A Pooled Analysis of Two Multicenter, Randomized Controlled Trials of a Single Intra-articular Injection of Gel-200 for Treatment of Osteoarthritis of the Knee

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Junko Takamura[1], Takayuki Seo[2] and Vibeke Strand[3]

[1]R&D Planning Department, Research & Development Division, Seikagaku Corporation, Tokyo, Japan. [2]Clinical Development Department, Research & Development Division, Seikagaku Corporation, Tokyo, Japan. [3]Division of Immunology and Rheumatology, Stanford University School of Medicine, Palo Alto, CA, USA.

ABSTRACT

BACKGROUND AND OBJECTIVE: To perform an integrated analysis of 2 randomized controlled trials (RCTs) to assess the efficacy and safety of a single intra-articular injection of Gel-200 compared with phosphate buffered saline (PBS) for treatment of osteoarthritis of the knee.

METHODS: Data from the intention-to-treat (ITT) populations of both RCTs were pooled for this integrated analysis. Mean changes from baseline in Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscores were assessed using a longitudinal model; treatment differences were compared between intra-articular Gel-200 and PBS injections. Analyses included secondary outcome measures repeated at individual time points. The safety populations of both RCTs were pooled for an integrated safety analysis to compare adverse events (AEs).

RESULTS: The pooled ITT population included 1184 subjects (649 Gel-200; 535 PBS); demographic characteristics were similar between treatment groups. Mean improvements in pain subscores from baseline to week 12 were −24.7 mm in Gel-200 and −21.8 mm in PBS groups, a statistically significant treatment group difference of −2.9 mm ($P = .047$). From weeks 3 to 26, mean improvements from baseline in pain subscores were −23.8 mm with Gel-200 and −20.8 mm with PBS; this treatment group difference of −3.0 mm was statistically significant ($P = .017$). The rate of AEs was similar between Gel-200 and PBS treatment groups.

CONCLUSION: This integrated analysis demonstrated the efficacy of a single intra-articular injection of Gel-200 compared with PBS for treatment of osteoarthritis of the knee over 26 weeks without major safety concerns.

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CORRESPONDING AUTHOR: Junko Takamura, R&D Planning Department, Research & Development Division, Seikagaku Corporation, Chiyoda-ku, Tokyo, 100-0005, Japan. Email: junko.takamura@seikagaku.co.jp

Introduction

Osteoarthritis (OA) is the most common arthritis worldwide causing pain and impairment in physical function.[1] Intra-articular hyaluronan (IA-HA) injections are believed to exert their therapeutic benefit by providing chondroprotection and anti-inflammatory effects, stimulating endogenous proteoglycan and HA synthesis, limiting subchondral bone changes, and reducing the activity of joint nociceptors, in addition to its mechanical benefit of lubricating the joint.[2,3] In the United States, IA-HA preparations approved for treatment of the pain of knee OA have been widely used for almost 20 years.[4,5] Despite the reported efficacy and safety of IA-HA injections and experience in clinical practice and the recommendation by American Medical Society for Sport Medicine (AMSSM),[6] recent OA treatment guidelines by the American Academy of Orthopedic Surgeons (AAOS) and the American College of Rheumatology (ACR) have queried their therapeutic utility.[7–9]

Gel-200 (Gel-One®; Seikagaku Corporation, Tokyo, Japan) is a sterile, transparent, and viscoelastic hydrogel composed of a cross-linked HA, a derivative of a highly purified HA product approved by the US Food and Drug Administration (FDA) in 2011 for treatment of pain of OA in the knee. There are 3 randomized controlled trials (RCTs) separately conducted in the United States. The safety and effectiveness of single and repeated injections of Gel-200 was demonstrated over 13 weeks (Study SI-6606/01 and Study Gel/1132).[10–12] In the 26-week RCT (Study Gel/1133), the efficacy over 26 weeks of a single injection of Gel-200 was demonstrated based on a noninferiority analysis compared with currently approved 3 weekly injections of IA-HA products that contributed to the FDA approval for efficacy over 26 weeks.[13] These RCTs have common efficacy measurements; however, there are difference in randomization allocations, statistical analyses approaches, and the primary endpoints in each RCT.

