Washington State Health Care Authority

Health Technology Clinical Committee
Date: May 14, 2010
Time: 8:00 am – 3:30 pm
Location: Marriott Hotel – 3201 South 176th Street, Seattle, WA 98188
Teleconference Bridge: 1-218-936-4700 Access Code: 9461464
Adopted:

HTCC MINUTES

Members Present: Brian Budenholzer; Michael Myint; Carson Odegard; Richard Phillips; C. Craige Blackmore; Louise Kaplan; Megan Morris; Christopher Standaert; Michelle Simon and Kevin Walsh.

Absent: Michael Souter

HTCC FORMAL ACTION

1. **Call to Order**: Dr. Budenholzer, Chair, called the meeting to order. Sufficient members were present to constitute a quorum.
2. **November 20th, 2009 Meeting Minutes**: Chair referred members to the draft minutes; motion to approve and second, and adopted by the committee.
   - *Action: Eight committee members approved the November 20th, 2009 meeting minutes, as amended to make minor corrections. One committee member abstained from voting. Amendment to include an editorial correction.*
3. **Cardiac Artery Calcium Scoring (CACS) draft Findings & Decision:** Chair referred members to the draft findings and decision and called for further discussion or objection. The Cardiac Artery Calcium Scoring findings & decision was approved and adopted by the committee.
   - *Action: Eight committee members approved the Cardiac Artery Calcium Scoring findings & decision document. One committee member abstained from voting. Amendment to include an editorial correction.*
4. **Hip Resurfacing draft Findings & Decision:** Chair referred members to the draft findings and decision and called for further discussion or objection. The Hip Resurfacing findings & decision was approved and adopted by the committee.
   - *Action: Eight committee members approved the Hip Resurfacing findings & decision document. One committee member abstained from voting.*
5. **Hyaluronic Acid / Viscosupplementation:** The HTCC reviewed and considered the Hyaluronic Acid / Viscosupplementation technology assessment report; information provided by the Administrator; state agencies; public members; and heard comments from the evidence reviewer, HTA program, the public and agency medical directors. The

committee considered all the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

HTCC COMMITTEE COVERAGE DETERMINATION VOTE			
	Not covered	**Covered Unconditionally**	**Covered Under Certain Conditions**
Hyaluronic Acid / Viscosupplementation	**3**	**0**	**7**

- *Action:* The committee chair directed HTA staff to prepare a Findings and Decision document on Hyaluronic Acid / Viscosupplementation reflective of the majority vote.

- Limitations of Coverage:

  - Based on the evidence about the technologies' safety, efficacy, and cost-effectiveness, Hyaluronic Acid / Viscosupplementation is a covered benefit for the treatment of pain associated with Osteoarthritis (OA) of the knee when all of the following conditions are met:
    1. In patients who have not had an adequate response to nonpharmacological conservative treatment and simple analgesics;
    2. Is limited to two courses per year with at least four months between courses; and
    3. Documented evidence of clinical benefit from the prior course of treatment is required for subsequent treatment courses.

- Additional Committee comments:

  - The committee also unanimously agreed that the evidence does not currently demonstrate that any one hyaluronic acid product or administration protocol is superior.

Washington State Health Care Authority

SUMMARY OF HTCC MEETING TOPICS, PRESENTATION, AND DISCUSSION

Agenda Item: Welcome & Introductions

- ✓ The Health Technology Clinical Committee (HTCC) met on May 14th, 2010.

Agenda Item: Meeting Open and HTA Program Update

Dr. Brian Budenholzer, HTCC Chair, opened the public meeting.

- ✓ Leah Hole-Curry, HTA Program Director, provided an overview of the agenda, meeting guide and purpose, room logistics and introductions.

Agenda Item: Previous Meeting Business

November 20th, 2009 Meeting Minutes: Chair referred members to the draft minutes and called for a motion and discussion. Minutes were circulated prior to the meeting and posted. The adoption amendment includes an editorial correction.

- ➢ *Action: Eight committee members approved, as amended, the November 20th, 2009 meeting minutes. One committee member abstained from voting. Amendment to include an editorial correction (found on page 16, bullet #3.1).*

Cardiac Artery Calcium Scoring (CACS) Findings and Decision: Chair referred members to the draft findings and decision and called for further discussion. The draft findings and decision document was circulated prior to the meeting and posted to the website for a two week comment period. No public comments were received by the program during the publication of the CACS draft findings and decision.

- ➢ *Action: Eight committee members approved the Cardiac Artery Calcium Scoring findings & decision document. One committee member abstained from voting. Amendment to include an editorial correction (found on page 3, bullet #3.1).*

Hip Resurfacing draft Findings & Decision: Chair referred members to the draft findings and decision and called for further discussion or objection. The Hip Resurfacing findings & decision was approved and adopted by the committee.

- ➢ *Action: Eight committee members approved the Hip Resurfacing findings & decision document. One committee member abstained from voting.*

Agenda Item: Hyaluronic Acid / Viscosupplementation Topic Review

Leah Hole-Curry, HTA Program Director, introduced the technology topic up for discussion:

- ✓ Hyaluronic Acid / Viscosupplementation: review of the evidence of the safety, efficacy and cost-effectiveness of Hyaluronic Acid / Viscosupplementation for osteoarthritis (OA) of the knee.

Hyaluronic Acid / Viscosupplementation –

- ✓ OA affects around 27 million people (US); OA is progressive and has no cure. OA of the knee may affect 37% of the over 60 year old population.
- ✓ Management options include: lifestyle changes – physical therapy and exercise; systemic and topical analgesics; bracing/orthotics; corticosteroid and ACS injections; alternative and complementary therapy; and surgical joint replacement.
- ✓ OA knee problems may involve a decreased level of synovial fluid in the joint, as well as loss of cartilage and inflammation.
- ✓ Varying HA types of treatment strategies: cross-linked derivative vs. natural; different molecular weights; and 1 to 3 to 5 injections per course of treatment.
- ✓ HA is a natural component of synovial fluid and lubricates joints and provides shock absorption which may decrease with OA. HA passes through joints cyclically, with residence in joint typically not more than hours to days.
- ✓ Intra-articular injection of HA categorized as a biological device, first FDA approval in 1997.
    - o Treatment of pain associated with knee OA; patients who have not responded adequately to conservative non-pharmacologic therapy (physical therapy) or simply analgesics (acetaminophen).
    - o Contraindications: known allergy to hyaluronate preparations, or to birds or bird products; or infections or skin diseases at the injection site of knee joint.
    - o Off label: reports of use in hip, ankle, shoulder and other joints; retreatment.
- ✓ Technology dissemination – rapid uptake in past several years, especially newer products; escalating utilization.
- ✓ Potential Benefits – pain relief and functional improvement.
- ✓ Potential Drawbacks – treatment is additive; uncertain benefit and duration; injection related harms; and cost.
- ✓ Prioritization Criteria Review – Safety = Low; Efficacy = Medium; and Cost = High.
- ✓ Medicare Coverage and Clinical Guidelines:
    - o There is no Medicare National coverage decision on Hyaluronic Acid / Viscosupplementation.
    - o Hyaluronic Acid Clinical Guidelines – 6 guidelines identified by evidence center:
        - ▪ American College of Rheumatology (ACR), 2000 – Intraarticular hyaluronan therapy is indicated. Quality = Poor.
        - ▪ American Pain Society (APS), 2002 – Injection of HA supplements into the knee may be considered in persons with OA. Quality = Poor.
        - ▪ American Academy of Orthopaedic Surgeons (AAOS), 2008 – concluded they could not recommend for or against as evidence is inconclusive. Quality = Good.
        - ▪ National Institute for Clinical Health & Excellence (NICE), 2008 – Intraarticular hyaluronan injections are not recommended for the treatment of OA of the knee, or any other joint. Quality = Good.

- Veterans Health Administration (VA), 2008 – Evidence supports the use of intraarticular hyaluronan or hylan injections for OA of the knee. Quality = Poor.
- Osteoarthritis Research Society International (OARSI), 2008 – Injections of intraarticular hyaluronate may be useful in patients with knee OA. Quality = Good.

Agenda Item: Public Comments

The Chair called for public comments.

- ✓ Scheduled Public Comments: Four stakeholder groups requested scheduled time for public comments.
  - o Bill Struyk, DePuy-Mitek, described other payer policies that cover Hyaluronic Acid / Viscosupplementation; commented on databases used to report the hyaluronic acid products; and appreciated the meeting materials being published prior to the public meeting.
  - o Vinod Dasa, MD; Gary Myerson, MD; and Phillip Band, MD, Smith & Nephew, stated that hyaluronic acid is more effective than corticosteroids and NSAID; and believes that hyaluronic acid injections maintain function and activity for their population. Requested for the committee to consider coverage as an effective treatment tool for OA of the knee.
  - o Johanna Lindsay, The Arthritis Foundation, Pacific Northwest Chapter, stated that based on her experience, the OA population want a quality of life increase for simple daily activities; HA provides this, and individuals with obesity or co-morbidities may not be eligible for surgery; access to HA as an option should be preserved.
  - o Jeff Peterson, MD, Washington State Rheumatology Alliance, disagreed with the technology report, based on argument that the use of hyaluronic acid injections are a cost-savings due to decreased surgeries, physical therapy, wheel chairs and time off from work.
- ✓ Open Public Comments: two individuals provided comments during the open portion (limited to three minute comments).
  - o Biji Joseph, Genzyme, Manufacturer, commented on how the evidence vendor should have looked at data prior to 2006 and that the Hayes report relied heavily on the effect size.
  - o Debra Colfort, Genzyme, Manufacturer, provided a statement regarding the single use of Hyaluronic Acid / Viscosupplementation injection changes the total cost of care which guarantees compliance and minimizes waste.

Agenda Item: Hyaluronic Acid / Viscosupplementation Topic – Agency Data

Dr. Gary Franklin, Department of Labor & Industries, Medical Director, presented to the committee the agency utilization and outcomes for Hyaluronic Acid / Viscosupplementation.

- ✓ Agency Concerns:

- Safety (LOW): adverse events increase with number of treatment courses, generally safe.
- Efficacy (Medium): unknown mechanism, unstudied duration of sub-clinical average result; additive not alternative.
- Cost (High): usage and costs escalating rapidly.

✓ Coverage Overview: currently covered by all WA state agencies. DSHS / UMP cover without restrictions. LNI covers when: OA of the knee retards recovery from accepted condition; single course of injections only; and after documented failure of all alternative therapies, including non-pharmacological (e.g. physical therapy), non-opioid analgesics (acetaminophen) and two different NSAID classes.

✓ Agency Experience with Products: HA products vary in cost; agency payment data shows: average injection payment range from $55 to $164 by product and evidence does not demonstrate superiority or difference in products.

✓ Scientific Evidence: Efficacy – despite 50+ trials, no large effect; no consistent clinically meaningful effect; statistically significant pain reduction in some patients. However, study focus on pain reduction in short term – some equivalent to placebo, or NSAIDS; inadequate evidence of functional improvement; inadequate long term studies and follow up; inadequate controls for other treatment; and recent longer (26 weeks) studies have found both exercise and ACS injections superior to Hyaluronic Acid / Viscosupplementation.

✓ Utilization Data – Completion of Treatment:

COMBINED AGENCY DATA, 2008

2008 Injection Series	Hyalgan/ Supartz*	Synvisc	Euflexxa	Orthovisc	All Injection Types
Background info					
Total Patients 2008	596	686	163	411	1856
FDA Injection Counts per Procedure	5(3-5)*	3	3	3	
Series Completions					
Patients completing at least 1 series of injections	39%	72%	64%	71%	61%
Patients completing 2 series or more	4%	12%	7%	10%	
Series Incompletions					
Patients who did not complete any injection series	61%	27%	29%	24%	37%
Patients with a single injection only	16%	12%	15%	12%	
Patients with two injections only	11%	15%	15%	12%	
Three injection incomplete series (Hyalgan/Supartz only)	24%				
Four injection incomplete series (Hyalgan/Supartz only)	11%				

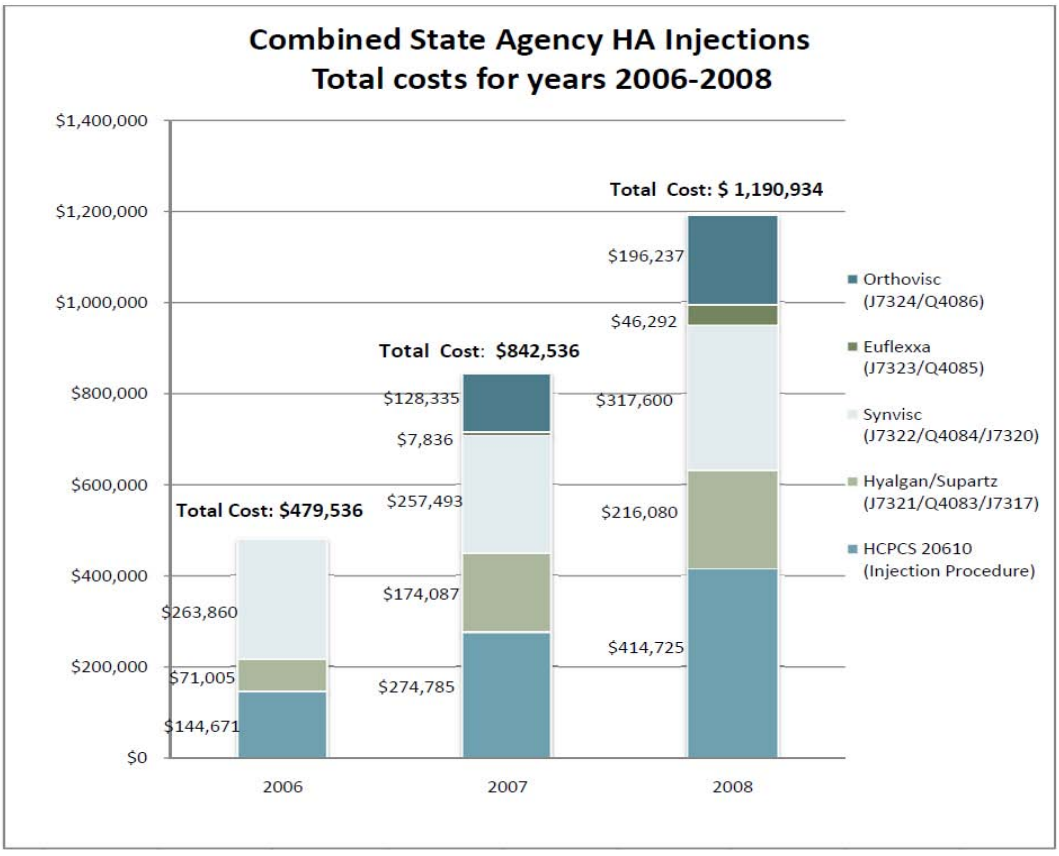
*Hyalgan (5 inj) and Supartz (3-5 inj) are combined due to a shared billing code. Completion data may be skewed by the proportion of each drug prescribed, the speed of adoption of FDA approved label changes in practice, and the severity of the patients' condition.

