. The device is administered by a single injection via the para-patellar approach under sterile conditions. The dosage delivered by the single injection is equivalent to three injections of Anika's FDA approved (P030019) ORTHOVISC® HA product.

Sodium hyaluronate is a natural complex sugar of the glycosaminoglycan family. The sodium hyaluronate polymer consists of repeating disaccharide units of sodium glucuronate-N-acetylglucosamine. The molecular weight range of hyaluronic acid in MONOVISC™ is between 1 and 2.9 million Daltons. MONOVISC™ has a nominal sodium hyaluronate concentration of 22 mg/mL, dissolved in physiologic saline. It is supplied in a 5.0 mL syringe containing 4.0 mL of MONOVISC™. The contents of the syringe are sterile, non-pyrogenic, and non-inflammatory.

MONOVISC™ is prepared by cross-linking hyaluronan (hyaluronic acid, HA) with a proprietary cross-linking agent. The HA is derived from bacterial fermentation (*Streptococcus equi)*. The HA used in MONOVISC™ is the same grade and specification used in ORTHOVISC® (P030019/S009)[1], and delivers a comparable amount of HA to the 3-injection ORTHOVISC® regimen.

Each pre-filled syringe with 4 mL of MONOVISC™ contains:

Sodium Hyaluronate	88 mg (nominal)
Sodium Chloride	36 mg
Potassium Chloride	0.8 mg
Sodium Phosphate, Dibasic	4.6 mg
Potassium Phosphate, Monobasic	0.8 mg
USP water for injection	q.s. to 4 mL

[1] ORTHOVISC® was approved for manufacture with HA source from bacterial fermentation in 2007; the original PMA was approved for ORTHOVISC® manufactured with HA that was avian sourced.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative therapies to MONOVISC™ may include conservative non-pharmacological therapy and simple analgesics (e.g., acetaminophen), nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular injection of corticosteroid, avoidance of activities that cause joint pain, exercise, weight loss, physical therapy, and removal of excess fluid from the knee. For patients who have failed the above treatments, surgical interventions such as arthroscopic surgery and total knee replacement are also alternative treatments.

VII. POTENTIAL ADVERSE EFFECTS ON HEALTH

Potential adverse effects for MONOVISC™, including complications associated with intra-articular injections, are as follows:

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

Incidences of rash, headache, dizziness, chills, hives, nausea, muscle cramps, peripheral edema, and malaise have also been reported in association with intra-articular injections.

Specific adverse events that occurred in the MONOVISC™ clinical study are listed in Section IX.

VIII. MARKETING HISTORY

MONOVISC™ obtained CE Mark approval in December 2007, and has been available in the European Union since 2008. MONOVISC™ is currently marketed globally in 30 countries. MONOVISC™ has not been withdrawn from marketing in any country for any reason related to safety or effectiveness of the device.

MONOVISC™ is formulated to provide the equivalent sodium hyaluronate dose in a single injection as three injections of the product ORTHOVISC® which was approved by the FDA in 2004 (PMA P030019).

IX. SUMMARY OF PRECLINICAL STUDIES

MONOVISC™ was tested for biocompatibility in accordance with the requirements of ISO 10993-1, Biological Evaluation of Medical Devices. MONOVISC™ is considered to be biocompatible under the conditions of the studies performed. Each of the tests is briefly summarized in **Table 1** below.

Table 1. Biological Evaluation of MONOVISC™

Test	Standard	Test Method	Results	Pass
Cytotoxicity	ISO 10993-5 *Tests for in vitro cytotoxicity* and USP 26, Chapter 87 *Biological reactivity tests in vitro*	ISO Agarose Overlay using L-929 Mouse Fibroblast Cells	Grade 0 – Non-Toxic	Yes
Sensitization/ Irritation	ISO 10993-10 *Tests for irritation and delayed-type hypersensitivity*	ISO Guinea Pig Maximization Sensitization Test (Method of Liquid Test Articles)	No evidence of sensitization response greater than the negative control	Yes

Test	Standard	Test Method	Results	Pass
Intracutaneous Reactivity	ISO 10993-10 *Tests for irritation and delayed-type hypersensitivity*	ISO Intracutaneous Reactivity Test	Non irritant	Yes
Acute Systemic Toxicity	ISO 10993-11 *Tests for Systemic Toxicity*	ISO Acute Systemic Injection Test	No evidence of systemic toxicity	Yes
Genotoxocity	ISO 10993-3 *Test for genotoxicity, carcinogenicity and reproductive toxicity*	Bacterial Mutagenicity Test – Ames Assay	Non-mutagenic	Yes
Implantation	ISO 10993-6 *Tests for local effects after implantation* and USP 26 *Biological reactivity tests, in vivo, implantation test*	ISO Intramuscular Implant Test	Nonirritant	Yes
Subacute Intraperitoneal Toxicity	ISO 10993-11 *Tests for systemic toxicity*	Subacute (14 Day) Intraperitoneal Toxicity Study in Rats, 5 Dose Exposure	No evidence of Systemic Toxicity	Yes

X. SUMMARY OF CLINICAL STUDIES AND SUPPLEMENTAL DATA

The safety and effectiveness of MONOVISC™ for the treatment of osteoarthritis of the knee was evaluated in a randomized, controlled, double-blind, multicenter study performed in the U.S. and Canada, MONOVISC™ 0702. A follow-on extension study, MONOVISC™ 0802, was conducted to demonstrate the safety of a repeat MONOVISC™ injection. The data from these studies, along with supplemental data analyses demonstrating non-inferiority of a single injection of MONOVISC™ compared to three injections of ORTHOVISC® and a review of the safety of MONOVISC™ compared to ORTHOVISC® (from both clinical studies and global complaint data), form the basis for the PMA approval decision.

A. CLINICAL TRIAL SUMMARY

Study Overview

The MONOVISC™ 0702 study was a randomized, double-blinded, saline-controlled pivotal study conducted under IDE G070196 to evaluate the safety and effectiveness of a single 4 mL injection of MONOVISC™ in patients with symptomatic osteoarthritis of the knee.

Investigational Plan

The study was conducted at 31 sites in the US (30 sites) and Canada (1 site) in two stages:

- A Main Study (protocol MONOVISC™ 0702) - an initial single injection of 4 mL of MONOVISC™, or saline control, evaluating safety and efficacy over a 26-week follow-up period, and

- An Extension Study (protocol MONOVISC™ 0802) - a repeat treatment to evaluate the safety of a second single injection of 4 mL of MONOVISC™ over a period of 4 weeks.

The trial included 369 patients with symptomatic primary OA of the knee. The first patient was injected on January 4, 2008. The last patient visit was on June 30, 2009. The study was conducted in compliance with the principles of GCP guidelines established by the U.S. 21 CFR Part 312, International Conference on Harmonization (ICH) Guidelines and the Declaration of Helsinki (October 1996).

Eligibility Criteria

Key inclusion criteria for the MONOVISC™ 0702 study included:

1. Baseline index knee Western Ontario and McMaster Universities Arthritis Index (WOMAC) Pain Score (sum of five 100-mm components) between 200 and 400 mm
2. Baseline contralateral knee WOMAC Pain Score <150 mm
3. Age range of 35-75 years
4. Wash-out of all NSAIDs, corticosteroids, and other analgesics prior to study initiation

5. Index knee Kellgren-Lawrence (K-L) Grade II or III

Exclusion criteria included:

1. Infection in the joint or surrounding skin
2. Intra-articular neoplasm
3. Inflammatory joint disease, OA in the hips, osteonecrosis, moderate to marked effusion from index knee
4. Positive synovial fluid culture
5. Reduced range of motion
6. Large knee circumference (>45 cm)
7. Recent intra-articular HA
8. Immunosuppressives, anti-coagulants, NSAIDs, antidepressants
9. Recent knee trauma or surgery
10. Bursitis
11. Full-thickness cartilage loss in index knee
12. Fibromyalgia
13. Vascular insufficiency and hemiparesis

Randomization

Patients that satisfied the inclusion / exclusion criteria were randomized into one of two treatment arms: arthrocentesis (as determined by physician) followed by a single intra-articular 4 mL injection of MONOVISC™, or arthrocentesis (as determined by physician) followed by a single intra-articular 4 mL injection of saline control. Randomization was performed by a third party, and was done in blocks of four.

Follow-up Schedule

After screening, baseline pain scores were recorded. The follow up visits were scheduled at 2, 4, 8, 12, 20, and 26 weeks following injection.

Safety Analysis

Safety analyses were performed on the safety population, which was defined as all randomized patients. Safety was assessed by comparing the incidence, timing, severity, and relationship to treatment of all adverse events (AEs) between treatment groups. Adverse events were coded using a standardized coding

dictionary (MedDRA). Adverse events were categorized as treatment-emergent AEs, device-related AEs, Serious Adverse Events (SAEs) and Unexpected Adverse Device Effects (UADEs).

To assess the safety of a repeat injection of 4 mL of MONOVISC™ the compliant patients from both arms were permitted to enter a 4-week, open-label repeat treatment phase after the completion of the initial study injection.