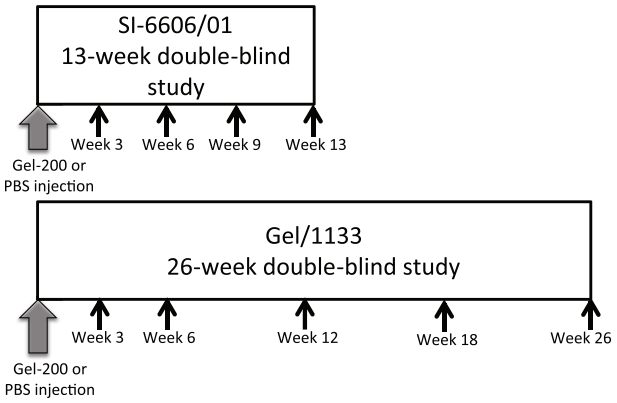

Figure 1. Overview of clinical studies.

Following a single injection, 3 IA-HA products marketed in the United States are indicated for 26-week efficacy; labeling for 2 products report only single clinical trial results in detail.[11,13–15]

To provide further clinical details of the 26-week efficacy and safety of a single injection of Gel-200 using common efficacy measurements and statistical analysis tests, we assessed the efficacy and safety of Gel-200 over 26 weeks following a single injection using established outcome measures by pooling data from 2 available RCTs with Gel-200 (SI-6606/01 and Gel/1133) with similar study designs and common efficacy measures.

Methods

Trial design

SI-6606/01 was a multi-center 13-week RCT. Patients were screened 1 to 2 weeks prior to randomization. Patients with pain >4 weeks, Kellgrean-Lawrence (K-L) grade 1 to 3 scores by X-ray, and Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscores ≥40 mm in the target knee were randomized to receive Gel-200 or phosphate buffered saline (PBS) in a 2:1 ratio at week 0. Patients returned for efficacy and safety evaluations at weeks 3, 6, 9, and 13 following a single injection of Gel-200 or PBS (Figure 1). Efficacy measurements included WOMAC total and subscores, physician and patient global assessments of disease activity, and Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International (OMERACT-OARSI) strict responders.[16–18]

Gel/1133 was a 26-week multi-center RCT. Patients were screened 1 to 2 weeks prior to randomization. Patients randomized to Gel-200 or PBS with a 1:1 ratio at week 0 were required to have had pain >4 weeks in the target knee, K-L grade 1 to 3 scores by X-ray, and WOMAC pain subscores of 50 to 90 mm following a 50-foot walk test. Patients returned for efficacy and safety evaluations at weeks 3, 6, 12, 18, and 26 following a single injection of Gel-200 or PBS (Figure 1).

Efficacy measurements included WOMAC scores following a 50-foot walk test, physician and patient global evaluations, and OMERACT-OARSI strict responders.[16–18]

Both RCTs allowed patients to take rescue of acetaminophen provided not before 24 h of scheduled visits. In SI-6606/01, patients were allowed to continue OA treatments such as nonsteroidal anti-inflammatory drugs (NSAIDS) provided they remained stable, while in Gel/1133, patients discontinued background OA treatment with exception of rescue of acetaminophen.

SI-6606/01 and Gel/1133 RCTs were both approved by a central institutional review board and registered with Clinical Trials.gov (identification numbers NTC 00449696 and NTC 01934218, respectively). Both trials were conducted in the United States from August 2006 to May 2008 for SI-6606/01 and August 2013 to February 2016 for Gel/1133.

Statistical analysis

WOMAC pain Visual Analog Scale (VAS) subscores were the primary outcome measures of treatment efficacy and used for this pooled analysis. All analyses for efficacy used intention-to-treat (ITT) populations from the RCTs, sharing the same definition of all randomized patients who received treatment and had at least 1 post-injection visit.