- ✓ FDA inconsistent in injection count approval – Supartz approved for 3, amended to 3 or 5 in 2006 and Orthovisc approved in 2004 for 3 or 4 injections. 8 – 16% of UMP and DSHS patients using Synvisc or Euflexxa (3 injections) receive more injections than FDA approved treatment.
- ✓ Agency Hyaluronic Acid / Viscosupplementation cost experience – average $838,000 per year, and costs escalating by 40% each year.

UMP, L&I, DSHS DATA 2006-2008

2006-2008	Patient count	Procedure Count	Total Cost
Unified Medical Plan	1969	8424	$1,201,323
Labor & Industry	934	2917	$850,330
Dept of Social and Health Services	848	2780	$461,353
All Agencies	3571	14121	$2,513,006

- ✓ A Picture of Escalating Costs:



- ✓ Safety Data: minor adverse events relatively common, increasing in frequency with repeated procedures; adverse events may be elevated with some product types; major adverse events are rare, but do occur; and comparative safety advantage with NSAIDS (systemic) questionable as not used as alternative and relief from Hyaluronic Acid / Viscosupplementation short term.
- ✓ Cost-effectiveness (CE) Evidence: no evidence of clinically significant improvement in outcomes; therefore, cost effective and economic studies are not appropriate. Current cost-effectiveness analysis unclear basis as clinically meaningful improvement not demonstrated; no high quality evidence that treatment is alternative, currently additive; no high quality evidence of number of patients with clinical improvement in pain and function; and assumption on duration of effect is unclear.
- ✓ AMD Recommendations: Non-coverage due to meaningful clinical effect on pain not demonstrated, low evidence on other patient outcomes; harms occur, usually minor, but include serious adverse event (pseudosepsis) and consistent with high quality guidelines weak to negative conclusions.
    - o If HTCC finds evidence suggestive of net health benefit, limit to: FDA indications; require evidence of conservative management; limit number of treatment courses and leave product type to agency discretion.

Agenda Item: Evidence Review Presentation

Hayes presented an overview of their evidence report on Hyaluronic Acid / Viscosupplementation for Osteoarthritis (OA) of the Knee.

- ✓ Background – OA: 27 million adults in the U.S.; most commonly affected joint is knee and prevalence is 12 – 16%.
    - o Treatment includes: physical therapy, exercise, and/or weight loss
    - o Acetaminophen → nonsteroidal anti-inflammatory drugs (NSAIDs) → intraarticular (IA) corticosteroid → total knee replacement (TKR).
- ✓ Background – Hyaluronic Acid / Viscosupplementation: names include hyaluronic acid (HA), hyaluronan sodium hyaluronate. Alternative to NSAIDs, IA corticosteroid. Natural substance in synovial fluid (appears to deplete with OA). FDA approval is for OA of the knee, off-label includes hip, shoulder, ankle, temporomandibular joint, rheumatoid arthritis, and caution of retreatment.
- ✓ Products marketed in the U.S. include: Euflexxa (Ferring); Hyalgan (Sanofi-Aventis); Orthovisc (Anika Therapeutics); Supartz (Seikaguku Corporation) and Synvisc (Genzyme). Different forms of HA: Hylan GF-20 – cross-linked polymer, derivative of HA, high molecular weight; medium molecular weight of HA; and low molecular weight of HA.
- ✓ PICO Methods – Patient Group: Adults with OA of the knee; Intervention(s): Viscosupplementation (hyaluronic acid injection – Hyalgan, Synvisc, Supartz, Orthovisc and Euflexxa); Comparator(s): NSAIDs, corticosteroid injection, physical therapy, oral pain medications, placebo, arthroscopic lavage and/or debridement; Outcome(s): pain, function, quality of life and adverse events.

- ✓ Search Methods – usual MED rapid review process; core sources; literature databases (MEDLINE, Jan 2006 – Dec 2009; systematic reviews (SRs); technology assessments and guidelines. MEDLINE and EMBASE, Sep 2009 – Dec. 2009; primary studies after latest SR search); study design, primary studies – randomized controlled studies (RCTs) only.
- ✓ Search Results:
  - o 3 general systematic reviews (SRs) –
    - Hayes Report (2009)
    - AHRQ technology assessment; review of 6 meta-analysis (MAs) plus supplemental analysis (Samson et al., 2007)
    - Cochrane Review with MA (Bellamy et al., 2006)
  - o 2 special-issue SRs with MA –
    - Hylan vs. HA (Reichenbach et al., 2007)
    - HA / hylan vs. IA corticosteroid (Bannuru et al., 2009)
  - o 4 recent RCTs (late 2009)
  - o Various sources of cost / cost-effectiveness data

- ✓ Placebo-Controlled RCTs:

Source	Meta-analysis?	# of placebo-controlled RCTs	SR Quality	RCT Quality
Hayes 2009	No	11	Fair-good	No individual rankings
Samson 2007 (AHRQ)	Yes; reviewed 6 MAs; add'l new analyses	42 (5-32 per MA)	Good (Variable MA quality)	Good (9), fair (16), poor (12), not evaluable (5)
Bellamy 2006 (Cochrane)	Yes (included in Samson 2007)	32	Fair-good	No individual rankings
Altman 2009 Baltzer 2009	N/A; trials from primary lit	2	N/A	Good Good

- ✓ Findings: Efficacy vs. Placebo (moderate-quality evidence; about 50 RCTs, 6 MAs)
  - o Statistically significant differences in pain and function, especially during ~1 to 2 months after treatment.

- Benefit may not be clinically important – pooled estimates of difference: < 20 points on 100-point scales (except hylan vs. placebo); standardized effects sizes: 0.0-0.32; 0.80 in 1 MA.
- Conflicting evidence, two 2009 primary RCTs.
- Response rates (2 RCTs): non-significant in ITT analysis (Altman 1998); 76% vs. 62% (*P*<0.03) (Neustadt 2005).

✓ Randomized Comparator Trials:

Comparison	Key Source	# trials	Quality of Source	Quality of Trials
HA vs NSAIDs	Bellamy 2006	6 total; 4 effectiveness and 2 safety	Fair-Good	Not individually assessed.
HA vs IA corticosteroid	Bannuru 2009 (Meta-analysis)	7	Good	Low
Hylan vs non-hylan HA	Reichenbach 2007 (Meta-analysis)	13	Good	Generally poor or incomplete reporting
HA vs conventional treatment	Hayes 2009	2 (Raynauld 2002; Kahan 2003)	Fair-Good	Not individually assessed.

✓ Findings: HA vs. Other Treatments (Low Quality Evidence) –

- Improvement comparable with NSAIDs (4 RCTs), fewer adverse events (2 RCTs).
- Longer-lasting benefit than IA corticosteroids (1 MA of 7 RCTs) – HA superior after first few weeks; largest effect size 0.39 (95% CI, 0.18-0.59), 17 – 26 weeks.
- Response rates (2 RCTs) – 62% vs. 35% (*P*=0.0001), ITT analysis; 65% vs. 40% (*P*=0.0001), ITT analysis.

✓ Findings: Effectiveness by Products (Low Quality Evidence) – Hylan may have superior benefit over non-cross linked HA; magnitude unlikely to be clinically important (1 MA of 13 comparator trials); no evidence of difference, low vs. medium molecular weight (2 MAs of placebo-controlled trials).

✓ Findings: Safety – best estimate* (*estimate available only from studies of hylan) is 2% (per injection) risk of local, transient reactions, serious reactions possible; HA vs. placebo = similar; HA vs. corticosteroid = unavailable; Hylan vs. non-hylan HA = small absolute increase in overall risk; and increasing risk with repeat courses of treatment* (*evidence available only from studies of hylan).

✓ Findings: Effectiveness by Subpopulation (Low Quality Evidence) – disease severity = conflicting evidence; age, individual trials = conflicting evidence; age, analysis of 20 trials = younger age, greater efficacy (vs. placebo); race/ethnicity, gender, primary vs. secondary OA, disease duration, weight, prior treatments = Not studied *or* 1 or 2 studies showed no relationship.

- ✓ Findings: Cost Implications -- $65 to $195 per injection (U.S. estimate); no cost-effectiveness conclusions: 2 randomized trials suggest acceptable cost effectiveness (Canada, France); Calecoxib more cost-effective than HA as an alternative to naproxen in patients who have declined TKR (Taiwan); unknown representativeness of effectiveness estimates; and may not apply to U.S.
- ✓ Guidelines: 3 high-quality guidelines –
  - o Weakly positive in favor of HA (OARSI); no recommendation because of unclear clinical importance of benefit (AAOS); and negative because of limited cost-effectiveness analysis (NICE).
  - o 3 poor-quality guidelines: Clinical option
- ✓ Limitations of the Evidence: Poorer-quality and smaller trials may have inflated estimates of efficacy; variation in study methods; few data on response rates, comparative effectiveness, and subpopulations; no safety data from large databases, except for hylan; no analysis of synergistic effects; and no U.S. economic evaluations.
- ✓ General Conclusion: On average, improvement in pain and function (most relief during 1-2 months after treatment). Magnitude of benefit may be too small to be clinically important. Safety risks small, generally non-serious.
- ✓ Practice Considerations: Longer-lasting benefit compared with intraarticular corticosteroids (low quality evidence). Potential alternative to NSAIDs after simpler treatments have failed or next step after NSAIDs have failed (assumed role in cost-effectiveness studies; sparse evidence). Ability to avert total knee replacement has not been studied.

Agenda Item: HTCC Hyaluronic Acid / Viscosupplementation Discussion and Findings

Brian Budenholzer, Committee Chair, led a discussion of the evidence related to the safety, efficacy, and cost effectiveness of Hyaluronic Acid / Viscosupplementation beginning with identification of key factors and health outcomes, and then a discussion of what evidence existed on those factors.

1. Evidence availability and technology features

1.1 The evidence based technology assessment report indicates that Osteoarthritis (OA) is the most common form of chronic articular disease. OA affects approximately 27 million adults in the United States. The most commonly affected joint is the knee, with prevalence estimates ranging from 12% to 16%. To date, there is no known cure for OA nor is there a disease-modifying agent. Optimal management generally requires a combination of both nonpharmacological and pharmacological therapies, and joint replacement surgery or a joint salvage procedure may be considered for selected patients with severe symptomatic OA who have not obtained adequate pain relief and functional movement from medical therapy.

1.2 The evidence based technology assessment report indicates that viscosupplementation with hyaluronan has been introduced as an alternative intraarticular injection therapy for OA. Hyaluronans are also known as sodium hyaluronate or hyaluronic acid (HA). HA is a normal component of synovial fluid and cartilage. The viscous nature of the compound allows it to act as a joint lubricant, whereas its elasticity allows it to act as a shock absorber. Hyaluronic products are characterized by their molecular weight, which varies according to the source of the compound and method of preparation.

1.3 Hyaluronate preparations have been approved by the Food and Drug Administration (FDA) for treatment of pain associated with OA of the knee in patients who have not had an adequate response to nonpharmacological, conservative treatment and simple analgesics.

1.4 The evidence based technology assessment report focused on three systematic reviews concerned primarily with the efficacy of viscosupplementation (Bellamy, 2006; Hayes, 2009 and Samson, 2007); a systematic review of trials comparing hylan with HA (reichenback, 2007); and a systematic review of trials comparing HA or hylan with corticosteroids (Bannuru, 2009).

1.5 The evidence based technology assessment report also conducted a literature search for evidence after the systematic reviews which yielded four RCTs published later than the last search date in the systematic reviews. These included two placebo-controlled trials (Altman, Rosen, Bloch, Hatoum and Korner, 2009; Baltzer, Moser, Jansen and Krauspe, 2009), a head-to-head comparison between hylan and non-cross-linked HA (Chou, Lue, Lee, Lin and Lu, 2009), and a head-to-head comparison between HA and exercise with placebo control (Kawasaki, 2009).

1.6 Cost and cost-effectiveness data were available in three systematic reviews (Hayes, 2009; VA, 2008; Waddell, 2007), and an additional two primary economic studies were selected from the National Health Service (NHS) Economic Evaluation Database (EED) (Kane, and Clarke, 2008; Turajane, Labpiboonpong and Maungsiri, 2007). Data from a cost-effectiveness analysis was abstracted from one of the selected guidelines (NICE, 2008).

1.7 The evidence based technology assessment report identified 6 expert treatment guidelines and no national Medicare policy relating to hyaluronic acid.

1.8 The committee also reviewed information provided by the state agencies, and public members; and heard comments from the evidence reviewer, HTA program, the public and agency medical directors.

2. Evidence about the technology's safety

The committee discussed multiple key factors and health outcomes that were important for consideration in their overall decision on whether the technology is safe. Summary of committee considerations follows.