Effectiveness Measures

The primary endpoint was to determine the superiority of a single injection of MONOVISC™ compared with a single injection of saline by evaluating the proportion of patients achieving ≥ 40% relative improvement and ≥ 15mm absolute improvement from baseline in the WOMAC VAS Pain Score (mean of 5 questions; maximum score is 100mm) through Week 12.

The secondary endpoints included:

- Improvement Success (proportion of patients with a ≥ 20 mm improvement)
- WOMAC physical function
- WOMAC walking pain
- WOMAC pain – stairs
- Investigator global assessment
- Patient global assessment
- Range of motion
- Acetaminophen usage

Statistical and Analytical Overview

Statistical inference for the primary endpoint was based on a Generalized Estimating Equations (GEE) analysis with covariates. The GEE models were performed separately for the patient success endpoints to simultaneously control for potential differences in age, K-L score in the index knee, and baseline contralateral WOMAC Pain Score plus site, time, site-treatment, and time-treatment interactions while testing for differences between MONOVISC™ and the Saline control.

MONOVISC™ 0702 Results

Accountability of Study Cohort

MONOVISC™ 0702 included 369 patients at 31 centers in the U.S. and Canada.

A total of 369 patients were randomized to either receive MONOVISC™ (n=184) or to receive 0.9% Sodium Chloride (Saline) control (n=185) as part of the initial treatment phase of the study. Table 2 shows the disposition of all patients enrolled in the study while Table 3 summarizes the demographic and clinical characteristics of the Intent-to-Treat (ITT) study population at screening and baseline.

The subjects with protocol violations that could affect the evaluations were excluded from the Per-Protocol Population (PP) (N= 334). A total of 331 patients (89.7%) completed the study. Twenty-two patients (12.0%) who received MONOVISC™ and sixteen patients (8.6%) who received control did not complete the study and were excluded from the efficacy evaluation.

The description and accountability of the patient populations are summarized in the Patient Tree (Figure 1).

Figure 1: MONOVISC™ 0702 Patient Accountability Flow Chart

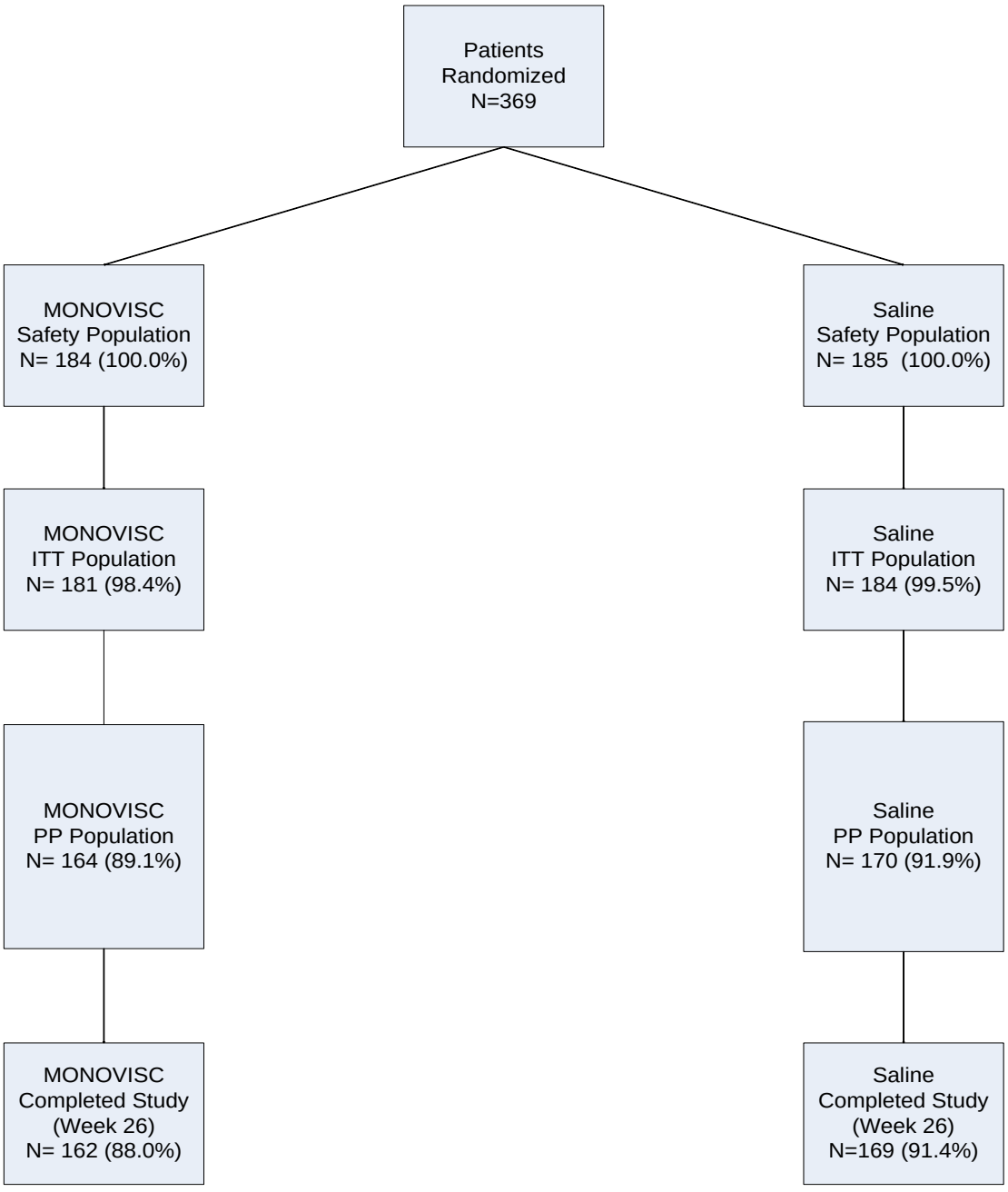

Table 2 shows the disposition of all patients enrolled in the study.

Table 2. Patient Disposition

Patient Disposition	All Patients (N=369)	MONOVISC™ (N=184)	Saline Control (N=185)
Not Randomized	0	0	0
Randomized	369	184	185
Completed Study	331 (89.7%)	162 (88%)	169 (91.4%)
Withdrew Early	38 (10.3%)	22 (12%)	16 (8.60%)
Reasons for Early Discontinuation:			
Investigator Request	0 (0.0%)	0 (0.0%)	0 (0.0%)
Adverse Event	5 (1.4%)	4 (2.2%)	1 (0.5%)
Safety Reason	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subject use/need of concomitant therapy	3 (0.8%)	2 (1.1%)	1 (0.5%)
Withdrew consent	9 (2.4%)	4 (2.2%)	5 (2.7%)
Lost to follow up	13 (3.5%)	7 (3.8%)	6 (3.2%)
Other	8 (2.2%)	5 (2.7%)	3 (1.6%)

Table 3 contains patient demographic and clinical characteristics at Screening.

Table 3. Demographics and Clinical Characteristics at Screening – ITT Population

Patient Screening Characteristics	All Patients (N=365)	MONOVISC™ (N=181)	Saline (N=184)
Age (years)			
Mean	59.2	59.7	58.7
Median	60.0	60.0	59.0
Standard Deviation	8.6	7.9	9.2
Gender [N (%)]			
Male	152 (41.6%)	74 (40.9%)	78 (42.4%)
Female	213 (58.4%)	107 (59.1%)	106 (57.6%)
Body Mass Index (kg/m^2)			
Mean	30.1	29.8	30.4
Median	29.6	29.1	30.0
Standard Deviation	4.6	4.7	4.6
Kellgren-Lawrence (K-L) Score - Study Knee			
Grade II	200 (54.8%)	103 (56.9%)	97 (52.7%)
Grade III	165 (45.2%)	78 (43.1%)	87 (47.3%)
Baseline WOMAC Pain Score – Index Knee (mm)			
Mean	293.0	294.0	291.5
Median	291.0	296.0	288.0
Standard Deviation	60.3	60.0	60.7
Baseline WOMAC Pain Score – Contralateral Knee (mm)			
Mean	62.5	59.5	65.5
Median	54.0	44.0	60.0
Standard Deviation	48.2	48.0	48.4

Safety Results for MONOVISC™ 0702

The safety population included all 369 patients that were injected in the treatment phase of the study: with MONOVISC™ (184) and with 0.9 % Sodium Chloride (Saline) control (185). Adverse events were collected for the whole study

population. There were no significant differences between the treatment and control study groups in the frequency and/or type of observed adverse events.

Regardless of the cause and device relatedness, there were 244 (66.1%) patients that experienced adverse events for the total study cohort, where 121 (65.8%) were observed in MONOVISC™ group and 123 (66.5%) were observed in control group.