The focus of the pooled analyses was WOMAC VAS scores assessed at weeks 3, 6, 9, and 13 in SI-6606/01 and at weeks 3, 6, 12, 18, and 26 in Gel/1133. Data from week 13 in SI-6606/01 and week 12 in Gel/1133 were pooled for these integrated analyses. Week 9 data were omitted from the SI-6606/01 analyses because there was no equivalent visit in the Gel/1133 trial. As data were not collected at weeks 18 and 26 in SI-6606/01, these visits were treated similar to those for subjects who withdrew early or had missing data in Gel/1133.

The primary efficacy analysis was based on changes in WOMAC pain subscores in the pooled ITT population, using longitudinal analysis to incorporate information from pain scores at scheduled time points in the 2 trials. A repeated-measures model was prespecified which expressed pain scores as a linear function of treatment, time, treatment-by-time interaction, clinically relevant covariates including baseline pain scores, and a fixed site effect.

The primary efficacy objective was tested using the null hypothesis that there were no differences in mean changes from baseline in WOMAC pain subscores between Gel-200 and PBS over 26 weeks, and group comparisons were defined as the average effect over weeks 3, 6, 12, 18, and 26. For the primary analysis, the pain measure covariate referred to the scores used in the eligibility criteria of each study which were baseline WOMAC VAS pain scores following a 50-foot walk in patients from Gel/1133 and WOMAC pain subscores in patients from SI 6606/01. This analysis was repeated for WOMAC total, physical function, and stiffness subscores; patient and physician global assessments and OMERACT-OARSI strict responders over 26 weeks as secondary analyses. OMERACT-OARSI strict responders were compared

Table 1. Baseline characteristics and demographics.

PARAMETER	PBS (N=535)	GEL-200 (N=649)
Gender		
Male	224 (41.9)	281 (43.3)
Female	311 (58.1)	368 (56.7)
Age, years (mean±SD)	60.0±9.47	59.9±9.60
K-L grade		
Grade 1	129 (24.1)	134 (20.6)
Grade 2	211 (39.4)	255 (39.3)
Grade 3	195 (36.4)	260 (40.1)
Body mass index, kg/m^2 (mean±SD)	28.8±3.90	28.5±4.17
Baseline WOMAC pain subscore, mm (mean±SD)	61.89±15.51	64.22±15. 89

Abbreviations: K-L, Kellgrean-Lawrence; WOMAC, Western Ontario and McMaster Universities Arthritis Index.
No statistically significant differences were identified between treatment groups.

between treatment groups for weeks 6 through 26 using a generalized estimating equation (GEE) regression model.

Safety was assessed in the combined safety populations from the RCTs, which included all patients who received treatment with Gel-200 or PBS.

All analyses were post hoc and specified following database lock and unblinding for both protocols.

Results

Patient population

Of the 2193 subjects screened for SI-6606/01 and Gel/1133 protocols, 1196 were randomized: 1191 subjects received treatment (653: Gel-200, 538: PBS), 1184 (99.0%) subjects (649: Gel-200, 535: PBS) were included in the combined ITT population, and 1062 (88.8%) randomized subjects completed the blinded treatment phase of both RCTs in which they were enrolled.

Demographic and baseline characteristics

Demographic characteristics of Gel-200 and PBS treatment groups were similar (Table 1). Baseline characteristics were similar between Gel-200 and PBS treatment groups with exception of baseline WOMAC VAS pain subscores, higher in the Gel-200 group than in the PBS group (P=.011). There were no statistically significant differences in other parameters between Gel-200 and PBS treatment groups.

Primary efficacy

Table 2 summarizes analyses of changes from baseline in WOMAC pain subscores in the pooled ITT population. Treatment group differences in mean (95% confidence interval [CI]) changes from baseline over 26 weeks were −3.0 (−5.4 to −0.5), statistically significant (P=.017). Statistically significant differences were also evident for most individual time points except weeks 3 and 26.

