TRIVISC® (SODIUM HYALURONATE)

For Treatment Of Osteoarthritis Knee Pain

Clinical Overview

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Supporting Clinical Evidence

TriVisc (sold outside the U.S. as Adant) has been on the market globally since 1995 and commercially available within the US since 2019. Over 35 million syringes have been distributed worldwide. TriVisc is a sterile, viscoelastic non-pyrogenic solution of purified, high molecular weight sodium hyaluronate. Each 2.5 mL of TriVisc contains 10mg/mL of sodium hyaluronate dissolved in aphysio-logical saline. The sodium hyaluronate is derived from bacterial fermentation. [1]

Placebo Controlled Safety And Efficacy Trials

Safety of TriVisc was established in two clinical studies, the AMELIA and Yong Ping studies. In a clinical trial of an identical chemical formulation of TriVisc of 306 patients, the frequency of adverse events was 2.9% which was identical to the frequency in the saline-control group.

In the first cycle of injections the most commonly reported adverse events in the TriVisc equivalent group included injection site pain (6), allergic reaction (3), arthralgia (2), and bleeding at the injection site (2).

In a clinical study involving 513 complete TriVisc equivalent treatment cycles and 487 complete PBS treatment cycles, the frequency of adverse events between the groups was the same and did not increase over the course of the three re-treatment cycles. TriVisc efficacy was established by equivalence to VISCO-3.[1]

Studies Utilized to Establish Reasonable Assurance of the Effectiveness of TriVisc[2]

Objectives:

Demonstrate non-inferiority of VISCO-3™ group to the active control group for the relief of knee joint pain in subjects with OA of the knee as measured by the Western Ontario and McMaster Universities Osteoarthritis Index Visual Analog Scale (WOMAC VAS) (0-100mm) pain subscale score change from baseline (CFB) over Week 3, Week 6, and Week 12.

Methods:

Comparative nonclinical test results were utilized to establish sufficient similarity of TriVisc and VISCO-3™. A pivotal, prospective, multi-center, randomized, double-blind, parallel arm, active controlled, and non-inferiority clinical study was utilized to provide reasonable assurance of the safety and effectiveness of VISCO-3™. The active comparator arm in this study was a commercially available hyaluronan, a legally marketed alternative with identical indications for use as TriVisc.

Primary Outcomes Measures:

The analysis of effectiveness was based on the 384 evaluable patients over the 12-week time point. Key effectiveness outcomes are presented in Table 6. No secondary endpoints for effectiveness were proposed. Mean baselines of WOMAC VAS pain subscale were 57.83 mm (standard deviation [SD]: 9.654) in the VISCO-3™ group and 58.40 mm (SD: 8.977) in the active control group. The least squares mean for CFB for VISCO-3™ minus that of the active control over Week 3, Week 6, and Week 12 for WOMAC VAS pain subscale score was −3.30 mm and the 95% CI lower bound of this difference was -6.77 mm. The lower bound −6.77 mm was greater than −8 mm, leading to the conclusion that VISCO-3™ is non-inferior to the active control, as shown in Table 6.

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

Average over Weeks 3, 6, 12	Active Control* (N=189)	VISCO-3™ (N=195)	VISCO-3™ (N=195)
Baseline WOMAC VAS Pain (mm) (Mean [SD])	58.40 (8.977)	57.83 (9.654)	
LS Mean (standard error [SE]) of Change from Baseline	30.15 (1.303)	26.85 (1.270)	-3.30 (1.762)
95% CI	27.59-32.71	24.35-29.35	-6.77-0.17

*FDA-approved three-injection HA product

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

Thus, this non-inferiority study served to demonstrate that the magnitude of the treatment effect for VISCO-3™ was statistically and clinically comparable to that of the commercially available hyaluronan approved for the same indication for use.

Non-Inferiority Study Comparing 3 Weekly Injections of SUPARTZ® vs 3 Weekly Injections of Euflexxa® for Knee OA[3]

Objective:

To demonstrate non-inferiority of a TriVisc equivalent to Euflexxa® for the relief of knee joint pain in subjects with osteoarthritis (OA) of the knee. (non-inferiority margin was 8% (-8mm).