The adverse events (AEs) most frequently reported (> 5 % in each group) and not related to the index knee were arthralgia (17.4% in the MONOVISC™ group and 14.6% in the saline group), headache (13.0% in the MONOVISC™ group and 15.1% in the saline group), back pain (8.7% in the MONOVISC™ group and 8.6% in the saline group), pain in extremity (8.2% in the MONOVISC™ group and 7.0% in the saline group), and upper respiratory tract infections (6.0% in the MONOVISC™ group and 7.6% in the saline group). Adverse events considered related to the treatment are listed in Table 4. Adverse Events related to treatment were considered typical of viscosupplementation injections in this patient population, were mild or moderate in severity, and resolved without sequelae. There were no Serious Adverse Events or Unexpected Adverse Device Effects.

Table 4. 0702 Patients with Device or Procedure-Related Adverse Events

AE Type	MONOVISC™ N=184	Control (Saline) N= 185
Any Adverse Event*	13 (7.1%)	10 (5.4%)
Arthralgia	7 (3.8%)	7 (3.8%)
Joint swelling	2 (1.1%)	2 (1.1%)
Joint stiffness	1 (0.5%)	2 (1.1%)
Injection site pain	3 (1.6%)	0 (0.0%)
Joint effusion	1 (0.5%)	0 (0.0%)
Pain in extremity	1 (0.5%)	0 (0.0%)
Synovitis	1 (0.5%)	0 (0.0%)
Contusion	1 (0.5%)	0 (0.0%)
Subcutaneous nodule	1 (0.5%)	0 (0.0%)
Baker's Cyst	1 (0.5%)	0 (0.0%)

* In some cases patients were involved in more than one AE

Effectiveness Results for MONOVISC™ 0702

In the 0702 study, MONOVISC™ did not demonstrate superiority over saline for the primary effectiveness endpoint of patients with ≥ 40 % relative improvement from baseline and ≥ 15 mm absolute improvement from baseline in the WOMAC VAS Pain Score through Week 12 (p=0.145).

Financial Disclosure for MONOVISC™ 0702

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 165 investigators, of which none were full-time or part-time employees of the sponsor and none of whom had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f). The information provided does not raise any questions about the reliability of the data.

B. MONOVISC™ NON-INFERIORITY ANALYSES

The FDA requested a new data analysis to support the reasonable assurance of safety and effectiveness of MONOVISC™ for its intended use. A non-inferiority analysis was conducted and submitted comparing MONOVISC™ with ORTHOVISC®, which was approved in PMA P030019 for treatment of knee pain due to osteoarthritis. MONOVISC™ offers in a single injection the equivalent dose of three injections of ORTHOVISC®.

ORTHOVISC® Basis of PMA Approval for Effectiveness

As described in the ORTHOVISC® PMA P030019 Summary of Safety and Effectiveness (SSED), the effectiveness of ORTHOVISC® for the treatment of knee pain due to osteoarthritis was evaluated using two randomized, controlled, double-blind, multicenter studies performed under IDE in the United States and Canada; OAK9501 and OAK2001.

The effectiveness analysis that served as the basis for approval used data combined from the two studies. The combined subgroup is referred to as the

"Effectiveness Subgroup" population. The revised eligibility criteria in the Effectiveness Subgroup population addressed confounding variables of contralateral knee pain in the OAK9501 study and inclusion of patients with K-L radiographic Grade I in OAK2001.

The combined studies "Effectiveness Subgroup" population consisted of the treatment groups listed in Table 5, and included a combined 3-injection ORTHOVISC® group (O3A1/O3):

Table 5. ORTHOVISC® "Effectiveness Subgroup" Treatment Arms

Group	Study	Description	N
O4	OAK2001	Four injections of ORTHOVISC®	104
O3	OAK9501	Three injections of ORTHOVISC®	83
O3A1	OAK2001	Three injections of ORTHOVISC® plus one arthrocentesis	90
O3A1/O3	OAK9501+ OAK2001	Combined group of three injections of ORTHOVISC®	173
A4	OAK2001	Four arthrocentesis procedures (control)	100
Saline	OAK9501	Three injections of Saline (control)	81

The primary effectiveness endpoints were the proportion of patients achieving a 20%, 40%, and 50% improvement in baseline in WOMAC Pain Score in conjunction with a minimum absolute improvement of 50mm (on a 500mm scale) in the WOMAC Pain Score in a GEE model for Weeks 7/8 through Weeks 21/22. There were four secondary endpoints that were all mean changes from baseline on a 100mm VAS Pain Scale: WOMAC Pain Score, Pain on Standing Score, Investigator Global Score, and Patient Global Score.

ORTHOVISC® Studies 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. Financial Disclosures for ORTHOVISC® studies OAK2001 and OAK9501 were submitted in PMA P030019. OAK2001 included 57 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). OAK9501, which was completed prior to February 2, 1999, had 10 investigators who complied with the Financial Disclosure

regulations effective at that time. None of the OAK9501 investigators had any of the three disclosable financial arrangements, as required by 21 CFR Part 54:

1. Any compensation made to the investigator by any sponsor of the covered clinical study in which the value of compensation could be affected by study outcome.

2. A proprietary interest in the tested product including, but not limited to, a patent, trademark, copyright or licensing agreement.

3. Any equity interest in any sponsor of the covered clinical study, i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices. The requirement applies to interests held during the time the clinical investigator is carrying out the study and for one year following completion of the study.

MONOVISC™ Non-Inferiority Analysis Plan

The analysis tested the non-inferiority of MONOVISC™ compared to ORTHOVISC® for equivalent doses; i.e. one injection of MONOVISC™ compared to three injections of ORTHOVISC®. The details of the analysis were agreed upon with the agency before the analysis was performed. The same patient data sets, timepoints, and endpoints from ORTHOVISC® studies OAK9501 and OAK2001 used to support the approval of PMA P030019 were utilized and compared with the equivalent data sets from the MONOVISC™ 0702 study.

Studies Utilized

The three pertinent studies, MONOVISC™ 0702, OAK9501, and OAK2001, are all multi-center, randomized, controlled, double-blind studies conducted under IDE at centers in the U.S. and Canada. Two of the studies utilized a Saline control (OAK9501 and MONOVISC™ 0702) whereas the third study (OAK2001) utilized an Arthrocentesis control.

The objective of all three studies was identical: to show safety and effectiveness for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and to simple analgesics. As MONOVISC™ is engineered with crosslinked HA to achieve the same dose as ORTHOVISC® in a smaller volume single injection, the main

difference between the products is in treatment regimen: MONOVISC™ gives the same dose in a single injection as three separate ORTHOVISC® injections.

Table 6, below, lists some of the characteristics of the studies included.

Table 6. Studies Included in Non-Inferiority Analysis

Study	IDE	Treatments	Dates Conducted	Number Centers	Total Enrollment
OAK9501	G950174	1:1 Randomization of ORTHOVISC® (3 injections) vs. Saline (3 injections)	May '96 – Jun '97	10	226
OAK2001	G990055	1:1:1 Randomization of ORTHOVISC® (4 injections) vs. ORTHOVISC® (3 injections/one Arthrocentesis) and 4 Arthrocentesis treatments	Jan '01 – Dec '02	24	373
MONOVISC™ 0702	G070196	1:1 Randomization of MONOVISC™ (1 injection) vs. Saline (1 injection)	Jan '08 – Jun '09	31	369

The studies were conducted over a 13-year range, from 1996 to 2009. A review of the PMA approvals for hyaluronan injections from 1997 to 2011 show the same "alternative treatments," specifically NSAIDs, intra-articular injection of steroids, avoidance of activities that cause joint pain, exercise, physical therapy, and removal of excess fluid from the knee. For patients who fail the above treatments, surgical interventions such as arthroscopic surgery and total knee replacement are also alternatives. The fact that the alternative treatments are the same over the time period in question suggests that the standard of care did not change significantly, and therefore data from the studies can be compared.

Treatment Arms from Studies to be used in Non-Inferiority Analysis

The treatment arms compared in the non-inferiority analysis are the same that were listed in Table 5 for the ORTHOVISC® effectiveness analysis, with the addition of the MONOVISC™ 0702 Intent-to-Treat population (M1 ITT) and MONOVISC™ 0702 Per Protocol (PP) population (M1 PP).

Comparisons for the Non-Inferiority Analysis

The MONOVISC™ ITT study population and the MONOVISC™ PP study population were each compared to the ORTHOVISC® three-injection groups O3A1 and O3, and the combined effectiveness subgroup (O3A1/O3) for purposes of establishing non-inferiority. Additional comparisons to the other treatment arms (O4, A4, Saline) that were used to support the ORTHOVISC® PMA approval were also made.

Timepoints for the Non-Inferiority Analysis

For the ORTHOVISC® PMA effectiveness analysis, the endpoints were assessed across four follow-up visits for OAK9501 and OAK2001: Week 7/8, Week 11/12, Week 15/16, and Week 21/22. In the MONOVISC™ 0702 there was not a follow-up visit conducted at Week 15/16. The non-inferiority analysis was, therefore, conducted with data from the following time-points: Baseline, Weeks 7/8, Weeks 11/12, and Weeks 20-22.

Non-Inferiority Endpoints

The same study endpoints utilized in the ORTHOVISC® PMA Effectiveness Assessment were utilized to test MONOVISC™ vs. ORTHOVISC® for non-inferiority, and are listed in Table 7 below.