Secondary efficacy

Table 3 summarizes changes from baseline in other WOMAC subscores in the pooled ITT population. Treatment group differences in mean (95% CI) changes from baseline over 26 weeks in WOMAC physical function subscores were −2.1 (−4.6 to 0.4); in WOMAC stiffness subscores, −2.7 (−5.2 to −0.2); and in WOMAC total scores, −2.1 (−4.5 to 0.3). The strict OMERACT-OARSI responders were statistically significantly higher at 26 weeks with Gel-200 than with PBS (P=.037; Table 4).

Safety

The rates of AEs and device-related AEs were similar without statistically significant differences between Gel-200 and PBS groups (Table 5). All serious AEs were judged unrelated to study treatment in each RCT.

Discussion

RCTs of Gel-200 evaluated responses at 13 and 26 weeks following a single injection of Gel-200. We focused on the efficacy of Gel-200 for treatment of knee OA pain over 26 weeks by comparing Gel-200 with PBS using pooled data from 2 well-controlled RCTs using all available clinical evidence, rather than individual clinical trial data.

Pooled analyses demonstrated that a single injection of Gel-200 resulted in statistically significant mean changes from baseline in WOMAC pain subscores compared with a single injection of PBS over 26 weeks (P=.017). Although measurements are different between the reported efficacy at 26 weeks by noninferiority analysis[13] and this pooled analysis, the efficacy of Gel-200 was demonstrated in both analyses. At 12 weeks, a statistically significant difference was evident in both the SI-6606/01 trial and the pooled analyses. These results at 2 time points support the clinical correlations of pain responses between the 2 trials. Although the primary endpoints between the 2 trials were different, the eligibility criteria, baseline characteristics, and demographics in each study were very similar except the baseline WOMAC pain subscores. Patients were randomly allocated into Gel-200 or PBS in each RCT. Pain eligibility score was not considered with WOMAC pain subscores in Gel/1133, where eligibility was the WOMAC pain score following 50-foot walk test. This might account for the difference between treatment groups in baseline WOMAC pain subscores.

Despite the different baseline pain scores in the Gel-200 combined group, treatment with Gel-200 resulted in clinically

Table 2. Change from baseline in WOMAC pain subscores.

TIME POINTS	GROUP	ESTIMATED CHANGES FROM BASELINE, MM	DIFFERENCES, MM	95% CI	*P* VALUE
Over 26 weeks	Gel-200	−23.8	−3.0	−5.4 to −0.5	.017
	PBS	−20.8			
At 3 weeks	Gel-200	−22.3	−2.6	−5.3 to 0.1	.055
	PBS	−19.6			
At 6 weeks	Gel-200	−24.8	−2.9	−5.7 to −0.0	.049
	PBS	−22.0			
At 12 weeks	Gel-200	−24.7	−2.9	−5.8 to −0.0	.047
	PBS	−21.8			
At 18 weeks	Gel-200	−25.1	−3.6	−6.7 to −0.4	.026
	PBS	−21.6			
At 26 weeks	Gel-200	−22.1	−3.0	−6.2 to 0.2	.069
	PBS	−19.1			

Abbreviations: WOMAC, Western Ontario and McMaster Universities Arthritis Index; CI, confidence interval; PBS, phosphate buffered saline.

Table 3. Changes from baseline in secondary endpoints over 26 weeks.

MEASUREMENTS	GROUP	ESTIMATED CHANGE FROM BASELINE, MM	DIFFERENCE, MM	95% CI	*P* VALUE
WOMAC function	Gel-200	−22.9	−2.1	−4.6 to 0.4	.096
	PBS	−20.8			
WOMAC stiffness	Gel-200	−23.4	−2.7	−5.2 to −0.2	.036
	PBS	−20.7			
WOMAC total	Gel-200	−22.8	−2.1	−4.5 to 0.3	.091
	PBS	−20.7			
Physician global evaluation	Gel-200	−21.9	−0.9	−3.2 to 1.3	.411
	PBS	−20.9			
Patient global evaluation	Gel-200	−18.3	−2.7	−5.4 to −0.1	.043
	PBS	−15.6			

Abbreviations: WOMAC, Western Ontario and McMaster Universities Arthritis Index; PBS, phosphate buffered saline.

Table 4. Summary of OMERACT-OARSI strict responders.