2.1 The evidence based technology assessment report indicates that overall strength of evidence regarding safety is moderate quality. Trial design (RCT), sample size and outcome measures limit identification of harms, however other trials and registries support similar findings of rare serious events (psuedosepsis) and common minor local reactions.

2.2 The Hayes and Bellamy reviews described adverse events as occurring at very low rates in RCTs. The Samson review, on the other hand, described minor adverse events as "common", and serious events as rare, using event rates from large case series.

2.3 Intraarticular injections, including vicosupplementation, carry a risk of local, transient reactions (in the range of 2% of patients in a single course of treatment). Serious adverse events include psuedosepsis, and are rare (less than 1%).

2.4 There is some evidence that repeat courses of treatment result in increased risk (in the range of 8% of patients) of adverse events, at least with the use of hylan.

3. Evidence about the technology's efficacy and effectiveness

The committee discussed multiple key factors and health outcomes that were important for consideration in their overall decision on whether the technology is effective. Summary of committee considerations follows.

3.1 The evidence based technology assessment report and committee discussion focused on a recent Agency for Healthcare Research and Quality (AHRQ) technology assessment (Samson, 2007) that summarized six meta-analyses. A total of 5,843 patients and 42 placebo-controlled RCTs are represented in the Samson review of meta-analysis. In addition, Samson performed several additional analyses on data abstracted from one of the reviewed meta-analysis: the Cochrane Review (Bellamy, 2006). Each of the six meta-analyses calculated pooled estimates for multiple follow-up intervals. Additionally, the evidence based technology assessment report identified 4 subsequent randomized trials, one of which (Altman 2009) was discussed extensively by the committee.

- The authors of the 5 meta-analysis summarized in the Samson review came to a variety of conclusions ranging from negative, to moderately positive, to strongly positive. The Samson reviewers concluded that only one meta-analysis had data to fully support their conclusion, which was that HA has not been proven effective; and Samson review itself concluded clinical benefit for HA not yet clearly demonstrated.

3.2 The evidence based technology report concluded that there was overall moderate quality of the body of evidence about efficacy, with approximately 50 RCTs comparing HA with placebo, consistently finding statistically significant differences in pain and function, especially during ~1 to 2 months after treatment.

- The evidence based technology report further concluded, that though consistent, the pain benefit may not be clinically important. Weighted mean differences ranged from 1 to 22 on a 100 point scale; with greater than 20 generally accepted as a minimum clinical effect. Weighted mean differences reported by meta-analyses were 7.3 at 22-30 weeks and 9.0 at 14 to 26 weeks, but no treatment effect was observed at 12 weeks. Standardized effects sizes in Bellamy were 0.8 where convention was that .3 is small; .5 is moderate; and .8 is large.
- The difficulty with the reporting in these trials is that a small mean effect does not convey whether only a few patients or a substantial portion of patients experienced improvement, and at what level (e.g. clinical significance).

3.3 The two later RCTs related to efficacy of HA compared to placebo had conflicting results with one showing no statistical difference and one RCT demonstrating efficacy at 26 weeks (Altman, 2009) with an adjusted mean difference in change in pain score of 8.8; which was similar to the meta analysis. Percent of individuals were also calculable for each arm, with: 58% in HA arm and 46% in Saline(placebo) arm achieving greater than 20 point improvement at 26 weeks (an odds ratio of 1.7), though non-significant at 12 weeks. Altman, rated as a good quality study, is a 36-site double blind, randomized trial with 588 participants, funded by industry (open label).

- The committee discussed the Altman trial; both as confirmatory of the body of literature suggesting benefit, and a continuation of the troubling reporting in mean effect size which makes evaluation of the magnitude of benefit difficult.
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3.4 Comparison with other therapies: the evidence based technology report indicates generally limited evidence comparing HA to alternatives:

- One systematic review (Hayes) reported comparisons with NSAIDs, appropriate care only, exercise, and intraarticular corticosteroids, the results were either conflicting or available from a single trial.
- Another review (Bellamy) reported 6 RCTs comparing HA with NSAIDs and found two treatments had comparable efficacy; and 7 RCTs with corticosteroids where HA appeared to confer a delayed but longer term benefit.

- o A double-blind RCT of good quality compared autologous conditioned serum (ACS) with HA and with saline placebo (Baltzer, Moser, Jansen and Krauspe, 2009). ACS was found to have a substantial effect on function, pain, and quality of life (QOL) at 7, 13, and 26 weeks, compared with both HA and with placebo. In a fair quality trial, differences between HA and placebo and home exercise were small and non-significant.

3.5 The evidence based technology assessment report indicated that there were fewer meta-analyses of functional outcomes than of pain outcomes. Of 15 analyses reported in the Samson review, 9 were significant and favorable, and again, those were for the longer follow-up periods. Effect sizes for function outcomes ranged from 0.16 at best in one meta-analysis to 0.32 in another meta-analysis to ≥ 0.8 in the Bellamy review.

3.6 Overall, high consistency of positive, though not always statistically or clinically significant benefit. Limitations of evidence included lack of reporting in useful terms; poorer trial quality; small sample sizes; outlier trials; protocol for use of escape medicine; patient age over 65; inconsistent methods and 55% of trials funded by industry. Unanswered questions regarding the role of the therapy (as replacement or addition) and the effect of combination with other therapies; the potential to delay surgical intervention; the length of pain relief and measures other than pain relief.

4. Special Populations

4.1 The evidence based technology reported rated overall strength of evidence as low quality with very few data studies available. Most subgroup analyses were based on post hoc subgroup analysis. No evidence based conclusions could be drawn regarding the differential effectiveness of viscosupplementation by age, race/ethnicity, gender, primary vs. secondary OA, disease severity and duration, weight (BMI), and prior treatments because of a paucity of data. Individual trial evidence regarding the influence of age and disease severity has been conflicting, but a meta-regression and subgroup analysis of 20 trials suggested that younger age predicts greater response. Factors other than age or disease severity have either not been studied or have been shown by one or two studies to be unrelated to treatment effect.

- One meta-analysis of 20 trials (Wang, 2005) included in the Samson review assessed the influence of patient factors on the treatment effect of HA (versus placebo). Using meta-regression and subgroup analysis, the authors found greater mean patient age to be associated with smaller treatment effect. However, (see below) this effect was not replicated in a follow on trial

4.2 The evidence based technology report indicated a Samson trial (also described in the Hayes review) comparing intraarticular HA with placebo found no overall treatment effect but did observe a significant effect in a subgroup of patients who were > 60 years of age and had more severe OA (Lequesne Index scores > 10). This finding was not replicated in a confirmatory study. Two RCTs failed to detect a differential effect according to age, sex, or body mass index (BMI)/weight. One of these two trials also failed to detect a differential effect by disease severity.

4.3 Differential by product or molecular weight: some head to head comparator trials were included in the overall Bellamy review, but authors concluded that they were too few in number to allow conclusions about the relative value of hylan over non-hylan HA or of any HA product compared to another. Four meta-analysis reported in Samson showed evidence that hylan had a superior effect to non-hylan products but a fifth meta analysis did not show differences and all analysis were indirect comparisons. Further, sensitivity analysis suggested significant heterogeneity and when poor quality trials were removed, pooled effect sizes did not cross the confidence interval. Similarly, Reichenbach analyzed differences in molecular weight and detected no statistically significant differences.

5. Evidence about the technology's value and cost-effectiveness

The committee discussed multiple key factors that were important for consideration in their overall decision on whether the technology has value and is cost-effective. Summary of committee considerations follows.

5.1 The evidence based technology report cited the following cost information (Hayes, 2009), obtained from the website of a supplier (Axon Medical Supplies):

- Hyalgan: $69 for one 2.0-mL syringe; 10 syringes for $570.
- Orthovisc: $706.27 for one 2.0-mL syringe; three syringes or 10 ampules for $1,950.
- Supartz: $318.99 for five 2.5-mL syringes.

5.2 The evidence based technology report indicated cost estimates from the Veterans Administration and Department of Defense, from the perspective of a payer/healthcare system (VA, 2008):

- Euflexxa: $87 per injection, $260 per course of treatment (three injections).
- Hyalgan: $65 per injection, $195 to $325 per course of treatment (three to five injections).
- Orthovisc: $198 per injection, $595 to $793 per course of treatment (three to five injections).
- Supartz: $68 per injection, $205 to $341 per course of treatment (three to five injections).
- Synvisc: $142 per injection, $426 per course of treatment (three to five injections).

5.3 Washington State Agency utilization and cost information indicated rising utilization; annual costs at $1.2 million and per treatment cost of $665.00.

5.4 The evidence based technology report included an economic analysis conducted by NICE related to their OA guidelines (NICE, 2008), which concluded that efficacy would have to be three to five times higher than estimates from trials before reaching standard threshold for cost effectiveness to the NHS.

5.5 The evidence based technology report found only two pragmatic cost studies of low quality (societal perspective, Canada and France) which reported an acceptable one-year cost-utility ratio for the addition of HA to appropriate care at $10,000 CAD in 1999 costs or similar cost and improved effectiveness when hylan was compared with conventional care. The results should be interpreted in light of the fact that comparisons of HA with placebo have generally shown less than clinically significant treatment effects.

5.6 Evidence pertaining to the cost-effectiveness of HA has several deficiencies: time frames were short (six months to one year); the number of cost analyses and cost-effectiveness studies is very small and estimates of clinical benefit cannot be assessed due to the paucity of comparable data; there were no cost data or cost-effectiveness data specific to single-injection treatments, now possible for at least one product (FDA, 2010); the full economic evaluations were not conducted in the United States, the results may not apple to U.S. due to differences in prices, reimbursement policies, standards of care, and definitions of cost-effectiveness limits; and there was no cost-effectiveness analysis of HA versus intraarticular corticosteroid injection.

6. Evidence on Medicare Decision and Expert guidelines

Committee reviewed and discussed the expert guidelines as identified and reported in the technology assessment report.

6.1 Centers for Medicare and Medicaid Services – no national Medicare coverage policy.

6.2 Guidelines – a search of the core sources and relevant specialty groups identified six publications from within the past ten years that addressed hyaluronic acid / viscosupplementation for OA of the knee (AAOS, 2008; ACR, 2000; APS, 2002; NICE, 2008; VA, 2008; and Zhang, 2007, 2008).

6.3 Three guidelines rated high quality based on modified AGREE international checklist for evidence based guidelines are summarized::

- (1) Osteoarthritis Research Society International (OARSI), 2007 and 2008 – injections of intraarticular hyaluronate may be useful in patients with knee OA (level of evidence, strength of recommendation 64% [95% CI, 43-85]). They are characterized by delayed onset, but prolonged duration, of symptomatic benefit when compared with intraarticular injections of corticosteroids.
- (2) American Academy of Orthopaedic Surgeons (AAOS), 2008 – concluded that they could not recommend for or against the use of intraarticular hyaluronic acid for patients with mild to moderate symptomatic OA of the knee (level of evidence I and II; grade of recommendation inconclusive).
- (3) National Institute for Clinical Health and Excellence (NICE), 2008 – intraarticular hyaluronan injections are not recommended for the treatment of OA of the knee, or any other joint.

6.4 Three guidelines rated low quality based on modified AGREE international checklist for evidence based guidelines supported use of OA for knee pain.

Committee Conclusions

Having made findings as to the most significant and relevant evidence regarding health outcomes, key factors and identified evidence related to those factors, primarily based on the evidence based technology assessment report, the committee concludes:

1. Evidence availability and technology features

The committee concludes that the best available evidence on hyaluronic acid / viscosupplementation has been collected and summarized.

1.1. Osteoarthritis (OA) is the most common form of chronic articular disease. The most commonly affected joint is the knee. To date, neither a known cure for OA nor a disease-modifying agent is available. Therefore, treatment is focused on reducing pain, maintaining and/or improving joint mobility, and limiting functional impairment.

1.2. Hyaluronate preparations have been approved by the Food and Drug Administration (FDA) for treatment of pain associated with OA of the knee in patients who have not had an adequate response to nonpharmacological, conservative treatment and simple analgesics.

2. Is it safe?

The committee concludes that the comprehensive evidence indicates that hyaluronic acid / viscosupplementation is equally safe to alternative treatments. Key factors to the committee's conclusion included:

2.1. The committee agreed that there are not mortality concerns.

2.2. In terms of morbidity, the committee agreed with the evidence report that serious complications were rare and minor complications included local reaction.

2.3. The committee agreed that the HA injection harms (mostly local) were comparable or less harmful than the systemic effects of NSAIDs, but that evidence was lacking that HA injections are a demonstrated alternative to NSAIDs.

3. Is it effective?

The majority of the committee concludes that the comprehensive evidence shows that hyaluronic Acid / Viscosupplementation is a more effective treatment than treatment without HA for OA of the knee.

3.1. Overall, the committee agreed with the evidence based report that there is moderate quality evidence of a consistent pain relief benefit of HA over placebo based on over 50 RCTs. While there is an impressive body of evidence, some committee members struggled with the limitations of the studies and were troubled that despite a decade of research and the number of trials; the number of patients and magnitude and duration of pain relief benefit are still uncertain, as well as the limited study on other important outcomes.

3.2. A well done, more recent RCT validated previous findings (Altman 2009); mean effect size of 6.6% at 26 weeks; patients with great than 20% improvement odds ratio of 1.7 (58% HA arm clinical improvement and 46% placebo arm clinical improvement) was convincing to many committee members.

3.3. The evidence does not permit conclusions on length of time for pain relief, though it appears to be a delayed effect of several weeks and several low quality trials demonstrate benefit beyond corticosteroid injections (2 to 6 months).

3.4. Functional status was less well studied and/or reported, but trended similar to pain reduction in over 15 studies with validated instruments (WOMAC and Lequesne).

3.5. No reliable information was available on important patient oriented outcomes of reduction in analgesic medication, quality of life, or delay in surgical intervention.

3.6. While promoted as an alternative, there is very little evidence that HA is an alternative rather than additional treatment, and the committee evaluated the technology as an additional option.