Table 7. Effectiveness Endpoints for Non-Inferiority Analysis

#	Type of Endpoint	Endpoint	Definition of Endpoint
1	Primary	Proportion Responders at 20% threshold	Proportion Responders in test vs. control arms, where a 'Responder' is defined as having a ≥20% relative improvement in WOMAC Pain Score from baseline and at least an absolute improvement of ≥ 50mm WOMAC Pain Score from baseline (500mm scale) from Weeks 7/8 to Weeks 20-22.
2	Primary	Proportion Responders at 40% threshold	Proportion Responders in test vs. control arms, where a 'Responder' is defined as having a ≥40% relative improvement in WOMAC Pain Score from baseline from Weeks 7/8 to Weeks 20-22.

#	Type of Endpoint	Endpoint	Definition of Endpoint
3	Primary	Proportion Responders at 50% threshold	Proportion Responders in test vs. control arms, where a 'Responder' is defined as having a ≥50% relative improvement in WOMAC Pain Score from baseline from Weeks 7/8 to Weeks 20-22.
4	Secondary	Change in WOMAC Score from Baseline	Comparison of mean absolute change in WOMAC Pain Score from baseline (100mm scale) for test vs. control arms for follow-up visits from Weeks 7/8 to Weeks 20-22.
5	Secondary	Pain on Standing Score	Comparison of mean change from baseline in discomfort in the index knee when standing after a seated position on a 100mm Visual Analog (VAS) Scale for test vs. control arms from Weeks 7/8 to Weeks 20-22.
6	Secondary	Investigator Global Score	Comparison of mean change from baseline for Investigator Global Assessment on a 100mm VAS scale for test vs. control arms from Weeks 7/8 to Weeks 20-22.
7	Secondary	Patient Global Score	Comparison of mean change from baseline for Patient Global Assessment on a 100mm VAS scale for test vs. control arms from Weeks 7/8 to Weeks 20-22.

Eligibility Criteria across Studies

Eligibility criteria from across the studies were reviewed to evaluate whether they were similar enough to allow making the cross-study comparisons. The criteria are identical, with the exception of age range; MONOVISC™ 0702 allowed patients 35-75 years to enroll, whereas the age range for the ORTHOVISC® Combined Effectiveness Subgroup was 40 – 75 years.

Demographic and Baseline Characteristics across Studies

The ORTHOVISC® patient baseline and demographic characteristics were listed in the ORTHOVISC® P030019 SSED. This table has been expanded to include demographics and baseline characteristics from the MONOVISC™ 0702 study (Table 8, below).

The patient and baseline demographics data from the MONOVISC™ 0702 ITT population fit within the study data from the populations assessed in the

ORTHOVISC® PMA. Therefore, the study data can be used for comparison purposes in a non-inferiority analysis.

Table 8. Patient Baseline and Demographics Summary

Variable	O3 N=83 N (%) Mean±SD	Saline (9501) N=81 N (%) Mean±SD	O4 N=104 N (%) Mean±SD	O3AI N=90 N (%) Mean±SD	A4 N=lOO N (%) Mean±SD	M1 (ITT) N=181 N (%) Mean±SD
Gender(% male)	32 (38.6)	32 (39.5)	58 (55.8)	45 (50.0)	50 (50.0)	74 (40.9)
Age (years)	64.6±8.2	67.7±8.5	58.6±8.9	59.2±8.6	59.0±8.1	59.7±7.9
BMI (kg/m^2)	32.0±6.5	29.7±6.2	29.0±4.2	29.9±4.3	29.6±3.9	29.8±4.7
K-L Grade II	37 (44.6)	32 (39.5)	56 (53.8)	58 (64.4)	53 (53.0)	103 (56.9)
K-L Grade III	46 (55.4)	49 (60.5)	48 (46.2)	32 (35.6)	47 (47.0)	78 (43.1)
*WOMAC Pain Score - index knee (mm)**	274.1±64.9	268.2±69.3	288.2±59.8	289.7±49.5	293.4±58.7	294.0±60.0
WOMAC Pain Score - contralateral knee (mm)	83.1±57.0	87.0±54.2	68.7±47.1	69.7±47.0	67.8±48.3	59.5±48.0
Pain on Standing Score (mm)	51.2±24.7	46.9±23.2	64.8±18.4	65.4±16.9	65.9±15.8	59.4±17.6
Investigator Global Score (mm)	53.3±19.0	50.6±19.4	58.8±14.3	58.2±14.3	57.8±14.7	59.1±15.5
Patient Global Score (mm)	55.7±20.4	53.4±21.6	67.3±14.9	62.4±16.5	64.3±14.9	62.9±17.5

* MONOVISC™ 0702 scores were the average of the 5 questions, i.e. on a 100mm scale, so values were multiplied by 5 to put on a 500mm scale

Non-Inferiority Analysis Methodology

The objective of the analysis was to demonstrate the non-inferiority of MONOVISC™ (M1) to three injections of ORTHOVISC®. To accomplish this, M1 was compared to the combined O3A1/O3 subgroup. The analysis for the non-inferiority of MONOVISC™ to the ORTHOVISC® 3-injection regimen was accomplished by testing the following hypotheses:

H_0: $\mu_M - \mu_O \leq -\Delta$ versus H_A: $-\Delta < \mu_M - \mu_O$

where μ_M is the mean response for MONOVISC™ and μ_O is the mean response for ORTHOVISC®. This is tested by constructing a lower one-sided 97.5% confidence interval and if the lower limit of the confidence interval is greater than $-\Delta$, then non-inferiority is said to be obtained. "Non-inferiority and superiority" is obtained when the lower level of the confidence interval is greater than 0.

Since the secondary endpoints involve mean change from baseline, and the variables are negative, the above hypotheses are reversed (since the Δ is negative) and the criterion is then that the upper confidence limit is less than Δ. That is,

H_0: $\Delta \leq \mu_M - \mu_O$ versus H_A: $\mu_M - \mu_O < \Delta$

where μ_M is the mean response for MONOVISC™ and μ_O is the mean response for ORTHOVISC®. This is tested by constructing an upper one-sided 97.5% confidence interval and if the upper limit of the confidence interval is less than Δ, then non-inferiority is said to be obtained.

These hypotheses were tested for the primary and secondary endpoints.

Analyses were conducted using a GEE repeated measures model. The GEE model contained terms for Treatment Group, Week, and the Treatment Group by Week Interaction. When the Treatment Group by Week Interaction was not significant, it was dropped from the model.

Non-inferiority Margins

The non-inferiority margins were set conservatively at Δ5.0mm (on a 100mm WOMAC VAS Scale), or 5% for endpoints expressed as percentages.

Results of Non-Inferiority Analysis

The primary endpoints for the non-inferiority analysis were the comparison of the Proportion of Responders at the 20%, 40%, and 50% threshold levels for MONOVISC™ (ITT and PP) vs. the three-injection ORTHOVISC® combined O3A1/O3 treatment group. Secondary endpoints included change from baseline in the following measures (all 100mm VAS Pain scales): WOMAC Pain Score, Pain on Standing, Investigator Global Assessment, and Patient Global Assessment.

Analyses were done utilizing the GEE repeated measures model for weeks 7-22. The mean Proportion of Responders for each threshold level by treatment group from the GEE analysis are summarized in Table 9, below.
For all the threshold levels, the MONOVISC™ ITT or PP populations have a higher Proportion of Responders as compared to the three-injection ORTHOVISC® groups (O3A1, O3, or the combined group O3A1/O3). The four-injection ORTHOVISC® Group, O4, had the highest Proportion of Responders and the two control groups (A4 and Saline) had the lowest Proportion of Responders. The four-injection series of ORTHOVISC® represents a 33% increase in HA dose compared to a single injection of MONOVISC™.

Table 9. Mean Proportion of Responders from GEE Model (Weeks 7-22)

Variable	M1 PP N=164 %, CI	M1 ITT N=181 %, CI	O3A1 N= 90 %, CI	O3 N= 83 %, CI	O3A1/O3 N=173 %, CI	O4 N= 104 %, CI	A4 N=100 %, CI	Saline N= 81 %, CI
20% Improvement in WOMAC	**74.2** (67.7, 80.7)	**72.4** (65.8,79.1)	**63.0** (52.8, 73.2)	**70.8** (60.8, 80.8)	**67.0** (52.8, 81.3)	**73.1** (64.4, 81.8)	**62.9** (53.7, 72.2)	**60.2** (49.3, 71.1)
40% Improvement in WOMAC	**61.8** (54.5, 69.0)	**58.9** (51.6, 66.2)	**50.2** (39.6, 60.7)	**54.5** (43.5, 65.4)	**52.5** (37.3, 67.7)	**63.4** (54.0, 72.9)	**48.0** (38.4, 57.6)	**41.0** (30.1, 52.0)
50% Improvement in WOMAC	**53.6** (46.2, 61.0)	**51.2** (43.8, 58.6)	**43.3** (32.9, 53.8)	**46.3** (35.4, 57.3)	**45.0** (29.9, 60.1)	**55.6** (45.9, 65.4)	**42.6** (33.2, 52.1)	**34.4** (23.8, 44.9)

Non-inferiority analyses for all endpoints were conducted using the GEE repeated measures model for weeks 7-22. The MONOVISC™ ITT and PP study populations were each compared to the ORTHOVISC® three-injection groups (O3A1, O3, and the combined effectiveness subgroup O3A1/O3) for purposes of establishing non-inferiority. Additional comparisons to the other treatment arms (O4, A4, and Saline) that were used to support the ORTHOVISC® PMA approval were also made. The results of the analyses are summarized in Tables 10a and 10b below, for comparisons against the MONOVISC™ PP and the MONOVISC™ ITT study populations.