Methods:

A double-blind, multi-center, randomized, controlled trial was conducted. The study enrolled a total of 421 subjects, ages 40-80.

Primary Outcome Measures:

Measured by the VAS (0-100 mm) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain subscale score Change from Baseline (CFB) over Weeks 3, 6, 12.

Criteria:

Inclusion Criteria:

- Clinical evidence of symptomatic osteoarthritis of the study knee as classified according to Altman criteria.
- Symptoms in study knee for at least one year prior to the screening visit.
- Verified OA of the study knee of Grade 2 or 3 according to a modification of the grading system of Kellgren-Lawrence (K-L) radiographic severity.
- Willingness to discontinue NSAIDs (systemic and topical) and non-acetaminophen analgesic use seven days or five half-lives prior to the first injection and throughout the study.

Exclusion Criteria:

- Inability to perform a 50 foot walk test.
- Subjects with rheumatoid arthritis, joint infection, other inflammatory and metabolic arthritis, Lupus or dermatologic disorder or skin conditions in close proximity to study knee that would preclude safe intra-articular injections.
- Prior hyaluronic acid injections into the study knee within six months of the screening visit.
- Intra-articular or intra-muscular steroid injections within three months of the screening visit or during study participation. Oral corticosteroids within four weeks of the screening visit or during study participation.
- History of surgical treatment to the study knee or arthroscopic intervention within three months prior to the screening visit.
- Clinically apparent tense effusion of the study knee on examination determined by either a positive bulge sign or positive ballottement of the patella (patellar tap).
- Subjects with clinically diagnosed symptomatic OA of the hip.

Average over Weeks 3, 6, and 12	Euflexxa (N = 189)	TriVisc Equivalent N = (195)	CFB Difference
Baseline WOMAC VAS Pain (mm) (Mean [SD])	58.40 (8.977)	57.83 (9.654)	
LS Mean (standard error [SE]) if change from Baseline (CFB)	30.15 (1.303)	26.85 (1.270)	- 3.30 (1.762)
95% CI	27.59-32.71	24.35-29.35	- 6.77 - 0.17

Results: TriVisc Equivalent demonstrated noninferior pain relief compared to patients treated with Euflexxa. This is concluded based upon the fact that the lower bound of the 95% CI (-6.77 mm) is greater than -8 mm.

On average, patients treated with the TriVisc Equivalent saw a 52% reduction in pain at week 12 compared to baseline. There was no significant difference in adverse events between the groups.

Supplemental Supportive Clinical Data

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

1. Ozgonenel Study[4]:

Comparison of Different Hyaluronates

Objective:

To investigate the clinical efficacy of two HA preparations with different molecular weights in the treatment of bilateral knee osteoarthritis.

Methods:

40 subjects received three weekly intra-articular injections of low molecular weight preparation of Hyalgan® to one knee and high molecular weight preparation of TriVisc to the other knee. All injections were given by a single physician (EA) with an anterolateral approach, keeping the knee in the 90° flexion position.

Clinical evaluations were conducted prior to treatment (baseline), immediately at the end of the therapy period, I month and 3 months after therapy. Outcome parameters included (i) measurement of range of motion (ROM) of the knee (ii) Visual Analog Scale (VAS) scored from I to 10 for pain at rest; and (iii) total scores of Western Ontario McMaster Universities Index (WOMAC) of global measurement of pain, stiffness, and disability.

Results: Mean WOMAC Scores $p < 0.001$

	Baseline	End of Therapy	1 Month Post	3 Month Post
TriVisc	47 ± 18	30 ± 19	29 ± 22	30 ± 21
Hyalgan	44 ± 20	27 ± 19	26 ± 20	29 ± 19

Results: Mean VAS Scores $p < 0.05$

	Baseline	End of Therapy	1 Month Post	3 Month Post
TriVisc	6 ± 2	5 ± 3	5 ± 3	5 ± 3
Hyalgan	6 ± 2	4 ± 3	4 ± 3	5 ± 3

Conclusions: Both TriVisc and Hyalgan groups showed sustained improvement in both WOMAC and VAS measurements. There was not a therapeutic difference in efficacy between the two groups.