4. Evidence about the technology's special populations, patient characteristics and adjunct treatment

The committee agreed that no compelling evidence exists to differentiate sub groups or special populations.

4.1. The committee agreed with the evidence based report that there is inadequate evidence to identify characteristics that either enhance or reduce the efficacy of HA such as age, race/ethnicity, gender, primary vs. secondary, BMI weight, disease severity and duration; prior treatments).

4.2. Specifically with respect to the difference in products and protocols, the committee concluded that there is insufficient data to demonstrate that any one product or administration protocol is superior.

5. Is it cost-effective?

The committee concludes that the HA/Viscosupplementation is unproven to be cost effective; agreeing with the comprehensive evidence review that no evidence based conclusions about cost effectiveness can be drawn.

5.1. The evidence report adequately summarized the poor cost evidence based primarily on the inability to evaluate the representativeness of the study models: short time-frames; the full

economic evaluations were not conducted in the United States; no cost data on specific single-injection treatments; assumptions about delay of total knee replacement surgery; and no cost-effectiveness analysis of HA versus intraarticular corticosteroid injection.

5.2. Committee acknowledged the state agency costs of hyaluronic acid / viscosupplementation treatment injections were nearly $2.5 million over three years; have risen steadily over past three years; to about $1.2 million per year. Current per series costs are about $670 to state.

5.3. Committee reviewed QALY from several (albeit low quality studies) in the $10,000 CAD to $50,000 range; noting this is well below any common QALY standard and that the treatment is relatively inexpensive.

Committee Decision

Based on the deliberations of key health outcomes, the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, and agency and state utilization information. The committee concluded that the current evidence on Hyaluronic Acid / Viscosupplementation demonstrates that there is sufficient evidence to cover with conditions the use of Hyaluronic Acid / Viscosupplementation for the treatment of pain associated with OA. The committee considered all the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable. Based on these findings, the committee voted 7 to 3 to cover with conditions Hyaluronic Acid / Viscosupplementation.

Hyaluronic Acid / Viscosupplementation Coverage Vote

The clinical committee utilized their decision tool to first gauge committee judgment on the status of the evidence in the three primary areas of safety, efficacy, and cost.

Hyaluronic Acid / Viscosupplementation Evidentiary Votes:

Is there sufficient evidence under some or all situations that Hyaluronic Acid / Viscosupplementation for the treatment of Osteoarthritis of the knee is:

	Unproven (no)	**Equivalent** (yes)	**Less** (yes)	**More** (yes)
Effective	**3**	**1**	0	**6**
Safe	0	**10**	0	0
Cost-effective Overall	**7**	0	**1**	**2**

Hyaluronic Acid / Viscosupplementation vote: Based on the evidence provided and the information and comments presented, the committee moved to a vote on coverage.

HTCC COMMITTEE COVERAGE DETERMINATION			
	Not covered	**Covered Unconditionally**	**Covered Under Certain Conditions**
Hyaluronic Acid / Viscosupplementation	**3**	0	**7**

Outcome: The committee chair directed HTA staff to prepare a Findings and Decision document on Hyaluronic Acid / Viscosupplementation reflective of the majority vote for final approval at the next public meeting.

- Based on the evidence about the technologies' safety, efficacy, and cost-effectiveness, Hyaluronic Acid / Viscosupplementation is a covered benefit for the treatment of pain associated with Osteoarthritis (OA) of the knee when all of the following conditions are met:
  1. In patients who have not had an adequate response to nonpharmacological conservative treatment and simple analgesics;
  2. Is limited to two courses per year with at least four months between courses; and
  3. Documented evidence of clinical benefit from the prior course of treatment is required for subsequent treatment courses.

➢ Additional Committee comments:

- The committee also unanimously agreed that the evidence does not currently demonstrate that any one hyaluronic acid product or administration protocol is superior.

Health Technology Clinical Committee Findings and Coverage Decision

Topic: Hyaluronic Acid / Viscosupplementation
Meeting Date: May 14, 2010
Final Adoption:

Number and Coverage Topic

20100514A – Hyaluronic Acid / Viscosupplementation

HTCC Coverage Determination

Hyaluronic Acid / Viscosupplementation is a **covered benefit with conditions** consistent with the criteria identified in the reimbursement determination.

HTCC Reimbursement Determination

❖ Limitations of Coverage

Hyaluronic Acid / Viscosupplementation coverage: Based on the evidence about the technologies' safety, efficacy, and cost-effectiveness, Hyaluronic Acid / Viscosupplementation is a covered benefit for the treatment of pain associated with Osteoarthritis (OA) of the knee when all of the following conditions are met:

- In patients who have not had an adequate response to nonpharmacological conservative treatment and simple analgesics;
- Is limited to two courses per year with at least four months between courses; and
- Documented evidence of clinical benefit from the prior course of treatment is required for subsequent treatment courses.

❖ Non-Covered Indicators

- All other joints

❖ Agency Contact Information

Agency	Contact Phone Number
Labor and Industries	1-800-547-8367
Public Employees Health Plan	1-800-762-6004
Health and Recovery Services Administration	1-800-562-3022

Health Technology Background

The Hyaluronic Acid / Viscosupplementation topic was selected and published in December 2009 to undergo an evidence review process. Hyaluronic Acid / Viscosupplementation for Osteoarthritis (OA) of the Knee impacts 27 million adults in the United States, and the most commonly affected joint is the knee, with prevalence estimates ranging from 12% to 16%. OA of the knee may affect 37% of the over 60 year old population. To date, there is no known cure for OA nor is there a disease-modifying agent. OA knee problems may involve a decreased level of synovial fluid in the joint, as well as loss of cartilage and inflammation. Optimal management generally requires a combination of both nonpharmacological and pharmacological therapies. Pharmacological therapy generally begins with Acetaminophen → nonsteroidal anti-inflammatory drugs (NSAIDs) → intraarticular (IA) corticosteroid → total knee replacement (TKR). Management options include: lifestyle changes – physical therapy and exercise; systemic and topical analgesics; bracing/orthotics; corticosteroid and ACS injections; alternative and complementary therapy; and surgical joint replacement.

Viscosupplementation with hyaluronan has been introduced as an alternative to NSAIDs or intra-articular injection therapy for OA. Hyaluronans are also known as sodium hyaluronate or hyaluronic acid (HA). HA is a natural component of synovial fluid and lubricates joints and provides shock absorption which may decrease with OA. HA passes through joints cyclically, with residence in joint typically not more than hours to days. Hyaluronic products can be characterized by varying molecular weight and on the course per treatment injections.

In March 2010, the HTA posted a draft and then followed with a final report from a contracted research organization that reviewed publicly submitted information; searched, summarized, and evaluated trials, articles, and other evidence about the topic. The comprehensive, public and peer reviewed Hyaluronic Acid / Viscosupplementation report is 95 pages, and identified a relatively large amount of literature.

An independent group of eleven clinicians who practice medicine locally meet in public to decide whether state agencies should pay for the health technology based on whether the evidence report and other presented information shows it is safe, effective and has value. The committee met on May 14th, reviewed the report, including peer and public feedback, and heard public and agency comments. Meeting minutes detailing the discussion are available through the HTA program or online at http://www.hta.hca.wa.gov under the committee section.

Committee Findings

Having considered the evidence based technology assessment report and the written and oral comments, the committee identified the following key factors and health outcomes, and evidence related to those health outcomes and key factors:

1. Evidence availability and technology features

The committee concludes that the best available evidence on hyaluronic acid / viscosupplementation has been collected and summarized. The evidence is presented below:

- Osteoarthritis (OA) is the most common form of chronic articular disease. OA affects approximately 27 million adults in the United States. The most commonly affected joint is the knee, with prevalence estimates ranging from 12% to 16%. To date, there is no known cure for OA nor is there a disease-modifying agent. Optimal management generally requires a combination of both nonpharmacological and pharmacological therapies, and joint replacement surgery or a joint salvage procedure may be considered for selected patients with severe symptomatic OA who have not obtained adequate pain relief and functional movement from medical therapy.
- Viscosupplementation with hyaluronan has been introduced as an alternative intraarticular injection therapy for OA. Hyaluronans are also known as sodium hyaluronate or hyaluronic acid (HA). HA is a normal component of synovial fluid and cartilage. The viscous nature of the compound allows it to act as a joint lubricant, whereas its elasticity allows it to act as a shock absorber. Hyaluronic products are characterized by their molecular weight, which varies according to the source of the compound and method of preparation.
- Hyaluronate preparations have been approved by the Food and Drug Administration (FDA) for treatment of pain associated with OA of the knee in patients who have not had an adequate response to nonpharmacological, conservative treatment and simple analgesics.
- *Systematic Reviews:* The evidence based technology assessment report focused on three systematic reviews concerned primarily with the efficacy of viscosupplementation (Bellamy, 2006; Hayes, 2009 and Samson, 2007); a systematic review of trials comparing hylan with HA (reichenback, 2007); and a systematic review of trials comparing HA or hylan with corticosteroids (Bannuru, 2009).
- *Literature Search:* The evidence based technology assessment report also conducted a literature search for evidence after the systematic reviews which yielded four RCTs published later than the last search date in the systematic reviews. These included two placebo-controlled trials (Altman, Rosen, Bloch, Hatoum and Korner, 2009; Baltzer, Moser, Jansen and Krauspe, 2009), a head-to-head comparison between hylan and non-cross-linked HA (Chou, Lue, Lee, Lin and Lu, 2009), and a head-to-head comparison between HA and exercise with placebo control (Kawasaki, 2009).
- *Cost and cost-effectiveness data:* were available in three systematic reviews (Hayes, 2009; VA, 2008; Waddell, 2007), and an additional two primary economic studies were selected from the National Health Service (NHS) Economic Evaluation Database (EED) (Kane, and Clarke, 2008; Turajane, Labpiboonpong and Maungsiri, 2007). Data from a cost-effectiveness analysis was abstracted from one of the selected guidelines (NICE, 2008).

- The evidence based technology assessment report identified 6 expert treatment guidelines and no national Medicare policy relating to hyaluronic acid.
- The committee also reviewed information provided by the state agencies, and public members; and heard comments from the evidence reviewer, HTA program, the public and agency medical directors.

2. Is the technology safe?

The committee discussed multiple key factors and health outcomes that were important for consideration in their overall decision on whether the technology is safe. Summary of committee considerations follows.

- The overall strength of evidence regarding safety is moderate quality. Trial design (RCT), sample size and outcome measures limit identification of harms, however other trials and registries support similar findings of rare serious events (psuedosepsis) and common minor local reactions.
- The Hayes and Bellamy reviews described adverse events as occurring at very low rates in RCTs. The Samson review, on the other hand, described minor adverse events as "common" and serious events as rare, using event rates from large case series.
- Intraarticular injections, including viscosupplementation, carry a risk of local, transient reactions (in the range of 2% of patients in a single course of treatment). Serious adverse events include psuedosepsis, and are rare (less than 1%).
- There is some evidence that repeat courses of treatment result in increased risk (in the range of 8% of patients) of adverse events, at least with the use of hylan.

3. Is the technology effective?

The committee discussed multiple key factors and health outcomes that were important for consideration in their overall decision on whether the technology is effective. Summary of committee considerations follows.

- The evidence based technology assessment report and committee discussion focused on a recent Agency for Healthcare Research and Quality (AHRQ) technology assessment (Samson, 2007) that summarized six meta-analyses. A total of 5,843 patients and 42 placebo-controlled RCTs are represented in the Samson review of meta-analysis. In addition, Samson performed several additional analyses on data abstracted from one of the reviewed meta-analysis: the Cochrane Review (Bellamy, 2006). Each of the six meta-analyses calculated pooled estimates for multiple follow-up intervals. Additionally, the evidence based technology assessment report identified 4 subsequent randomized trials, one of which (Altman 2009) was discussed extensively by the committee.
  - The authors of the 5 meta-analysis summarized in the Samson review came to a variety of conclusions ranging from negative, to moderately positive, to strongly positive. The Samson reviewers concluded that only one meta-analysis had data to fully support their conclusion, which was that HA has not been proven effective; and Samson review itself concluded clinical benefit for HA not yet clearly demonstrated.
- The evidence based technology report concluded that there was overall moderate quality of the body of evidence about efficacy, with approximately 50 RCTs

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comparing HA with placebo, consistently finding statistically significant differences in pain and function, especially during ~1 to 2 months after treatment.
  - The evidence based technology report further concluded, that though consistent, the pain benefit may not be clinically important. Weighted mean differences ranged from 1 to 22 on a 100 point scale; with greater than 20 generally accepted as a minimum clinical effect. Weighted mean differences reported by meta-analyses were 7.3 at 22-30 weeks and 9.0 at 14 to 26 weeks, but no treatment effect was observed at 12 weeks. Standardized effects sizes in Bellamy were 0.8 where convention was that .3 is small; .5 is moderate; and .8 is large.
  - The difficulty with the reporting in these trials is that a small mean effect does not convey whether only a few patients or a substantial portion of patients experienced improvement, and at what level (e.g. clinical significance).
- The two later RCTs related to efficacy of HA compared to placebo had conflicting results with one showing no statistical difference and one RCT demonstrating efficacy at 26 weeks (Altman, 2009) with an adjusted mean difference in change in pain score of 8.8; which was similar to the meta analysis. Percent of individuals were also calculable for each arm, with: 58% in HA arm and 46% in Saline(placebo) arm achieving greater than 20 point improvement at 26 weeks (an odds ratio of 1.7), though non-significant at 12 weeks. Altman, rated as a good quality study, is a 36-site double blind, randomized trial with 588 participants, funded by industry (open label).
  - The committee discussed the Altman trial; both as confirmatory of the body of literature suggesting benefit, and a continuation of the troubling reporting in mean effect size which makes evaluation of the magnitude of benefit difficult.
- Comparison with other therapies: the evidence based technology report indicates generally limited evidence comparing HA to alternatives:
  - One systematic review (Hayes) reported comparisons with NSAIDs, appropriate care only, exercise, and intraarticular corticosteroids, the results were either conflicting or available from a single trial.
  - Another review (Bellamy) reported 6 RCTs comparing HA with NSAIDs and found two treatments had comparable efficacy; and 7 RCTs with corticosteroids where HA appeared to confer a delayed but longer term benefit.
  - A double-blind RCT of good quality compared autologous conditioned serum (ACS) with HA and with saline placebo (Baltzer, Moser, Jansen and Krauspe, 2009). ACS was found to have a substantial effect on function, pain, and quality of life (QOL) at 7, 13, and 26 weeks, compared with both HA and with placebo. In a fair quality trial, differences between HA and placebo and home exercise were small and non-significant.
- The evidence based technology assessment report indicated that there were fewer meta-analyses of functional outcomes than of pain outcomes. Of 15 analyses reported in the Samson review, 9 were significant and favorable, and again, those were for the longer follow-up periods. Effect sizes for function outcomes ranged from 0.16 at best in one meta-analysis to 0.32 in another meta-analysis to ≥ 0.8 in the Bellamy review.
- Overall, high consistency of positive, though not always statistically or clinically significant benefit. Limitations of evidence included lack of reporting in useful terms; poorer trial quality; small sample sizes; outlier trials; protocol for use of escape medicine; patient age over 65; inconsistent methods and 55% of trials

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funded by industry. Unanswered questions regarding the role of the therapy (as replacement or addition) and the effect of combination with other therapies; the potential to delay surgical intervention; the length of pain relief and measures other than pain relief.