The results of the primary endpoint analysis show that MONOVISC™ (ITT or PP) is non-inferior to three injections of ORTHOVISC® for the O3A1 group, and also for the combined O3A1/O3 group, for all threshold levels. Non-inferiority was not demonstrated against the O3 group with the chosen margin.

The results from the secondary endpoints show that MONOVISC™ (ITT or PP) was non-inferior to the three-injection ORTHOVISC® groups O3 and combined O3A1/O3 for Change in WOMAC Pain Score, Pain on Standing Score, Investigator Global Score, and Patient Global Score. MONOVISC™ was non-inferior to the O3A1 group for Change in WOMAC Pain Score, Investigator Global Score, and Patient Global Score (PP only).

MONOVISC™ was not shown to be non-inferior to four injections of ORTHOVISC® (O4). The four-injection series of ORTHOVISC® represents a 33% increase in HA dose compared to a single injection of MONOVISC™.

MONOVISC™ (ITT or PP) was non-inferior or 'non-inferior and superior' against the control groups A4 and Saline.

Table 10a. Non-Inferiority Results from GEE Analysis (MONOVISC™ PP)

Endpoint	M1 PP vs. O3A1	M1 PP vs. O3	M1 PP vs. O3A1/O3	M1 PP vs. O4	M1 PP vs. A4	M1 PP vs. Saline
20% Improvement in WOMAC	**Non-inferior**	*Not Non-Inferior*	**Non-inferior**	*Not Non-Inferior*	**Non-inferior and superior**	**Non-inferior and superior**
40% Improvement in WOMAC	**Non-inferior**	*Not Non-Inferior*	**Non-inferior**	*Not Non-Inferior*	**Non-inferior and superior**	**Non-inferior and superior**
50% Improvement in WOMAC	**Non-inferior**	*Not Non-Inferior*	**Non-inferior**	*Not Non-Inferior*	**Non-inferior**	**Non-inferior and superior**
Change in WOMAC Pain Score	**Non-inferior**	**Non-inferior**	**Non-inferior**	*Not Non-Inferior*	**Non-inferior**	**Non-inferior and superior**
Change in Pain on Standing Score	*Not Non-Inferior*	**Non-inferior**	**Non-inferior**	*Not Non-Inferior*	**Non-inferior**	**Non-inferior and superior**
Change in Investigator Global Score	**Non-inferior and superior**	**Non-inferior and superior**	**Non-inferior and superior**	**Non-inferior**	**Non-inferior and superior**	**Non-inferior and superior**
Change in Patient Global Score	**Non-inferior**	**Non-inferior and superior**	**Non-inferior and superior**	*Not Non-Inferior*	**Non-inferior**	**Non-inferior and superior**

Table 10b. Non-Inferiority Results from GEE Analysis (MONOVISC™ ITT)

Endpoint	M1 ITT vs. O3A1	M1 ITT vs. O3	M1 ITT vs. O3A1/O3	M1 ITT vs. O4	M1 ITT vs. A4	M1 ITT vs. Saline
20% Improvement in WOMAC	**Non-inferior**	*Not Non-Inferior*	**Non-inferior**	*Not Non-Inferior*	**Non-inferior**	**Non-inferior**
40% Improvement in WOMAC	**Non-inferior**	*Not Non-Inferior*	**Non-inferior**	*Not Non-Inferior*	**Non-inferior**	**Non-inferior and superior**
50% Improvement in WOMAC	**Non-inferior**	*Not Non-Inferior*	**Non-inferior**	*Not Non-Inferior*	**Non-inferior**	**Non-inferior and superior**
Change in WOMAC Pain Score	**Non-inferior**	**Non-inferior**	**Non-inferior**	*Not Non-Inferior*	**Non-inferior**	**Non-inferior and superior**
Change in Pain on Standing Score	*Not Non-Inferior*	**Non-inferior**	**Non-inferior**	*Not Non-Inferior*	*Not Non-Inferior*	**Non-inferior and superior**
Change in Investigator Global Score	**Non-inferior and superior**	**Non-inferior and superior**	**Non-inferior and superior**	**Non-inferior**	**Non-inferior and superior**	**Non-inferior and superior**
Change in Patient Global Score	*Not Non-Inferior*	**Non-inferior and superior**	**Non-inferior and superior**	*Not Non-Inferior*	**Non-inferior**	**Non-inferior and superior**

Clinical Significance of Secondary Endpoints

The agency requested a distribution-based method for determining clinical significance of the change from baseline for each of the endpoints: Womac Pain Score, Pain on Standing Score, Investigator Global Score and Patient Global Score. Cumulative Distribution Function (CDF) plots comparing the MONOVISC™ 0702 Per-Protocol population to the ORTHOVISC® three-injection combined effectiveness subgroup (O3A1/O3) were provided for each secondary endpoint at each timepoint. Each plot includes a vertical dashed black line at -6.0 mm, which represents a "minimum clinically important difference" (MCID). The agency considers a mean difference of 6.0mm on a 100mm WOMAC VAS scale to be the MCID and an acceptable difference for HA injectable products based on a meta-analysis of literature.

Change in WOMAC Pain Score from Baseline

Figures 2-4 below show the Cumulative Distribution Plots for Change in WOMAC Pain Score from Baseline at each timepoint. MONOVISC™ 0702 PP shows a higher percentage of patients with clinical improvement compared to the ORTHOVISC® three-injection combined effectiveness subgroup (O3A1/O3) at every timepoint.

Figure 2. Cumulative Distribution Function for Change in WOMAC Pain Score from Baseline for M1 PP vs. O3A1/O3 Treatment Groups (Weeks 7/8)

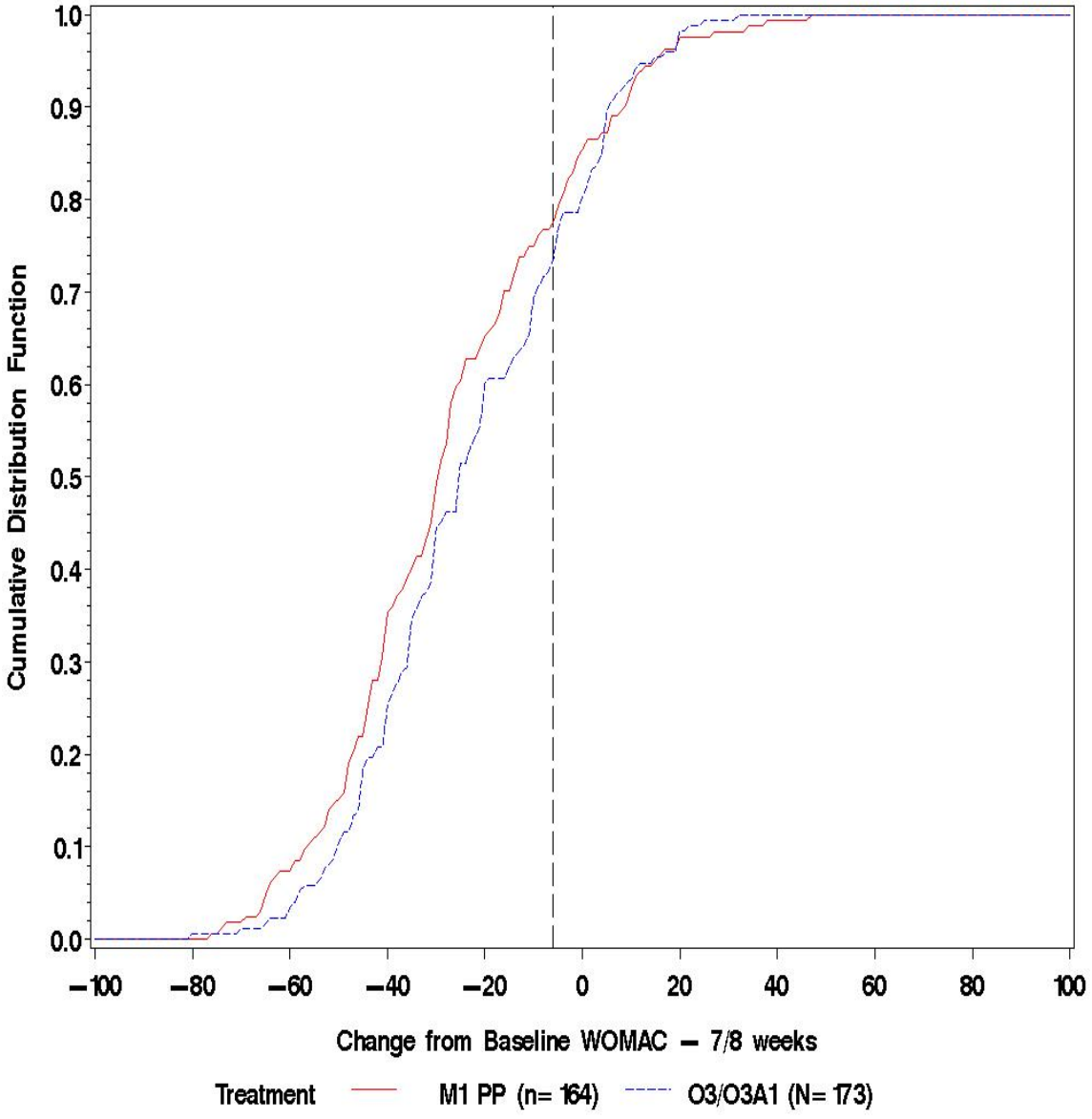

Figure 3. Cumulative Distribution Function for Change in WOMAC Pain Score from Baseline for M1 PP vs. O3A1/O3 Treatment Groups (Weeks 11/12)