	RESPONDER, NO. (%)		ODDS RATIO OVER 26 WEEKS	
	GEL-200	PBS	ESTIMATE (95% CI)	*P* VALUE[a]
Week 6	272 (43.2)	215 (41.2)	1.2 (1.0-1.5)	.037
Week 12	265 (42.3)	210 (40.9)		
Week 18	167 (44.2)	153 (40.0)		
Week 26	146 (39.9)	134 (36.1)		

Abbreviations: OMERACT-OARSI, Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International; PBS, phosphate buffered saline; CI, confidence interval.
[a]When odds ratio >1, then in favor of Gel-200.

Table 5. Overall summary of AEs.

	GEL-200 (N=653)		PBS (N=538)	
	PATIENTS, NO. (%)	EVENTS, N	PATIENTS, NO. (%)	EVENTS, N
Total AEs	356 (54.5)	902	278 (51.7)	637
Serious AEs	15 (2.3)	26	6 (1.1)	7
Related AEs	92 (14.1)	163	60 (11.2)	100
Related AEs occurring in ≥5% of patients				
Joint swelling	103 (15.8)	125	78 (14.5)	87
Joint effusion	88 (13.5)	103	62 (11.5)	74
Arthralgia	87 (13.3)	107	57 (10.6)	72

Abbreviation: AEs, adverse events.

meaningful improvements from baseline. Minimal clinically important improvements (MCID) have variously been reported as 19.9 mm on the WOMAC 100-mm pain subscore and 9.1 mm on the WOMAC function subscore for knee OA or 10 on a 100 mm VAS score.[19–21] Improvements from baseline with Gel-200 were >20 mm in WOMAC pain subscores at every time point and WOMAC function subscores over 26 weeks. Few trials of IA-HA products have reported statistically significant benefits by WOMAC stiffness[22,23]; yet, statistically significant improvements were evident[10] over 13 weeks. Our pooled analyses demonstrated improvement in stiffness with Gel-200 treatment over 26 weeks. More importantly, OMERACT-OARSI strict responders, requiring 50% and ≥20 mm improvements in either WOMAC pain or function, a more stringent outcome, were statistically significant over 26 weeks.

We also pooled the safety data from 2 trials. No safety concerns were identified in the pooled data as well as the results from the individual 3 studies including those following repeat injections of Gel-200.[10-13] Rutjes et al[24] reported that IA-HA treatment has a small and clinically irrelevant benefit and an increased risk for serious AEs in their systematic review. However, no evidence of increased risk of Gel-200 is identified in our safety results.

In summary, these pooled analyses provide evidence of statistically significant improvements in WOMAC pain subscores, as well as other WOMAC measures over 26 weeks following a single or repeat intra-articular injections of Gel-200 compared with PBS without major safety concerns.

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Author Contributions

JT designed the statistical analysis plan, interpreted the data, and drafted, revised, and approved the final manuscript. TS designed the statistical analysis plan and conducted the statistical analysis, and approved the final manuscript. VS provided clinical input for the analysis and interpretation of study results and conclusions, and approved the final manuscript.