4. Special Populations?

- The evidence based technology reported rated overall strength of evidence as low quality with very few data studies available. Most subgroup analyses were based on post hoc subgroup analysis. No evidence based conclusions could be drawn regarding the differential effectiveness of viscosupplementation by age, race/ethnicity, gender, primary vs. secondary OA, disease severity and duration, weight (BMI), and prior treatments because of a paucity of data. Individual trial evidence regarding the influence of age and disease severity has been conflicting, but a meta-regression and subgroup analysis of 20 trials suggested that younger age predicts greater response. Factors other than age or disease severity have either not been studied or have been shown by one or two studies to be unrelated to treatment effect.
  - One meta-analysis of 20 trials (Wang, 2005) included in the Samson review assessed the influence of patient factors on the treatment effect of HA (versus placebo). Using meta-regression and subgroup analysis, the authors found greater mean patient age to be associated with smaller treatment effect. However, (see below) this effect was not replicated in a follow on trial
- The evidence based technology report indicated a Samson trial (also described in the Hayes review) comparing intraarticular HA with placebo found no overall treatment effect but did observe a significant effect in a subgroup of patients who were > 60 years of age and had more severe OA (Lequesne Index scores > 10). This finding was not replicated in a confirmatory study. Two RCTs failed to detect a differential effect according to age, sex, or body mass index (BMI)/weight. One of these two trials also failed to detect a differential effect by disease severity.
- Differential by product or molecular weight: some head to head comparator trials were included in the overall Bellamy review, but authors concluded that they were too few in number to allow conclusions about the relative value of hylan over non-hylan HA or of any HA product compared to another. Four meta-analysis reported in Samson showed evidence that hylan had a superior effect to non-hylan products but a fifth meta analysis did not show differences and all analysis were indirect comparisons. Further, sensitivity analysis suggested significant heterogeneity and when poor quality trials were removed, pooled effect sizes did not cross the confidence interval. Similarly, Reichenbach analyzed differences in molecular weight and detected no statistically significant differences.

5. Is the technology cost-effective?

The committee discussed multiple key factors that were important for consideration in their overall decision on whether the technology has value and is cost-effective. Summary of committee considerations follows.

- The evidence based technology report cited the following cost information (Hayes, 2009), obtained from the website of a supplier (Axon Medical Supplies):
  - Hyalgan: $69 for one 2.0-mL syringe; 10 syringes for $570.

  - Orthovisc: $706.27 for one 2.0-mL syringe; three syringes or 10 ampules for $1,950.
  - Supartz: $318.99 for five 2.5-mL syringes.
- The evidence based technology report indicated cost estimates from the Veterans Administration and Department of Defense, from the perspective of a payer/healthcare system (VA, 2008):
  - Euflexxa: $87 per injection, $260 per course of treatment (three injections).
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- The evidence based technology report included an economic analysis conducted by NICE related to their OA guidelines (NICE, 2008), which concluded that efficacy would have to be three to five times higher than estimates from trials before reaching standard threshold for cost effectiveness to the NHS.
- The evidence based technology report found only two pragmatic cost studies of low quality (societal perspective, Canada and France) which reported an acceptable one-year cost-utility ratio for the addition of HA to appropriate care at $10,000 CAD in 1999 costs or similar cost and improved effectiveness when hylan was compared with conventional care. The results should be interpreted in light of the fact that comparisons of HA with placebo have generally shown less than clinically significant treatment effects.
- Evidence pertaining to the cost-effectiveness of HA has several deficiencies: time frames were short (six months to one year); the number of cost analyses and cost-effectiveness studies is very small and estimates of clinical benefit cannot be assessed due to the paucity of comparable data; there were no cost data or cost-effectiveness data specific to single-injection treatments, now possible for at least one product (FDA, 2010); the full economic evaluations were not conducted in the United States, the results may not apple to U.S. due to differences in prices, reimbursement policies, standards of care, and definitions of cost-effectiveness limits; and there was no cost-effectiveness analysis of HA versus intraarticular corticosteroid injection.

6. Medicare Decision and Expert Treatment Guidelines

Committee reviewed and discussed the expert guidelines as identified and reported in the technology assessment report.

- Centers for Medicare and Medicaid Services – no national Medicare coverage policy.
- Guidelines – a search of the core sources and relevant specialty groups identified six publications from within the past ten years that addressed hyaluronic acid / viscosupplementation for OA of the knee (AAOS, 2008; ACR, 2000; APS, 2002; NICE, 2008; VA, 2008; and Zhang, 2007, 2008).

- Three guidelines rated high quality based on modified AGREE international checklist for evidence based guidelines are summarized::
  - (1) Osteoarthritis Research Society International (OARSI), 2007 and 2008 – injections of intraarticular hyaluronate may be useful in patients with knee OA (level of evidence, strength of recommendation 64% [95% CI, 43-85]). They are characterized by delayed onset, but prolonged duration, of symptomatic benefit when compared with intraarticular injections of corticosteroids.
  - (2) American Academy of Orthopaedic Surgeons (AAOS), 2008 – concluded that they could not recommend for or against the use of intraarticular hyaluronic acid for patients with mild to moderate symptomatic OA of the knee (level of evidence I and II; grade of recommendation inconclusive).
  - (3) National Institute for Clinical Health and Excellence (NICE), 2008 – intraarticular hyaluronan injections are not recommended for the treatment of OA of the knee, or any other joint.
- Three guidelines rated low quality based on modified AGREE international checklist for evidence based guidelines supported use of OA for knee pain.

Committee Decision

Based on the deliberations of key health outcomes, the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, and agency and state utilization information. The committee considered all the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

The committee concluded unanimously that the current evidence on Hyaluronic Acid / Viscosupplementation demonstrates that there is sufficient evidence to indicate that hyaluronic acid / viscosupplementation is equally safe to alternative treatments. The majority of the committee concludes that the comprehensive evidence shows that hyaluronic Acid / Viscosupplementation is a more effective treatment than treatment without HA for OA of the knee. The committee agreed that no compelling evidence exists to differentiate sub groups or special populations. The committee concludes that the HA/Viscosupplementation is unproven to be cost effective; agreeing with the comprehensive evidence review that no evidence based conclusions about cost effectiveness can be drawn.

Based on the deliberations the committee concluded that the current evidence on Hyaluronic Acid / Viscosupplementation demonstrates that there is sufficient evidence to cover with conditions the use of Hyaluronic Acid / Viscosupplementation for the treatment of pain associated with OA. The committee considered all the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Based on these findings, the committee voted 7 to 3 to cover with conditions Hyaluronic Acid / Viscosupplementation. Hyaluronic Acid / Viscosupplementation is a covered benefit for the treatment of pain associated with Osteoarthritis (OA) of the knee when all of the following conditions are met:

- In patients who have not had an adequate response to nonpharmacological conservative treatment and simple analgesics;
- Is limited to two courses per year with at least four months between courses; and
- Documented evidence of clinical benefit from the prior course of treatment is required for subsequent treatment courses.

Additional Committee comments: The committee also unanimously agreed that the evidence does not currently demonstrate that any one hyaluronic acid product or administration protocol is superior.

Health Technology Clinical Committee Authority

Washington State's legislature believes it is important to use a scientific based, clinician centered approach for difficult and important health care benefit decisions. Pursuant to chapter 70.14 RCW, the legislature has directed the Washington State Health Care Authority, through its Health Technology Assessment program to engage in a process for evaluation process that gathers and assesses the quality of the latest medical evidence using a scientific research company and takes public input at all stages. Pursuant to RCW 70.14.110 a Health Technology Clinical Committee (HTCC) composed of eleven independent health care professionals reviews all the information and renders a decision at an open public meeting. The Washington State Health Technology Clinical Committee (HTCC), determines how selected health technologies are covered by several state agencies. RCW 70.14.080-140. These technologies may include medical or surgical devices and procedures, medical equipment, and diagnostic tests. HTCC bases their decisions on evidence of the technology's safety, efficacy, and cost effectiveness. Participating state agencies are required to comply with the decisions of the HTCC. HTCC decisions may be re-reviewed at the determination of the HCA Administrator.

HYALURONIC ACID / VISCOSUPPLEMENTATION

Draft Findings & Decision Timeline and Overview of Comments

Actual Timeline		*Total Public Comment Days*
Preliminary recommendations published	*October 27, 2009*	
Public comments due:	***November 10, 2009***	**15 days**
Selected set of topics published:	*December 8, 2009*	
Public comments due:	***January 11, 2010***	**35 days**
Draft Key Questions Published:	January 20, 2010	
Public comments due:	**February 3, 2010**	**15 days**
Key Questions Finalized:	*February 19, 2010*	
Draft report due:	*March 17, 2010*	
Draft report published:	*March 19, 2010*	
Public Comments due:	***April 2, 2010***	**14 days**
Final report due:	*April 14, 2010*	
Final report published:	*April 15, 2010*	
Public meeting Date:	*May 14, 2010*	
Findings & Decision Published	*June 21, 2010*	
Public Comments due:	***July 9, 2010***	**19 days**
Findings & Decision Adopted	***August 20, 2010***	

Comments Received:

Product Manufacturer - One comment

1. Stephen Westing, Senior Medical Science Liaison, Genzyme Biosurgery
    - Requests the opportunity to meet directly with members of the health technology clinical committee
    - Agrees with committee decision but feels key research omitted
        - Limit of the review to studies published no earlier than 1999; and
        - SOUND trial (publ. Jan 2010) absent from the Hayes review and HTCC would benefit from full knowledge of SOUND, which is the evidence for only FDA approved single injection viscosupplement product
    - Requested inclusion of Genzyme public comment sent in response to draft key questions be submitted to HTCC

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Genzyme Biosurgery
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July 1, 2010

Leah Hole-Curry, JD
Program Director, Health Technology Assessment
Washington State Health Care Authority
676 Woodland Square Loop SE
Lacey, WA 98503

Dear Ms. Hole-Curry:

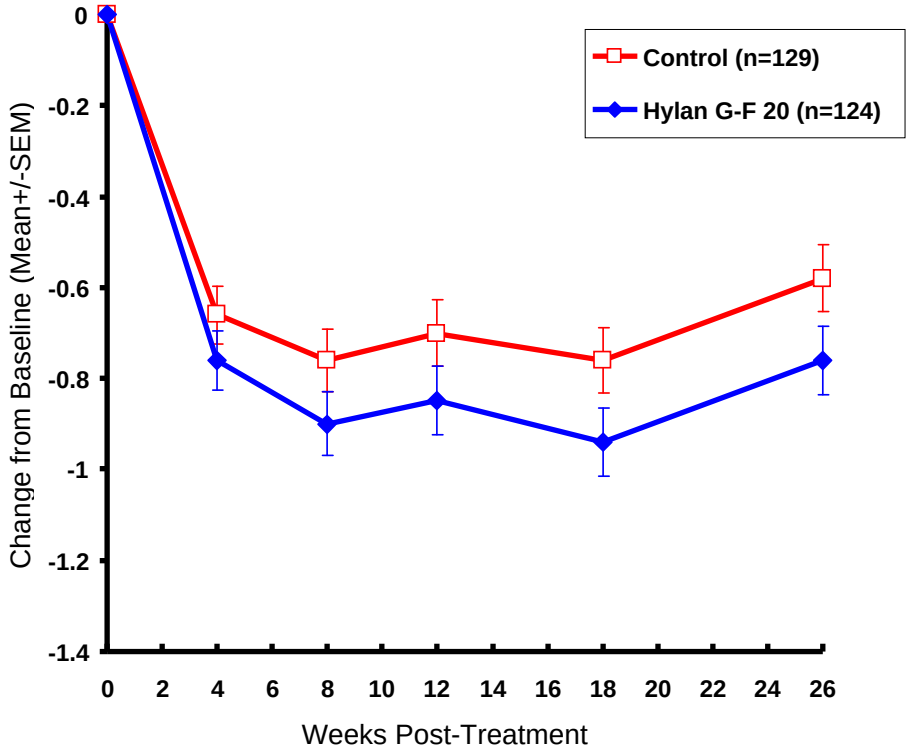
Genzyme wishes to respond to the Draft Findings and Decision document (herein referred to as the HTA Draft Document) regarding the Washington State Health Care Authority Health Technology Assessment of Hyaluronic (HA) / Viscosupplementation.