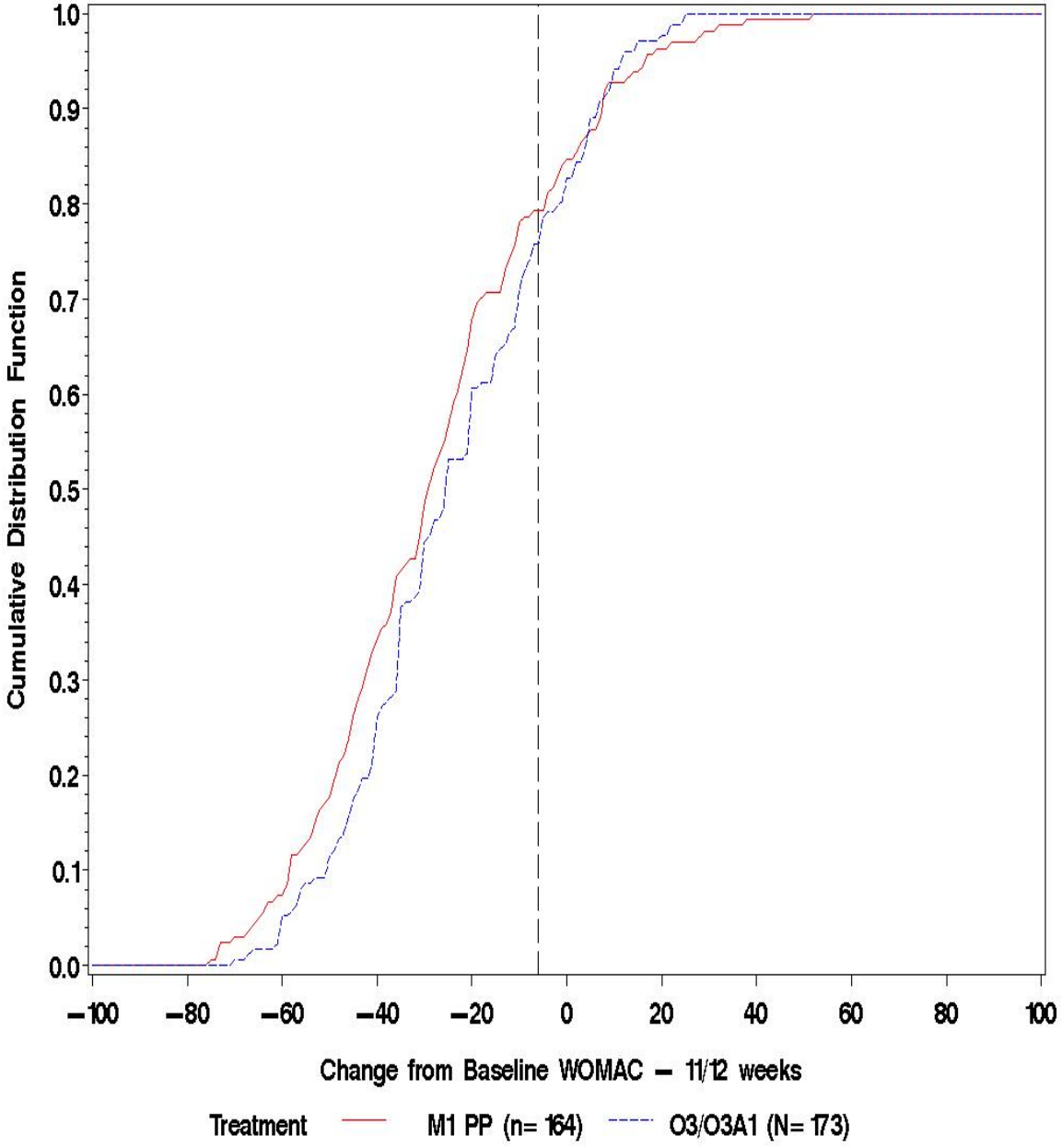

Figure 4. Cumulative Distribution Function for Change in WOMAC Pain Score from Baseline for M1 PP vs. O3A1/O3 Treatment Groups (Weeks 20-22)

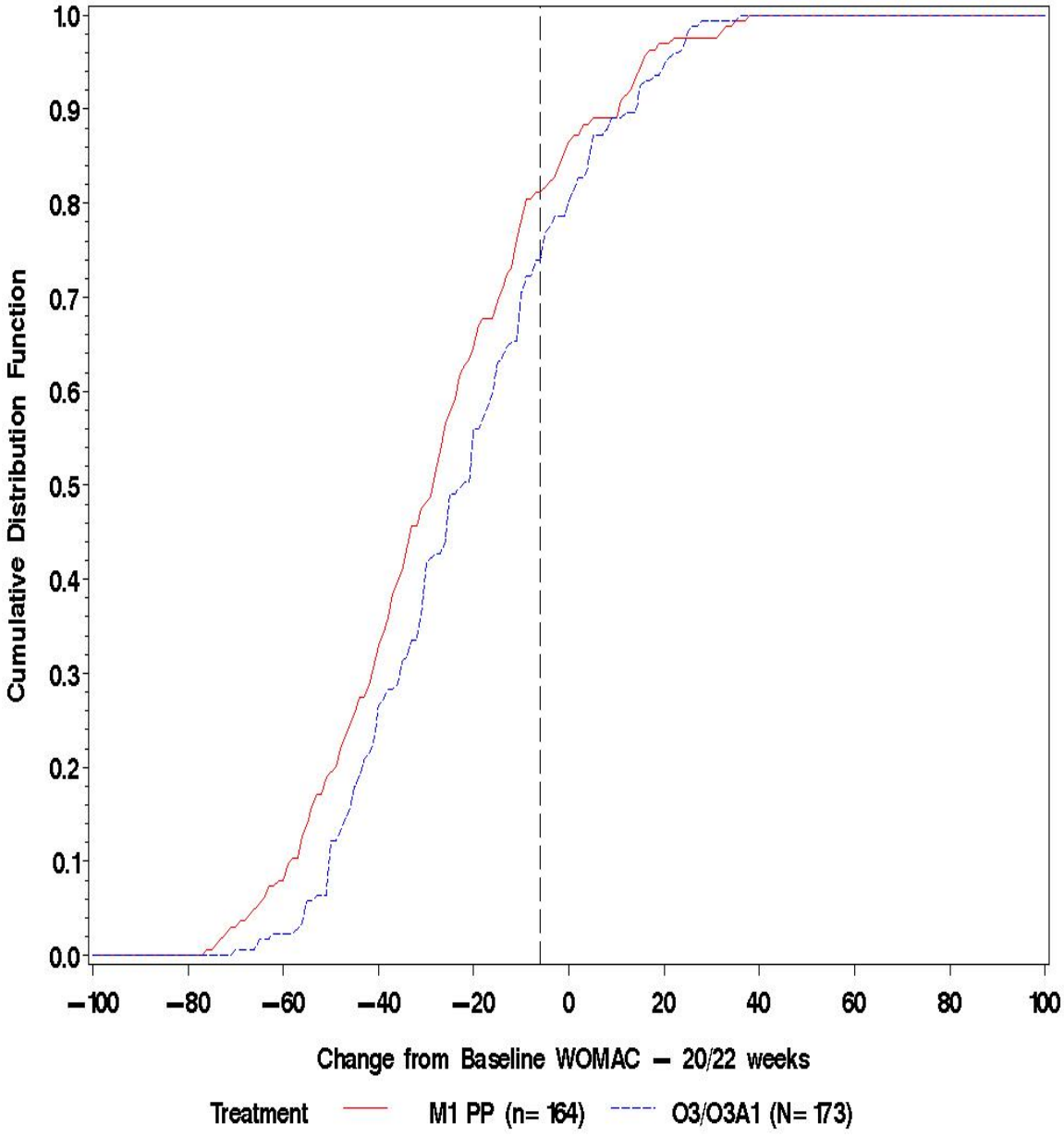

Table 11, below, summarizes the data from the CDF curves for the Change in WOMAC Pain Score from Baseline for each timepoint. The percent of patients in each group who improved from baseline, stayed the same, or deteriorated from baseline is reported. Degree of improvement is stratified by 1x, 3x, and 5x the MCID.