Results: Mean ROM Scores $p < 0.001$

	Baseline	End of Therapy	1 Month Post	3 Month Post
TriVisc	108.6° ± 8.8°	113.8° ± 8.5°	115.5° ± 7.5°	114.0° ± 9.4°
Hyalgan	108.7° ± 11.6°	114.4° ± 10.7°	114.8° ± 9.8°	114.4° ± 10.3°

Conclusions: Knee ROM measurements increased in both TriVisc and Hyalgan groups. showed sustained improvement in both.
Post-therapy ROM measurements were not different among treatment groups.

No adverse events were reported in subjects receiving either TriVisc or Hyalgan.

[4] ÖzgÖnenel, L. et. al. Istanbul Tıp Dergisi 2008:1 ;53-57. Comparison of Different Hyaluronates.

2. Diracoglu Study[5]:

Single versus multiple dose hyaluronic acid: Comparison of the results

Objective:

To compare the effectiveness of three injections of TriVisc† versus single injection Monovisc® in patients with knee OA.

Methods:

Forty subjects were randomized into two groups. The first group received single dose intra-articular injection of 4 ml Monovisc and the second group received three consecutive intra-articular injections of 2.5 ml TriVisc† with one week intervals.

Evaluation:

A patient satisfaction questionnaire, Visual analog scale (VAS)-pain and Western Ontario and McMaster University Osteoarthritis Index (WOMAC) scores were measured before and three weeks after the last injection.

Inclusion criteria:

Knee OA patient of either sex, aged 45-70 years, classified with radiological stage II or III on the Kellgren-Lawrence classification system.

Exclusion criteria:

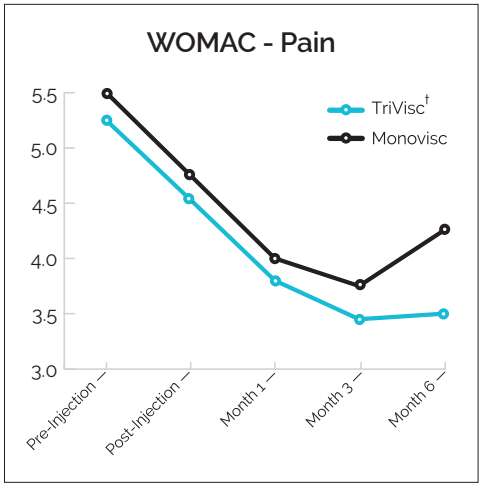
Exclusion criteria were Age > 70, < 45 years; 49 Kellgren-Lawrence score > 3; systemic disorders such 50 as hematological diseases (coagulopathy), severe cardiovascular diseases, infections, immunodepression, patients in therapy with anticoagulants or antiaggregants, patients with Hb values < 11 g/dl and platelet values < 150,000/mm, history of total knee replacement, any knee injection within 3 months, inflammatory or post-infectious knee arthritis, allergy or intolerance to study medication, body mass index (BMI) 58 greater than 40 kg/m2.

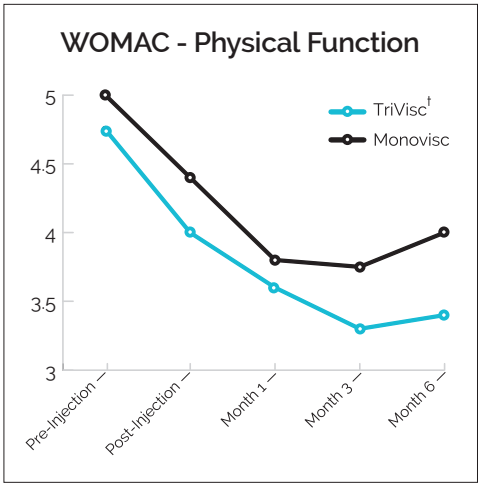
Demographics:

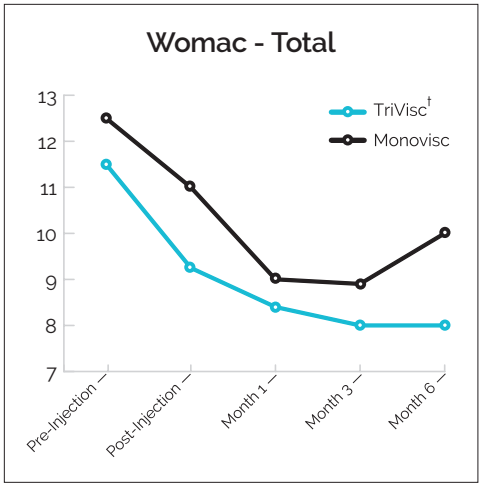
100% of participants completed the trial. The average age was 58 years in the Monovisc group and 67% of the subjects were female. The average age was 56 years in the TriVisc group and 71% of the subjects were female. The BMI was 30.5 and 30.8 for Monovisc and Trivisc groups, respectively.

Results: Analyses of both groups demonstrated statistically significant improvement in WOMAC-pain, WOMAC physical function and WOMAC-total value for the two products lasting up until the 6th month with respect to pre-injection values ($p < 0.001$).[†]

No subjects revealed any adverse events



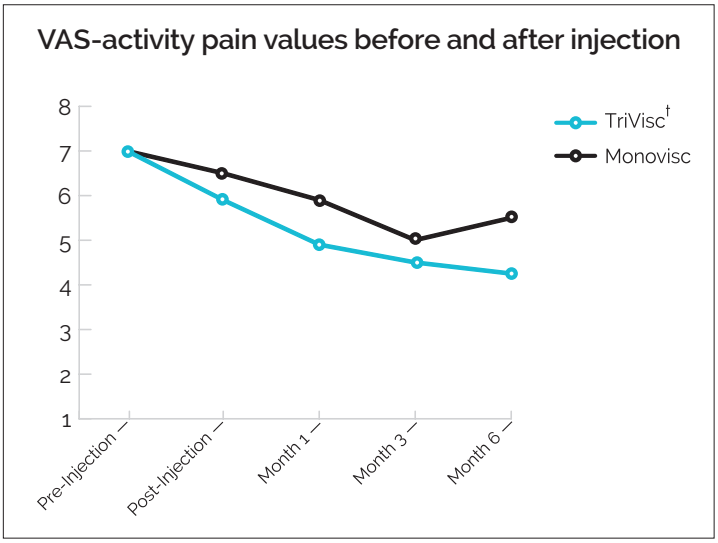


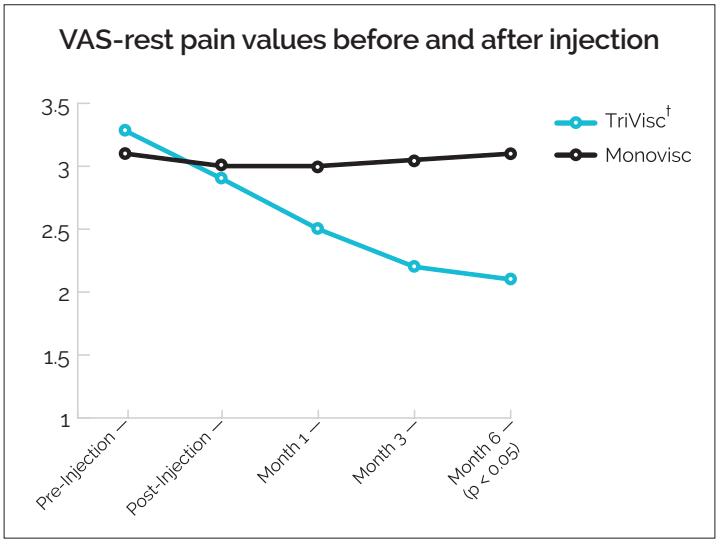


There were no statistical differences in WOMAC scores after injections ($p > 0.05$) in both groups.

Results: In both groups*, VAS-pain was improved statistically lasting up to the 6th month with respect to before injection values ($p < 0.001$).

No subjects revealed any adverse events





There were no statistical differences in WOMAC scores after injections ($p > 0.05$) in both groups.