As discussed during our meeting on May 27th, we additionally request the opportunity to meet directly with members of the Health Technology Clinical Committee. While we are not at odds with the Committee's overall coverage decision or the conditions they set forth to qualify for treatment, we feel that the Hayes report had certain distinct deficiencies and omissions of key research. This concerns us as future reviewers of your finalized Findings and Coverage Decision document and supportive information could derive different conclusions based on this incomplete information.

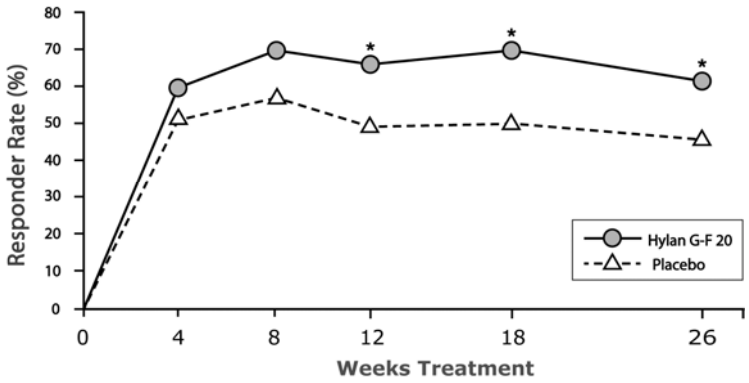
By limiting their review to studies published no earlier than 1999, the Hayes group omitted the majority of pivotal, label enabling studies that led to the approval of the very viscosupplement products they were tasked to review. The viscosupplement field is mature so this time cutoff is difficult to understand. Also absent from the Hayes review, and the principal focus of this response, was the so-called SOUND trial,[1] published on-line by Chevalier et al. in the Annals of the Rheumatic Diseases in early 2009 and in printed form in January 2010. This randomized, multicenter, double-blind, placebo controlled, intent-to-treat analyzed, pivotal study directly compared a single injection of 6 mL of hylan G-F 20 with a single injection of 6 mL of saline for knee osteoarthritis (OA) and tracked outcomes for 26 weeks. The SOUND trial further included a retreat treatment phase that began at week 26 to assess safety of a second treatment course.

Genzyme received FDA approval in 2009 for hylan G-F 20 in the form of Synvisc-One, a single injection viscosupplement product that can provide up to six months of analgesia for knee OA.[2] We believe the Health Technology Clinical Committee would benefit from full knowledge of the SOUND trial along with supportive knowledge of Synvisc-One. In addition to Synvisc-One being the only FDA approved single-injection viscosupplement product available in the US, it is also the most prescribed product in its class in the nation.[3]

SOUND[1] is similar in design and methodological quality to the Altman 2009 trial[4] reviewed at length in the Hayes report, during the public meeting on May 14th, and in the current HTA Draft Document. In SOUND,[1] a statistically significant and clinically meaningful 36% improvement from baseline was observed over 26 weeks as well as significantly differentiating from the Control group in the primary outcome measure (WOMAC A (pain) subscale) plus several secondary variables (please refer to figure below). The effect size associated with this comparison was 0.23, in line with other viscosupplements reviewed in the Hayes report and other therapies commonly used to treat OA.[5]



SOUND[1] also included a pre-specified "responder" analysis useful for declaring a treatment clinically effective (please refer to figure below). Here, a responder was defined as a patient that improved at least one category from baseline on the Likert five-point scale for WOMAC A1 (walking on a flat surface; a one point change of the Likert scale being comparable to the 20% threshold chosen by the Health Technology Clinical Committee as being the minimum change from baseline considered clinically meaningful in this setting). Using this definition, 71% of the hylan G-F 20 treatment group were responders at week 18 versus 54% of Controls (p=0.003), while 64% of the hylan G-F 20 treatment group were responders at week 26 versus 50% of Controls (p=0.028). Although beyond the scope of this brief response, published literature for SYNVISC (three injection course of hylan G-F 20) also includes randomized clinical trials reporting favorable responder analyses.[6,7]



In the HTA Draft Document section entitled "Is the technology safe?" the authors note that some evidence exists that repeat courses of treatment result in increased risk at least with the use of hylan. While this phenomenon is reflected in the FDA label for our three-dose configuration of hylan G-F 20 (brand name: SYNVISC),[8] increases of this nature were not observed in SOUND[1] and are not in the FDA label for our single-dose configuration (brand name: Synvisc-One).[2] For Synvisc-One, device-related adverse events in the injected knee were comparable for the dose given at baseline (5.7%) and the second dose given at week 26 (5.2%).[1,2] While the reason is unknown for the discrepancy between SYNVISC and Synvisc-One regarding repeat course adverse events, many experts have speculated that this apparent lack of increase in adverse events seen with a second course of Synvisc-One is due to the lower number of total invasive procedures (please refer to table below).

% of patients	**1st Course**	**2nd Course**
Synvisc-One: Device-related adverse events in injected knee[2]	5.7%	5.2%
SYNVISC: Local pain and/or swelling in injected knee[8]	7.2%	22.3%

It is important to keep in mind that the events listed in the above table for SYNVISC include all causes and the entire range of severity. For Synvisc-One, the table shows related events and the entire range of severity observed in the pivotal trial. For Synvisc-One, the pivotal trial investigators recorded only mild and moderate local AEs, none of which were serious. Since Genzyme has been maintaining a safety database for hylan G-F 20, the spontaneous reporting rate for local AEs has been very low and stable across time.[3]

In the HTA Draft Document section entitled "Health Technology Background" is the phrase "HA passes through the joint cyclically, with residence in the joint typically not more than hours or days". Hylan G-F 20 is unique among viscosupplements marketed in the United States in that it is manufactured from two components (gel and fluid), both of which are chemically cross-linked.[2,8,9] The chemical composition leads to distinct physical properties (see Table I-4 below), distinct pharmacokinetics, and more convenient and cost-effective injection schedules.

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Table I-4. Comparison of the Physical Properties of Viscosupplementation Products†

	Molecular Weight (million daltons)	Elasticity Pa at 2.5 Hz	Viscosity Pa at 2.5 Hz
Osteoarthritic synovial fluid[11, 13]	1.9	1.9	1.4
Healthy, young synovial fluid[1, 20]	6*	117**	45**
SYNVISC and Synvisc-One (hylan G-F 20)[1, 2]	6	111	25
Hyalgan (sodium hyaluronate)[3, 16]	0.5-0.7	0.6	3
Supartz (sodium hyaluronate)[3, 19]	0.6-1.2	9	16
Orthovisc (high molecular weight hyaluronan)[11, 17]	1-2.9	60	46
Euflexxa (1% sodium hyaluronate)[3, 18]	2.4-3.6	92	37

† The clinical significance of these physical properties is unknown. * As in 21- to 45-year-olds ** As in 18- to 27-year-olds

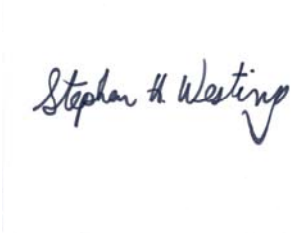
While a relatively short joint residence time is certainly accurate for low- to medium- Molecular Weight viscosupplements, joint residence time for the gel component of hylan G-F 20 exceeds 50 days.[10] This has important clinical implications as the longer residence of hylan G-F 20 is widely thought to result in the need for fewer intra-articular injections to achieve comparable long-term analgesic effects. In the case of Synvisc-One, a single 6 mL injection of hylan G-F 20 provides up to six months of pain relief for knee OA.[1,2]

Finally, in the HTA Draft Document section entitled "Is the technology cost effective?" SYNVISC treatment is incorrectly described as involving three to five injections. SYNVISC is a three injection treatment only. While not available in the VA system in 2008, Synvisc-One is missing from this section. By the convention used in your document it would seem appropriate to add a final bullet as follows (we charge the same for a kit of SYNVISC and Synvisc-One):

- Synvisc-One: $426 per course of treatment (one injection)

We appreciate the open line of communication you have established with us and look forward to meeting with members of the Health Technology Clinical Committee. If you have further questions after reviewing this information, please feel free to contact me at 435-640-9665 or by email at stephen.westing@genzyme.com. I look forward to our continued dialog.

Sincerely,



Stephen H. Westing, Dr.Med.Sc.
Senior Medical Science Liaison
Medical Affairs
Genzyme Biosurgery

Enclosures

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1. Chevalier X, Jerosch J, Goupille P, et al. Single, intra-articular treatment with 6 mL of hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: A randomised, multi-centre, double-blind, placebo-controlled trial (the SOUND trial). *Ann Rheum Dis* 2010;69:113-119.
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8. SYNVISC Prescribing Information. Genzyme Corporation, 2006.
9. Frampton JE. Hylan G-F 20 Single-Injection Formulation. *Drugs Aging* 2010;27:77-85.
10. Jackson DW, Simon TM. Intra-articular distribution and residence time of Hylan A and B: a study in the goat knee. *OA Cartilage* 2006;14:1248-1257.

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February 2, 2010

Denise Santoyo
Program Coordinator, Health Technology Assessment
Washington State Health Care Authority
676 Woodland Square Loop SE
P.O. Box 42712
Olympia, WA 98504-2712

Dear Ms. Santoyo:

Genzyme Medical Affairs recently became aware of a request for public comment regarding the Washington State Health Care Authority's interests in the viscosupplement class as used to treat pain associated with osteoarthritis (OA). We presuppose that you are considering a review of this class pursuant to a coverage decision or other policy update.

Genzyme is the manufacturer and marketer of a viscosupplement (VS) product with the generic name hylan G-F 20. It is sold in two forms: SYNVISC® (3 injections per course) and Synvisc-One® (1 injection per course). A course of VS therapy can provide up to 6 months of analgesia. Based on the considerable available evidence, we believe that these two products provide significant clinical and economic value to patients, health care providers, and payers.

We empathize that the clinical data surrounding the VS class is viewed by some as inconsistent, and is subject to skepticism. We would like to avail ourselves of the current opportunity for public comment to help you and your colleagues better understand the evidence in support of the class. As you can probably appreciate, we are most familiar with the data pertaining to our own product, and will devote a portion of this letter and package to describing for WA State HTA staff the highlights of the many investigations that have been done over an approximately 20-year period.

The indication currently approved by the US Food and Drug Administration (FDA) for all VS products can be summarized as treatment of pain due to OA of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics (e.g., acetaminophen). Clinical data described in this letter will be limited to that approved indication. Disease modification is not an approved indication for any OA product in the US. Nonetheless, since you inquired about it in the Policy Context, we will summarize available data for the class, most of which are preclinical.

We will of course address the four Key Questions you posted, as well as the Policy Context described in your communication of 1/20/2010. Combining these two sets of issues, the topics covered in this letter and package will include:

- Clinical Effectiveness in Knee OA
  - Symptoms
  - Disease Status
  - Comparative Effectiveness versus Other Presently Available Treatments
- Safety Profile
  - Adverse Events
  - Benefit-Risk Analysis
- Viscosupplements Are Recommended by Professional Societies
- Effectiveness in Special Populations
- Cost Effectiveness

For each topic, we will first discuss *class-level* data, then discuss data *specific to hylan G-F 20*.

Included in the package with this letter is an AMCP Dossier for SYNVISC and Synvisc-One. This document begins with a disease state overview, and more importantly is also an extensive compendium and summary of evidence supporting the clinical efficacy and safety profiles of both products. We invite you to review it completely to attain the broadest understanding of the data. Describing all its content is beyond the scope of this letter; however, it is an excellent reference and we will refer you to specific sections as highlights. The Dossier contains the following hylan G-F 20-related reprints: Kemper et al.; Waddell et al.; Wobig et al.; Chevalier et al.; Raman et al. FDA-approved full Prescribing Information for SYNVISC and Synvisc-One are found in the Dossier as well. It also includes Wang et al.; this is a class-level meta-analysis discussed herein. Additional reprints will be enclosed in this package as deemed appropriate for your review, and will be called out in the current letter.

Hylan G-F 20 is unique among VS in that it is manufactured from two components (gel and fluid), both of which are chemically cross-linked.[1-3] A diagram of the chemical structures of the components can be found in reference 3 [enclosed]. The chemical composition leads to distinct physical properties (see Table I-4 from Dossier below), distinct pharmacokinetics, separate J-codes from non-cross-linked products, and more convenient and cost-effective injection schedules. [Please see Dossier pgs. 15-18.] Please note that since the publication of this Dossier, the HCPCS codes for both hylan G-F 20 products have been updated to the same unique code (**J-7325**).

Page 23 of the Dossier contains a table summarizing for all FDA-approved VS the specifications, injection schedules, durations of analgesic effect per approved labeling, common adverse events, and contraindications.

Genzyme believes that it would be in the best interest of appropriate patients with osteoarthritis (OA) of the knee to have unrestricted access to all VS products, including coverage for repeat treatment for those products having repeat treatment information in their FDA-approved labeling. This includes both SYNVISC and Synvisc-One.[1,2]

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Table I-4. Comparison of the Physical Properties of Viscosupplementation Products†

	Molecular Weight (million daltons)	Elasticity Pa at 2.5 Hz	Viscosity Pa at 2.5 Hz
Osteoarthritic synovial fluid[11, 13]	1.9	1.9	1.4
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Supartz (sodium hyaluronate)[3, 19]	0.6-1.2	9	16
Orthovisc (high molecular weight hyaluronan)[11, 17]	1-2.9	60	46
Euflexxa (1% sodium hyaluronate)[3, 18]	2.4-3.6	92	37

† The clinical significance of these physical properties is unknown. * As in 21- to 45-year-olds ** As in 18- to 27-year-olds

Clinical Effectiveness in Knee OA

Symptoms (i.e., pain due to OA)

Viscosupplement Class

The VS class evidence contains clinical studies sponsored by manufacturers and used for regulatory approvals around the world. In addition, the literature also contains smaller scale investigator-sponsored and independent studies that were not designed or powered for regulatory approvals. Some are preliminary or exploratory studies. Adding to the complexity, some of the regulatory trials met only the standard for approval of a device in Europe, a less rigorous standard than for a drug in Europe or even a Class III Medical Device in the US (the current FDA designation for VS).