REFERENCES

1. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Ann Rheum Dis*. 2001;60:91–97.
2. Altman RD, Manjoo A, Fierlinger A, Niazi F, Nicholls M. The mechanism of action for hyaluronic acid treatment in the osteoarthritic knee: a systematic review. *BMC Musculoskelet Disord*. 2015;16:1–10.
3. Migliore A, Procopio S. Effectiveness and utility of hyaluronic acid in osteoarthritis. *Clin Cases Miner Bone Metab*. 2015;12:31–33.
4. Goldberg VM, Goldberg L. Intra-articular hyaluronans: the treatment of knee pain in osteoarthritis. *J Pain Res*. 2010;3:51–56.
5. Strand V, Conaghan PG, Lohmander LS, et al. An integrated analysis of five double-blind, randomized controlled trials evaluating the safety and efficacy of a hyaluronan product for intra-articular injection in osteoarthritis of the knee. *Osteoarthritis Cartilage*. 2006;14:859–866.
6. Trojian TH, Concoff AL, Joy SM, Hatzenbuehler JR, Saulsberry WJ, Coleman CI. AMSSM scientific statement concerning viscosupplementation injections for knee osteoarthritis: importance for individual patient outcomes. *BMJ Sports Med*. 2016;50:84–92.
7. American Academy of Orthopaedic Surgeons. *Treatment of Osteoarthritis of the Knee Evidence-Based Guideline*. 2nd ed. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2013, http://www.aaos.org/research/guidelines/TreatmentofOsteoarthritisoftheKneeGuideline.pdf. Accessed September 22, 2015.
8. Hochberg MC, Altman RD, April KT, et al. American college of rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res*. 2012;64:465–474.
9. Cooper C, Rannou F, Richette P, et al. Use of intra-articular hyaluronic acid in the management of knee osteoarthritis in clinical practice. *Arthritis Care Res*. 2017;69:1287–1296.
10. Strand V, Baraf HSB, Lavin PT, Lim S, Hosokawa H. A multicenter, randomized controlled trial comparing a single intra-articular injection of Gel-200, a new cross-linked formulation of hyaluronic acid, to phosphate buffered saline for treatment of osteoarthritis of the knee. *Osteoarthritis Cartilage*. 2012;20:350–356.
11. Strand V, Baraf HSB, Lavin PT, Lim S, Hosokawa H. Effectiveness and safety of a multicenter extension and retreatment trial of Gel-200 in patients with knee. *Osteoarthritis Cartilage*. 2012;3:297–304.
12. Strand V, Lim S, Takamura J. Evidence for safety of retreatment with a single intra-articular injection of Gel-200 for treatment of osteoarthritis of the knee

from the double-blind pivotal and open-label retreatment clinical trials. *BMC Musculoskelet Disord*. 2016;17:240–247.
13. Food Drug Administration. Summary of safety and effectiveness data, Gel-One®—P080020/S020; 2016, https://www.accessdata.fda.gov/cdrh_docs/pdf8/P080020S020B.pdf. Accessed June 19, 2017.
14. Chevalier X, Jerosch J, Goupille P, et al. Single, intra-articular treatment with 6 mL Hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: a randomised, multicentre, double-blind, placebo-controlled trial. *Ann Rheum Dis*. 2010;69:113–119.
15. Food Drug Administration. Summary of safety and effectiveness data, Monovisc™—P090031; 2014, https://www.accessdata.fda.gov/cdrh_docs/pdf9/P090031B.pdf. Accessed June 19, 2017.
16. Dougados M, Leclaire P, van der Heijde D, Bloch DA, Bellamy N, Altman RD. Response criteria for clinical trials on osteoarthritis of the knee and hip: a report of the Osteoarthritis Research Society International Standing Committee for Clinical Trials response criteria initiative. *Osteoarthritis Cartilage*. 2000;8:395–403.
17. Pham T, van der Heijde D, Lassare M, et al. Outcome variables for osteoarthritis clinical trials: the OMERACT-OARSI set of responder criteria. *J Rheumatol*. 2003;30:1648–1654.
18. Pham T, van der Heijde D, Altman RD, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis Cartilage*. 2004;12:389–399.
19. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. *Ann Rheum Dis*. 2005;64:29–33.
20. Strand V, Kelman A. Outcome measures in osteoarthritis: randomized controlled trials. *Curr Rheumatol Rep*. 2004;6:20–30.
21. Strand V, Boers M, Inzerada L, et al. It's good to feel better but it's better to feel good and even better to feel good as soon as possible for as long as possible: response criteria and the importance of change at OMERACT 10. *J Rheumatol*. 2011;38:1720–1727.
22. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Weels G. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev*. 2006;2:CD005321.
23. Arrich J, Piribauer F, Mad P, Schmid D, Klaushofer K, Mullner M. Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: systematic review and meta-analysis. *CMAJ*. 2005;172:1039–1043.
24. Rutjes AW, Jüni P, da Costa BR, Trelle S, Nüesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. *Ann Intern Med*. 2012:157:180–191.