† Adant is the TriVisc branded equivalent product outside the U.S. Market

5 Dıraçöglu, D. et al. J Back and Musculo ehab. 2016;16: 53. Single versus multiple dose hyaluronic acid: Comparison of the results

3. Ulucay Study[6]:

The use of arthroscopic debridement and viscosupplementation in knee osteoarthritis[†6]

Objective:

Investigate the effectiveness of different hyaluronic acid (HA) products in selected patients with knee osteoarthritis post arthroscopic debridement.

Methods:

77 women (mean age 50 ± 5 years) with mild knee osteoarthritis and degenerative meniscal tears.

Subjects were randomly assigned to HA injections 3 weeks post arthroscopic treatment: TriVisc[†] (n = 21) Orthovisc® (n = 38) Synvisc® (n = 18)

Evaluation:

A patient satisfaction questionnaire, Visual analog scale (VAS)-pain and Western Ontario and McMaster University Osteoarthritis Index (WOMAC) scores were measured.

All Subjects VAS scores, WOMAC and satisfaction status of subjects, pre-arthroscopy, post-arthroscopy and 3 weeks post last injection

	Satisfaction	WOMAC	VAS	P Value
Pre-Arthroscopy	3.4 ± 0.8	76.9 ± 17.0	8.3 ± 1.2	< 0.0001
Post-Arthroscopy	1.4 ± 0.7	39.2 ± 9.2	3.7 ± 1.0	< 0.0001
Post Injection	1.0 + 0.8	35.19 + 0.8	3.1 + 1.2	< 0.0001

Results: All subjects had significant improvement following both arthroscopic treatment and viscosupplementation ($p < 0.0001$).

Subgroup Comparison

	N	Satisfaction	WOMAC	VAS	P Value
TriVisc[†]	21	13.0 + 63.0	7.4 + 18.2	8.5 + 43.6	> 0.05
OrthoVisc	38	27.8 + 46.6	11.5 + 13.1	12.8 + 23.2	> 0.05
Synvisc	18	32.4 + 41.8	10.8 + 41.8	13.2 + 21.9	> 0.05

Results: There was no significant difference between hyaluronates for satisfaction status, WOMAC survey results and VAS scores with post injection evaluation. ($P < 0.05$)

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

† Adant is the TriVisc branded equivalent product outside the U.S. Market

Important Safety Information

TriVisc is contraindicated in patients with known hypersensitivity to hyaluronate preparations. Intra-articular injections are contraindicated in cases of present infections or skin diseases in the area of the injection site to reduce the potential for developing septic arthritis.

The effectiveness of a single treatment cycle of less than 3 injections has not been established.

TriVisc was established in two clinical studies of an identical chemical formulation of TriVisc. In a clinical trial of 306 patients, the frequency of adverse events was 2.9% which was identical to the frequency in the saline-control group. In the first cycle of injections the most commonly reported adverse events in the TriVisc equivalent group included injection site pain (6), allergic reaction (3), arthralgia (2), and bleeding at the injection site (2). In a clinical study involving 513 complete TriVisc equivalent treatment cycles and 487 complete PBS treatment cycles, the frequency of adverse events between the groups was the same and did not increase over the course of the three re-treatment cycles.

Indications and Usage

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

References

1. TriVisc Package Insert https://trivisc.com/patients/assets/info.pdf
2. FDA summary of safety and effectiveness data (SSED). TriVisc®
https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160057B.pdf
3. Non-Inferiority Study Comparing 3 Weekly Injections of SUPARTZ® vs 3 Weekly Injections of Euflexxa® for Knee OA.
https://clinicaltrials.gov/ct2/show/results/NCT02110238?term=Supartz&view=results
4. ÖzgÖnenel, L. et. al. Istanbul Tıp Dergisi 2008:1 ;53-57. Comparison of Different Hyaluronates
http://cms.galenos.com.tr/Uploads/Article_21339/IMJ-9-53-En.pdf
5. Dıraçöglu, D. et al. J Back and Musculo Rehab. 2016;16: 53. Single versus multiple dose hyaluronic acid: Comparison of the results.
https://bit.ly/34nM2iU
6. Ulucay, I. et al. Acta Orthop Traumatol Turc 2007;41: 337-342. The use of arthroscopic debridement and viscosupplementation in knee osteoarthritis. https://www.aott.org.tr/Content/files/sayilar/436/436-4657.pdf

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