Published literature for the VS class also includes systematic reviews and meta-analyses. Such analyses have often been considered by policy-makers during their evaluation of the class. However, further complexity is introduced into the literature by the different methodological approaches used by the authors of the meta-analyses, which has sometimes resulted in different conclusions.

The heterogeneity in the sizes, designs and degree of rigor among these published (and sometimes unpublished) trials has led to understandable confusion when attempting to interpret this literature, especially since meta-analyses of the class typically tried to be inclusive. Given the challenges involved in conducting clinical trials, and the large placebo effects observed in VS studies,[4] such heterogeneity is to be expected. Inclusion of some of the smaller and less rigorous trials has resulted in a diminution in the calculated treatment effect or effect size of the class, especially when regulatory trials of SYNVISC were excluded from the analysis. Also understandably, confusion has resulted from the sometimes varying conclusions of the different meta-analyses. This topic is covered in pgs. 26-28 and 100-102 of the Dossier.

Our first major point is this: **The more rigorous and more inclusive meta-analyses of the VS class have concluded that it is effective for the treatment of osteoarthritis pain.** Such analyses include a Cochrane Review[5] and an analysis published in a higher tier orthopaedic

journal, the *Journal of Bone and Joint Surgery (US)* [included with Dossier].[6] The methods and findings of these two publications, both of which were independent of industry, are described in some detail in the Dossier on pgs. 69-77. Briefly, the Cochrane Review [Bellamy et al.] exhaustively split out the various time point ranges and individual outcome measures. In contrast, Wang and colleagues[6] combined outcomes related to three categories: pain on motion, pain at rest, functionality. These authors also were able to pool results from different time points by normalizing to percent differences from the control group summed across the study observation period (e.g., % summed pain intensity difference). Notwithstanding the methodology differences, both sets of authors concluded that their analysis supported the use of VS to treat OA patients.

As a reference point, the Forest plot from the Wang et al. paper[6] for pain intensity differences is shown below. The individual studies included are shown in order of increasing quality score. The trial heterogeneity and variability in treatment effect can be seen; nonetheless, the pooled HA results are significantly better than for "placebo" (saline control), ranging from 8-13% *delta*.

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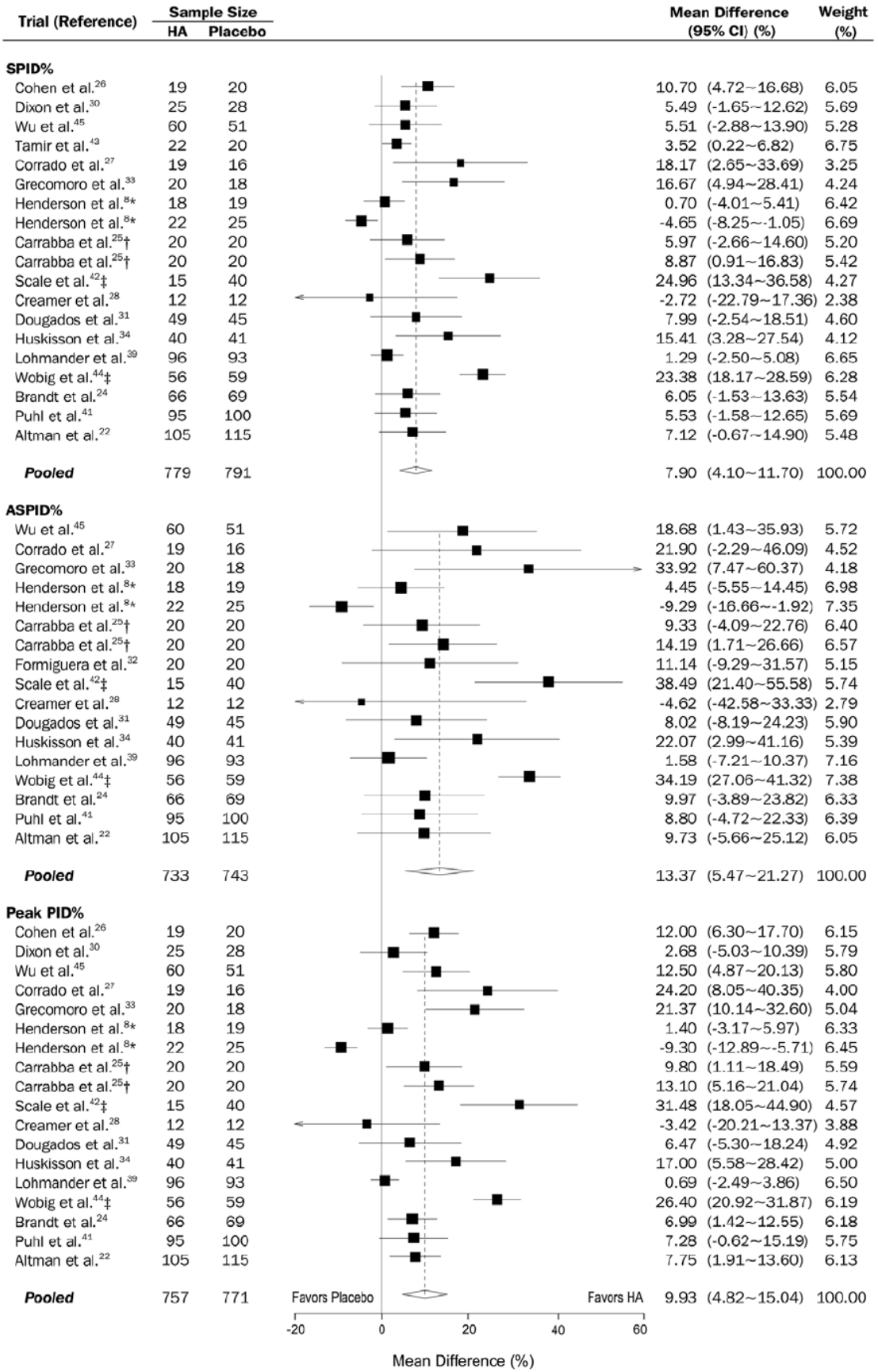
Trial (Reference)
Sample Size
HA
Placebo
Mean Difference (95% CI) (%)
Weight (%)
SPID%
Cohen et al.[26] 19 20 10.70 (4.72~16.68) 6.05
Dixon et al.[30] 25 28 5.49 (-1.65~12.62) 5.69
Wu et al.[45] 60 51 5.51 (-2.88~13.90) 5.28
Tamir et al.[43] 22 20 3.52 (0.22~6.82) 6.75
Corrado et al.[27] 19 16 18.17 (2.65~33.69) 3.25
Grecomoro et al.[33] 20 18 16.67 (4.94~28.41) 4.24
Henderson et al.[8]* 18 19 0.70 (-4.01~5.41) 6.42
Henderson et al.[8]* 22 25 -4.65 (-8.25~-1.05) 6.69
Carrabba et al.[25]† 20 20 5.97 (-2.66~14.60) 5.20
Carrabba et al.[25]† 20 20 8.87 (0.91~16.83) 5.42
Scale et al.[42]‡ 15 40 24.96 (13.34~36.58) 4.27
Creamer et al.[28] 12 12 -2.72 (-22.79~17.36) 2.38
Dougados et al.[31] 49 45 7.99 (-2.54~18.51) 4.60
Huskisson et al.[34] 40 41 15.41 (3.28~27.54) 4.12
Lohmander et al.[39] 96 93 1.29 (-2.50~5.08) 6.65
Wobig et al.[44]‡ 56 59 23.38 (18.17~28.59) 6.28
Brandt et al.[24] 66 69 6.05 (-1.53~13.63) 5.54
Puhl et al.[41] 95 100 5.53 (-1.58~12.65) 5.69
Altman et al.[22] 105 115 7.12 (-0.67~14.90) 5.48
Pooled 779 791 7.90 (4.10~11.70) 100.00
ASPID%
Wu et al.[45] 60 51 18.68 (1.43~35.93) 5.72
Corrado et al.[27] 19 16 21.90 (-2.29~46.09) 4.52
Grecomoro et al.[33] 20 18 33.92 (7.47~60.37) 4.18
Henderson et al.[8]* 18 19 4.45 (-5.55~14.45) 6.98
Henderson et al.[8]* 22 25 -9.29 (-16.66~-1.92) 7.35
Carrabba et al.[25]† 20 20 9.33 (-4.09~22.76) 6.40
Carrabba et al.[25]† 20 20 14.19 (1.71~26.66) 6.57
Formiguera et al.[32] 20 20 11.14 (-9.29~31.57) 5.15
Scale et al.[42]‡ 15 40 38.49 (21.40~55.58) 5.74
Creamer et al.[28] 12 12 -4.62 (-42.58~33.33) 2.79
Dougados et al.[31] 49 45 8.02 (-8.19~24.23) 5.90
Huskisson et al.[34] 40 41 22.07 (2.99~41.16) 5.39
Lohmander et al.[39] 96 93 1.58 (-7.21~10.37) 7.16
Wobig et al.[44]‡ 56 59 34.19 (27.06~41.32) 7.38
Brandt et al.[24] 66 69 9.97 (-3.89~23.82) 6.33
Puhl et al.[41] 95 100 8.80 (-4.72~22.33) 6.39
Altman et al.[22] 105 115 9.73 (-5.66~25.12) 6.05
Pooled 733 743 13.37 (5.47~21.27) 100.00
Peak PID%
Cohen et al.[26] 19 20 12.00 (6.30~17.70) 6.15
Dixon et al.[30] 25 28 2.68 (-5.03~10.39) 5.79
Wu et al.[45] 60 51 12.50 (4.87~20.13) 5.80
Corrado et al.[27] 19 16 24.20 (8.05~40.35) 4.00
Grecomoro et al.[33] 20 18 21.37 (10.14~32.60) 5.04
Henderson et al.[8]* 18 19 1.40 (-3.17~5.97) 6.33
Henderson et al.[8]* 22 25 -9.30 (-12.89~-5.71) 6.45
Carrabba et al.[25]† 20 20 9.80 (1.11~18.49) 5.59
Carrabba et al.[25]† 20 20 13.10 (5.16~21.04) 5.74
Scale et al.[42]‡ 15 40 31.48 (18.05~44.90) 4.57
Creamer et al.[28] 12 12 -3.42 (-20.21~13.37) 3.88
Dougados et al.[31] 49 45 6.47 (-5.30~18.24) 4.92
Huskisson et al.[34] 40 41 17.00 (5.58~28.42) 5.00
Lohmander et al.[39] 96 93 0.69 (-2.49~3.86) 6.50
Wobig et al.[44]‡ 56 59 26.40 (20.92~31.87) 6.19
Brandt et al.[24] 66 69 6.99 (1.42~12.55) 6.18
Puhl et al.[41] 95 100 7.28 (-0.62~15.19) 5.75
Altman et al.[22] 105 115 7.75 (1.91~13.60) 6.13
Pooled 757 771 9.93 (4.82~15.04) 100.00
Favors Placebo
Favors HA
-20
0
20
40
60
Mean Difference (%)

Fortunately, two more recent publications addressed directly the variance in analytical techniques, and help to provide better clarity. The first was by Divine et al. [enclosed].[7] These authors analyzed and compared multiple VS vs. "placebo" meta-analyses. They noted that each meta-analysis used different search strategies, study selection criteria, data collection and pooling methods, and quality assessment and statistical methods, but that each analysis employed reasonable and scientifically sound methods. Divine et al. noted that despite these differences, "when the strictest quality tools and interpretation of the heterogeneity are used, Level 1 evidence demonstrates that the use of HA [hyaluronic acid] in patients with OA results in modest improvement in validated outcomes…" Their overall summary was:

> **The question that the clinician faces is whether HA should be used for the treatment of their patients. They need to determine if the results of the meta-analyses can be applied to their specific patient population and if the benefits outweigh the risks and the costs. In addition, physicians must decide how and when to use HA as a treatment alternative in their armamentarium. Based upon this systemic review, we conclude that although they differ in several methods for determining individual trial quality, each of the five meta analyses presented offer scientifically sound Level 1 evidence to support the efficacy of HA use in select patients with OA.**

The second of the two articles focused specifically on how the differences in the meta-analysis methods could have led to the different results and/or interpretations, and is beyond the scope of this letter.[8]

Based on review of the class-level clinical data, the reasonable conclusion is that the VS class provided inconsistent yet moderate analgesic and functional effects in OA patients. Considering that these are aggregate data, policy makers should keep in mind that individual patients treated with SYNVISC have experienced large improvements from baseline.[1-3,9] In fact, analysis of individual patient data from a large pragmatic trial of SYNVISC added to usual care found that the addition of the VS to usual care resulted in faster onset of a low-intensity symptom state (i.e., a "patient acceptable symptom state"), and longer duration of low-intensity symptom states.[10] These types of data argue strongly in favor of patient access to the VS class, despite the inconsistency among trials.

Hylan G-F 20

The bibliography of published clinical trial data for hylan G-F in knee OA is robust (see Dossier p. 32). The seven registration trials for SYNVISC efficacy included controlled studies vs. intra-articular saline, arthrocentesis, 2 injections of hylan G-F 20, Supartz® (sodium hyaluronate), Healon® (non-inflammatory fraction of sodium hyaluronate; not currently marketed), denatured hylan, and non-steroidal anti-inflammatory drugs (NSAIDs).[1] SYNVISC was found consistently superior to saline control and at least as good as NSAID therapy with fewer GI side effects in these trials. Published post-marketing studies included data vs. the following active controls: intra-articular triamcinolone hexacetonide, usual care, diclofenac, physical therapy, Supartz, Hyalgan® (sodium hyaluronate), Orthovisc® (high molecular weight hyaluronan), Euflexxa® (1% sodium hyaluronate), Ostenil® (sodium hyaluronate 1%; not approved in US), Adant (not approved in US), Suplasyn® (sodium hyaluronate; not approved in US), and SYNVISC plus lavage. **We are unaware of any published prospective clinical trial demonstrating that another VS had statistically superior efficacy to SYNVISC or Synvisc-One.** Uncontrolled studies of SYNVISC, both pre- and post-marketing, have been published as well. Highlights of all these data can be found in the Dossier on pgs. 5-6, 30, 33-34, 36-68, 80-88, and 92-99.