Table 11. CDF Data for Change in WOMAC Pain Score from Baseline

WOMAC Pain Score			Subjects who had improvement of:				
Timepoint	**Subgroup**	**% Subjects improved from BL**	**≥1x MDIC (6mm)**	**≥ 3x MDIC (18mm)**	**≥5x MDIC (30mm)**	**% Subjects stayed same from BL**	**% Subjects deteriorated from BL**
7/8 Weeks	M1 PP (n=164)	84.76	77.44	66.46	49.39	0.61	14.63
	O3A1/O3 (n=173)	78.61	73.41	60.69	44.51	1.73	19.65
11/12 Wks	M1 PP (n=164)	84.15	79.27	70.12	48.78	0.61	15.24
	O3A1/O3 (n=173)	80.35	75.72	61.27	44.51	2.31	17.34
20-22 Wks	M1 PP (n=164)	85.37	81.10	67.68	48.17	1.22	13.41
	O3A1/O3 (n=173)	78.61	73.99	57.23	41.62	1.73	19.65

The data from the CDF curves demonstrate that the MONOVISC™ PP population has a higher degree of clinical improvement at every time-point relative to the ORTHOVISC® 3-injection combined effectiveness group (O3A1/O3) for the for the change in WOMAC Pain Score from Baseline.

Change in Pain on Standing Score from Baseline

Table 12, below, summarizes the data from the CDF curves for the Change in Pain on Standing Score from Baseline for each timepoint.

Table 12. CDF Data for Change in Pain on Standing Score from Baseline

Pain on Standing Score			Subjects who had improvement of:				
Timepoint	**Subgroup**	**% Subjects improved from BL**	**≥1x MDIC (6mm)**	**≥ 3x MDIC (18mm)**	**≥5x MDIC (30mm)**	**% Subjects stayed same from BL**	**% Subjects deteriorated from BL**
7/8 Weeks	M1 PP (n=164)	85.37	80.49	67.07	50.00	0.00	14.63
	O3A1/O3 (n=173)	71.10	67.63	59.54	39.88	16.18	12.72
11/12 Wks	M1 PP (n=164)	84.76	81.71	67.07	52.44	1.22	14.02
	O3A1/O3 (n=173)	69.36	67.05	63.58	39.88	13.29	17.34
20-22 Wks	M1 PP (n=164)	87.80	81.10	67.07	50.61	0.61	11.59
	O3A1/O3 (n=173)	71.10	68.21	61.27	39.88	14.45	14.45

The data from the CDF curves demonstrate that the MONOVISC™ PP population has a higher degree of clinical improvement at every timepoint relative to the ORTHOVISC® 3-injection combined effectiveness group (O3A1/O3) for the change in Pain on Standing Score from Baseline.

Change in Investigator Global Score from Baseline

Table 13, below, summarizes the data from the CDF curves for the Change in Investigator Global Score from Baseline for each timepoint.

Table 13. CDF Data for Change in Investigator Global Score from Baseline

Investigator Global Score			Subjects who had improvement of:				
Timepoint	**Subgroup**	**% Subjects improved from BL**	**≥1x MDIC (6mm)**	**≥ 3x MDIC (18mm)**	**≥5x MDIC (30mm)**	**% Subjects stayed same from BL**	**% Subjects deteriorated from BL**
7/8 Weeks	M1 PP (n=164)	85.37	81.71	66.46	51.22	2.44	12.20
	O3A1/O3 (n=173)	71.10	69.36	58.96	27.75	17.92	10.98
11/12 Wks	M1 PP (n=164)	82.93	79.88	66.46	49.39	1.22	15.85
	O3A1/O3 (n=173)	72.25	68.21	61.85	34.10	14.45	13.29
20-22 Wks	M1 PP (n=164)	85.37	82.32	68.90	54.27	0.61	14.02
	O3A1/O3 (n=173)	68.79	64.74	55.49	30.06	14.45	16.76

The data from the CDF curves demonstrate that the MONOVISC™ PP population has a higher degree of clinical improvement at every timepoint relative to the ORTHOVISC® 3-injection combined effectiveness group (O3A1/O3) for the change in Investigator Global Score from Baseline.

Change in Patient Global Score from Baseline

Table 14, below, summarizes the data from the CDF curves for the Change in Patient Global Score from Baseline for each timepoint.

Table 14. CDF Data for Change in Patient Global Score from Baseline

Patient Global Score			Subjects who had improvement of:				
Timepoint	**Subgroup**	**% Subjects improved from BL**	**≥1x MDIC (6mm)**	**≥ 3x MDIC (18mm)**	**≥5x MDIC (30mm)**	**% Subjects stayed same from BL**	**% Subjects deteriorated from BL**
7/8 Weeks	M1 PP (n=164)	84.15	79.88	67.07	54.88	1.22	14.63
	O3A1/O3 (n=173)	70.52	67.63	62.43	36.99	15.61	13.87
11/12 Wks	M1 PP (n=164)	81.10	79.88	65.85	53.05	1.22	17.68
	O3A1/O3 (n=173)	70.52	68.79	62.43	38.73	13.29	16.18
20-22 Wks	M1 PP (n=164)	85.37	79.88	67.68	55.49	1.22	13.41
	O3A1/O3 (n=173)	67.63	65.32	60.12	37.57	13.29	19.08

The data from the CDF curves demonstrate that the MONOVISC™ patient population has a higher degree of clinical improvement at every timepoint relative to the ORTHOVISC® 3-injection combined effectiveness group (O3A1/O3) for the change in Patient Global Score from Baseline.

The CDF curves and associated data for the secondary endpoints show similar results. In all cases the MONOVISC™ patient population demonstrates a higher degree of clinical improvement at every timepoint relative to the ORTHOVISC® 3-injection combined effectiveness group (O3A1/O3).

C. MONOVISC™ 0802 EXTENSION CLINICAL STUDY

Study Design

An extension study to MONOVISC™ 0702, protocol MONOVISC™ 0802, was conducted to evaluate the safety of a second single injection of 4 mL of MONOVISC™. The design of this phase of the study was open-label, where all patients received a MONOVISC™ injection. To avoid bias, the investigators remained blinded to the initial injection (MONOVISC™ or Saline) received by the patient.

Study Results

Two hundred and forty (240) patients were treated during this phase of the study, of which 119 (49.8%) patients received a second injection of MONOVISC™ and 121

(51.2%) patients received an injection of MONOVISC™ after receiving a Saline injection during the initial treatment.

During the 0802 study, 186 distinct AEs, device related or not, were reported in 114 (47.5%) patients. The percentage of patients experiencing AEs was similar for those who were previously injected with MONOVISC™ (49.6%) and those previously injected with Saline (45.5%). There were no deaths or UADEs reported in the study. There were no Serious Adverse Events related to the study device and/or treatment. The overall rate of AEs in the MONOVISC™ 0802 study, device related or not, was lower than the rate in the MONOVISC™ 0702 study (47.5% vs. 66.1%).

Table 15 summarizes the AEs that were assessed as related to the study device or treatment in the MONOVISC™ 0802 study.

Table 15. 0802 Patients with Device or Procedure-Related Adverse Events

AE Type	MONOVISC™/MONOVISC™ n=119	Saline/MONOVISC™ n=121
Arthralgia	6 (5.0%)	7 (5.8%)
Joint swelling	1 (0.8%)	2 (1.7%)
Joint stiffness	1 (0.8%)	1 (0.8%)
Injection site pain	6 (5.0%)	4 (3.3%)
Joint effusion	1 (0.8%)	1 (0.8%)
Pain in extremity	1 (0.8%)	1 (0.8%)
Injection site bruising	1 (0.8%)	0 (0.0%)
Injection site erythema	0 (0.0%)	1 (0.8%)
Injection site reaction	1 (0.8%)	1 (0.8%)
Injection site swelling	2 (1.7%)	2 (1.7%)
Peripheral edema	0 (0.0%)	1 (0.8%)

The AE profile after the second injection of MONOVISC™ was similar to the AE profile after the first treatment; with arthralgia, injection site pain, and injection site or joint swelling as the most common events. The majority of AEs experienced by patients in either group was rated as mild or moderate and resolved without sequelae.

Financial Disclosure for MONOVISC™ 0802

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 110 investigators, of which none were full-time or part-time employees of the sponsor and none of whom had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f). The information provided does not raise any questions about the reliability of the data.

D. SAFETY COMPARISONS

Safety Comparison of MONOVISC™ and ORTHOVISC® Clinical Data

A safety analysis was completed comparing the MONOVISC™ 0702 study to the combined ORTHOVISC® studies (OAK9501, OAK9801, and OAK2001) safety data used to support the ORTHOVISC® PMA approval. The OAK9501 and OAK2001 studies were described in Table 6. The OAK9801 study was a multicenter, randomized, double-blind, saline-controlled, 27-week study conducted at 22 sites in the United States. The study assessed the safety and effectiveness of three injections of ORTHOVISC® to treat knee pain in patients with bilateral knee osteoarthritis. A total of 385 patients (201 ORTHOVISC®; 184 Saline) were enrolled from April 1999 to February 2000. Because bilateral treatment confounded the effectiveness results, the OAK9801 study results were utilized in the safety analysis, but not the effectiveness analysis, for the PMA approval of ORTHOVISC®.

The populations compared consisted of the combined ORTHOVISC® ITT population (n=562 ORTHOVISC® patients; 434 receiving 3 injections and 128 receiving 4 injections), the OAK9501 Saline control (n=296 patients), the OAK2001 A4 control (n=123), the MONOVISC™ ITT population (n=184 patients receiving one injection), and the MONOVISC™ Saline control (n=185 patients).

All medical events that occurred during the entire study period of each trial, regardless of relationship to study procedures, were considered adverse events. Adverse events, device related or not, occurred in 62% of ORTHOVISC® patients, 69% of OAK9501 saline control patients, 53% of OAK2001 Arthrocentesis control patients, 66% of MONOVISC™ 0702 patients, and 66% of the 0702 Saline control patients.

Table 16 lists the individual adverse events, device related or not, by patient for these study populations. There are no statistically significant differences in the incidence of adverse events among the ORTHOVISC® patients, the MONOVISC™ patients, or any of the control groups.

Table 16. Adverse Event Comparisons (Regardless of relationship to device)

Adverse Event	ORTHOVISC® Combined (OAK9501, 9801, 2001) N=562	Saline (OAK9501+ OAK9801 controls) N=296	A4 (OAK2001 control) N=123	MONOVISC™ 0702 N=184	Saline (0702 control) N=185
Any Adverse Event	349 (62.1%)	204 (68.9%)	65 (52.8%)	121 (65.8%)	123 (66.5%)
Injection site erythema	2 (0.4%)	0 (0.0%)	0 (0.0%)	2 (1.1%)	1 (0.5%)
Injection site edema	5 (0.9%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Injection site pain	14 (2.5%)	6 (2.0%)	1 (0.8%)	3 (1.6%)	1 (0.5%)
Injection site reaction	1 (0.2%)	2 (0.7%)	1 (0.8%)	0 (0.0%)	1 (0.5%)
Pain NOS[1]	14 (2.5%)	11 (3.7%)	1 (0.8%)	3 (1.6%)	2 (1.1%)
Arthralgia	71 (12.6%)	51 (17.2%)	1 (0.8%)	32 (17.4%)	27 (14.6%)
Arthritis NOS[1]	4 (0.7%)	5 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Arthropathy NOS[1]	5 (0.9%)	3 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Baker's cyst	2 (0.4%)	2 (0.7%)	0 (0.0%)	2 (1.1%)	0 (0.0%)
Bursitis	6 (1.1%)	6 (2.0%)	2 (1.6%)	1 (0.5%)	1 (0.5%)
Joint disorder NOS[1]	2 (0.4%)	0 (0.0%)	0 (0.0%)	2 (1.1%)	1 (0.5%)
Joint effusion	2 (0.4%)	1 (0.3%)	1 (0.8%)	5 (2.7%)	0 (0.0%)
Joint stiffness	3 (0.5%)	2 (0.7%)	0 (0.0%)	2 (1.1%)	1 (0.5%)
Joint swelling	4 (0.7%)	2 (0.7%)	1 (0.8%)	2 (1.1%)	4 (2.2%)
Localized osteoarthritis	5 (0.9%)	1 (0.3%)	1 (0.8%)	2 (1.1%)	3 (1.6%)
Aggravated osteoarthritis	2 (0.4%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)
Knee arthroplasty	3 (0.5%)	2 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Headache NOS[1]	68 (12.1%)	49 (16.6%)	22 (17.9%)	24 (13.0%)	28 (15.1%)

[1]NOS=Not Otherwise Specified

The incidence of Adverse Events which were assessed by the investigator as possibly, probably, or definitely related to the study device or procedure were much lower. A comparison of device or procedure-related adverse events across the studies is summarized in Table 17, below.

The combined ORTHOVISC® group had a 7.5% rate of adverse events that were considered study-related, while the MONOVISC™ arm of the 0702 study had a 7.1% rate. The control groups ranged from 3.3% to 7.7%.

Overall, the safety data across both ORTHOVISC® and MONOVISC™ studies were comparable. Both products demonstrate an excellent safety profile.

Table 17. Adverse Event Comparisons for Device or Procedure Related AEs

Adverse Event	ORTHOVISC® Combined (OAK9501, 9801, 2001) N=562	Saline (OAK9501+OAK9801 controls) N=296	A4 (OAK2001 control) N=123	MONOVISC™ 0702 N=184	Saline (0702 control) N=185
Device or Procedure-related Adverse Events	42 (7.5%)	23 (7.7%)	4 (3.3%)	13 (7.1%)	10 (5.4%)

Comparison of MONOVISC™ and ORTHOVISC® Global Complaint Data

The FDA requested global real-world complaint data for MONOVISC™ compared to ORTHOVISC®.

MONOVISC™ has been marketed globally since 2008, and has demonstrated extremely low complaint rates (<0.008% for patient adverse events and <0.004% for product quality complaints). MONOVISC™ has never been withdrawn from marketing for any reason related to the safety or effectiveness of the device.

Since MONOVISC™ is a single-injection equivalent of three injections of ORTHOVISC®, it is also reasonable to review the real-world safety data for ORTHOVISC®. ORTHOVISC® has been used worldwide since 1996, and also has a low complaint rate (<0.007% for patient adverse events and <0.004% for product quality complaints). ORTHOVISC® has never been withdrawn from marketing for any reason related to safety or effectiveness of the device.

The most common side effects for either ORTHOVISC® or MONOVISC™ injections are transitory pain (including burning, tenderness, and tingling) and swelling. There have been no reports of deaths for either product.

The complaint data shows that both MONOVISC™ and ORTHOVISC® products have equivalent and excellent safety profiles on a per-injection basis. Although the dose of MONOVISC™ is higher (3x) than that of a single injection of

ORTHOVISC®, there is no increase in the rate of adverse events or change in the adverse events profile in the complaint data comparison.

XI. PANEL RECOMMENDATION

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 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 STUDIES, CLINICAL STUDIES AND SUPPLEMENTAL DATA

A. EFFECTIVENESS CONCLUSIONS

The effectiveness data obtained from the post-hoc non-inferiority analysis comparing MONOVISC™ 0702 to the combined effectiveness subgroup population from two ORTHOVISC® randomized studies (OAK9501 and OAK2001) provides evidence of the effectiveness of MONOVISC™ for the treatment of pain of osteoarthritis of the knee in patients who have failed to adequately respond to conservative non-pharmacological therapy and simple analgesics (e.g., acetaminophen).

B. SAFETY CONCLUSIONS

The safety of MONOVISC™ was confirmed in the MONOVISC™ 0702 study, which showed comparable adverse event rates between MONOVISC™ and saline control. The retreatment study, MONOVISC™ 0802, confirmed there were no differences in adverse event rates between patients receiving a second injection of MONOVISC™ compared with patients receiving their first injection. A comparison of MONOVISC™ and ORTHOVISC® clinical study data and global complaint data showed comparable adverse event rates. The most common side effects for either MONOVISC™ or ORTHOVISC® injections are transitory pain (including burning, tenderness, and tingling) and swelling.

C. BENEFIT-RISK CONCLUSIONS

A single injection of MONOVISC™ provides the potential benefit for pain reduction in a proportion of patients with osteoarthritis in the knee. MONOVISC™ provides an additional benefit for patients in that they can have their knee pain treated with a single injection, as compared to having to return to the doctor several times for a series of injections. The data supports that the probable benefits outweigh the probable risks of transitory adverse events such as pain and swelling in the treatment of pain of osteoarthritis of the knee in patients who have failed to adequately respond to conservative non-pharmacological therapy and simple analgesics (e.g., acetaminophen).

D. OVERALL CONCLUSIONS

The non-inferiority analysis and safety analyses, in addition to the safety results submitted from MONOVISC™ studies 0702 and 0802, provide the necessary and sufficient valid scientific evidence of reasonable assurance of safety and effectiveness of MONOVISC™ for the treatment of pain of osteoarthritis of the knee in patients who have failed to adequately respond to conservative non-pharmacological therapy and simple analgesics (e.g., acetaminophen).

XIII. CDRH DECISION

CDRH issued an approval order on February 25, 2014. The applicant's manufacturing facility has 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.

XV. REFERENCES

1. Murphy L, Schwartz TA, Helmick CG, et al. Lifetime risk of symptomatic knee osteoarthritis. *Arthritis Rheum*. 2008 Sep 15; 59(9):1207-13.