Our clinical advisors reinforce observations in the medical literature which suggest that pain on motion is a hallmark symptom of early to moderate stage OA. In the product-specific text of the Cochrane Review, the authors pooled the pain on motion 100 mm visual analog scale (VAS) data for SYNVISC and stated (emphasis supplied):[5]

> …At 14 to 26 weeks postinjection, there was a statistically significant difference in favour of Hylan G-F 20 compared to placebo (**WMD** (random-effects model) **-20.70**; 95% CI -35.56 to -5.83, P value 0.006) (Karlsson 2002b (SvP); Scale 1994a (2 inj); Scale 1994b (3 inj);Wobig 1998). Hylan G-F 20 was 1 to 49% more effective than placebo.
>
> *[Note from Genzyme: WMD stands for weighted mean difference, defined as the pooled difference between the active treatment (in this case SYNVISC) and the control group, weighted by trial N. A negative value favors active treatment.]*

Wang and coworkers noticed that the treatment effect of SYNVISC vs. placebo appeared larger than for the non-cross–linked VS products. They therefore did a secondary analysis. Their suspicion was confirmed, and the paper noted the findings as follows (emphasis supplied):[6]

> The trials involving cross-linked hyaluronic acid had much greater pooled mean differences than did those involving non-cross-linked hyaluronic acid (**pain with activities: 23.6%** compared with 5.4% for SPID%, **34.8%** compared with 8.7% for ASPID%, and **27.1%** compared with 7.4% for peak PID%; function: **21.9%** compared with 5.3% for SFID%, **38.3%** compared with 11.7% for ASFID%, and **26.8%** compared with 8.2% for peak FID%). However, there was significant between-study heterogeneity in the estimates of hyaluronic acid efficacy among the trials involving non-cross-linked hyaluronic acid ($p \leq 0.1$, chi-square test) (see Appendix).

These observations were confirmed indirectly by an earlier VS class meta-analysis published by Lo et al. in *JAMA*.[11] The authors found that the effect size (a unitless metric defined as the difference from control group divided by the control group or overall standard deviation) of the VS class was decreased from 0.32 to 0.19 when the SYNVISC vs. saline trials, which were considered outliers by these authors, were removed. (Please see Dossier pgs. 78-79 and 101.)

The findings of Lo et al. and Wang et al. were confirmed in a subsequent meta-analysis by Reichenbach and colleagues.[12] Unlike all prior VS class meta-analyses, these authors focused mainly on data from direct, head-to-head trials of VS vs. VS. However, they also performed a novel "indirect" analysis of SYNVISC-placebo trials vs. non-cross–linked VS/placebo trials. Reichenbach et al. observed a moderate effect size in the indirect comparisons vs. placebo of **-0.64 standard deviations in favor of Synvisc**, which was statistically significant (95% confidence interval around the difference = -1.25 to -0.02). (See "Figure 4" from the paper below.) They also found a **-0.27 effect size favoring SYNVISC** in the analysis of the direct comparisons; however, this difference barely missed statistical significance. Based on the latter observation only, the authors interpreted their findings to recommend that there was no rationale to use SYNVISC, given its higher price in Switzerland. However, based on the totality of the evidence described above, and the fact that their findings all directionally favored SYNVISC, we believe their conclusion to be unjustified.

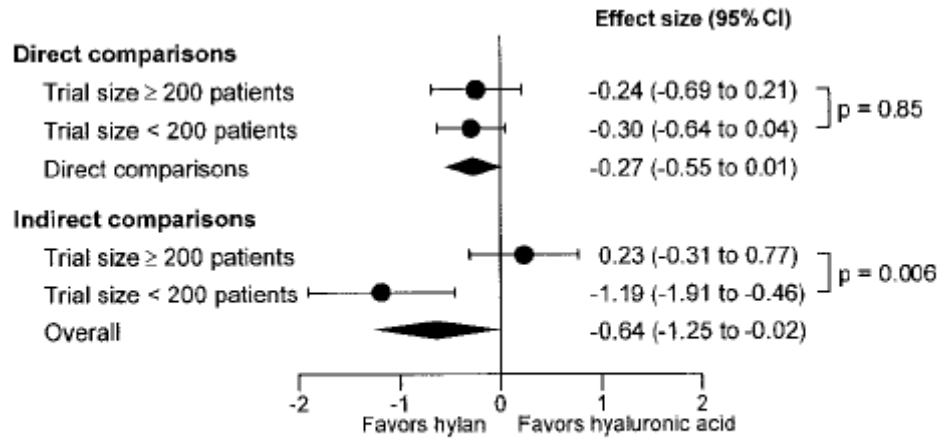

Figure 4. Comparison of meta-analyses of direct and indirect comparisons. 95% CI = 95% confidence interval.

Synvisc-One is a newly launched product, the evidence at this point including two studies—a dose-finding pilot trial, and a well-controlled pivotal trial vs. saline control. The latter found a clinically meaningful improvement from baseline which was maintained over 26 weeks and was statistically significant vs. the control group in the primary outcome measure plus several secondary variables.[2,3,13] These clinical outcomes were provided with the advantage of a single-dose administration schedule.[13]

To summarize this sub-section, a substantial bibliography of both registration and post-marketing studies have established and confirmed the clinical efficacy of hylan G-F 20 in the treatment of knee OA for up to 26 weeks. Independent meta-analyses have noted that the treatment effect of SYNVISC appears to be larger than for non-cross–linked VS.

Disease Status

Viscosupplement Class

As discussed earlier, disease modification is not approved labeling for any VS in the US. However, there is evidence, mostly preclinical, to suggest a so-called disease modifying OA drug (DMOAD) effect for VS. This evidence was reviewed in total most recently by rheumatologist Larry Moreland and orthopaedic surgeons Victor Goldberg and Jodi Buckwalter.[14,15] Briefly, numerous groups of researchers have found in animal models of OA that joint structure, especially cartilage integrity, are significantly preserved in groups of animals treated with VS compared with controls. Animals models have mostly been surgical (ligament transection or meniscal damage), and have involved multiple species with histology observations. Various investigators have observed an inhibitory effect on matrix metalloproteinases and other enzymes which break down cartilage matrix, which could be the basis for the histology findings. Please see references 14 and 15 for more details and for bibliographies of the primary research.

In addition, two clinical trials have been published regarding a potential DMOAD effect for Hyalgan in human OA patients. In one, the outcome measure was arthroscopic visualization of

cartilage surface changes [Frizziero et al. 2002]. In the other, the outcome measure was joint space width via plain X-rays [Jubb et al. 2003]. Both of these studies were noted by experts that have consulted with Genzyme to have methodology challenges, which is why we await more definitive controlled trials using MRI. Nonetheless, this work has been published in peer-reviewed journals and was discussed in the Goldberg and Buckwalter review, to which the reader is referred.[15]

Hylan G-F 20

Included in the reviews mentioned above is a SYNVISC-specific animal study in a dog ligament transection model of OA. Cartilage structure was better preserved in knees that had been treated with SYNVISC [enclosed].[16] A slightly earlier study performed in a rabbit surgical model of OA had similar findings, and additionally noted that the animals had better results with SYNVISC than with a lower molecular weight VS [enclosed].[17] Genzyme scientists recently presented SYNVISC data from a similar rabbit model (since submitted for publication) [enclosed].[18]

More currently, we have become aware of an independent, small controlled clinical study in which MRI was used to assess cartilage integrity in human OA patients treated with SYNVISC. The website for the Arthroscopy Association of North America (AANA) (www.aana.org) shows that a podium presentation is scheduled for Friday May 21 at its 2010 Annual Meeting in Hollywood, FL. The presenting author's name is Stephen Hall, M.D. We are eager to see these results as the senior author Dr. Cicuttini is a well-known expert in the field of quantitative MRI.

Comparative Effectiveness versus Other Presently Available Treatments

Viscosupplement Class

Effect size, described above, is a statistical calculation sometimes used to compare different types of treatments. The drawback is that it is a function of both treatment effect and sample size. Nonetheless, it may be useful to address your question of relative efficacy of the VS class in the context of other available therapies.

The mainstays of pharmacologic treatment of OA are acetaminophen and oral NSAIDs. The recent OARSI expert consensus Guidelines for the treatment of OA of the knee and hip noted an effect size of **0.32** (moderate) for the NSAID/cyclo-oxygenase-2-selective (COX-2) inhibitor class and 0.21 for acetaminophen.[19] The effect size that they cite for the VS class is exactly the same as that of NSAIDs: **0.32**.[19] These effect sizes are consistent with results of head-to-head studies of VS and NSAIDs we are familiar with—they have shown the VS to be at least as efficacious as the NSAID.

Physicians will also treat inflammatory episodes of OA with an intra-articular corticosteroid. These agents can have treatment effects similar to those of VS; however, they are known to have a much *shorter duration of action*, and concerns have been expressed about the possible risk of cartilage damage with long-term repeated use.[20-21]

Hylan G-F 20

As mentioned above, the published literature for SYNVISC includes a registration trial and a post-marketing study vs. NSAIDs. In both cases, SYNVISC was found to be at least as effective as the NSAID. These studies are discussed on p. 86 of the Dossier.

SYNVISC has also been specifically studied vs. intra-articular corticosteroid. These trials are summarized on pgs. 84-85 of the Dossier. The Caborn et al. study exemplifies the class-level meta-analysis cited above in that SYNVISC was shown to have more durable efficacy than triamcinolone hexacetonide. Please see pages 48-51 of the Dossier for details.

Safety Profile

Adverse Events

Viscosupplement Class

Hyaluronan-based VS products are local treatments for knee OA. All are polymer biomaterials sourced from bacterial fermentation (Euflexxa and Orthovisc) or chicken combs (all other FDA-approved VS).

The vast majority of adverse events (AEs) occurring in trials and clinical use are localized to the injected knee. Perusal of the FDA-approved Prescribing Information for VS products will quickly confirm this fact. There are rare systemic AEs, mostly allergic reactions, which reach the status of anaphylactoid-type reactions even more rarely. Such events have been described in the Prescribing Information for Hyalgan and Supartz.

The safety profile of the VS class has been reviewed by Adams et al.[22] and by Peterson and Hodler.[23] In these reviews, the authors explain that the most commonly occurring local AEs consist of injection site pain, and pain and/or swelling in the injected joint. It is often difficult to discern these events from exacerbations of the disease state, since these are also symptoms of OA. Investigators typically use temporal association as a guide, since HA, especially non-cross-linked, is cleared from the joint space relatively quickly. Local AEs occurring more than a week post-injection are often considered unrelated.

Local AE information from FDA-approved Prescribing Information for multi-injection VS is summarized in the following table. It can be readily seen that the descriptions of local events occurring most frequently are similar among products, as are the incidences. (See also p. 23 of the Dossier.)

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	SYNVISC® (hylan G-F 20)	Hyalgan® (sodium hyaluronate)[2]	Supartz® (sodium hyaluronate)[3]	Orthovisc® (high molecular weight hyaluronan)[4]	Euflexxa™ (1% sodium hyaluronate)[5]
Molecular weight (daltons)	6,000,000	500,000-730,000	620,000-1,700,000	1,000,000-2,900,000	2,400,000-3,600,000
Directions for use	3 injections; 1 week apart	3-5 injections; 1 week apart	3-5 injections; 1 week apart	3-4 injections; 1 week apart	3 injections; 1 week apart
Selected local adverse events (all causes, % of patients)	Knee pain and/or swelling: 7.2% (2.2% of injections)	Injection site pain: 23% Local joint pain and swelling: 13%	Arthralgia: 17.8% Injection site reaction: 5.7%* Injection site pain: 4.2%	Arthralgia: 12.6% Injection site pain: 2.5% Joint swelling: 0.7% Joint effusion: 0.4% Injection site edema: 0.9%	Multicenter study†: Arthralgia: 8.8% Joint effusion: 0.6% Joint swelling: 1.9% Single-center study: Knee pain: 53% Knee swelling: 3%
Number of patients in safety population	511 patients	164 patients	619 patients	562 patients	Multicenter study: 160 patients Single-center study: 25 patients

As has been described in the Adams and Peterson/Hodler reviews and the products' Prescribing Information, the local adverse events are usually mild-to-moderate in nature, and usually resolve on their own without intervention. Occasionally, conservative measures such as rest, ice, and NSAIDs are required. More rarely, a larger effusion can occur which typically responds well to aspiration and intra-articular injection of a corticosteroid.[24]

To our knowledge, there has never been a case of septic arthritis directly attributed to a contaminated lot of VS product. The few existing case reports of post-VS sepsis have been associated with poor aseptic injection technique on the part of the provider.

Hylan G-F 20

The specific safety profiles for SYNVISC and Synvisc-One for knee OA are explained in great detail in the Dossier on pgs. 5-6, 18-21, 56-58, 66-68, 91, 97-100. Qualitatively, the types of events observed are consistent with those described above for the class.

The major distinction between the AE profiles for SYNVISC and Synvisc-One is that for SYNVISC, there is an approximately 3-fold increase in the risk of a local AE when going from a first to a repeat course, whereas for Synvisc-One, no such increase is observed.[1,2]

The reason for the increased incidence of repeat local AEs with SYNVISC in unknown. A summary of the data from the prescribing information:

% of patients	**1st Course**	**2nd Course**
Synvisc-One: Device-related adverse events in injected knee[2]	5.7%	5.2%
SYNVISC: Local pain and/or swelling in injected knee (related & not)[1]	7.2%	22.3%

It is important to keep in mind that the events listed in the above table for SYNVISC include **all causes and the entire range of severity**. For Synvisc-One, the table shows related events and the entire range of severity observed in the pivotal trial. For Synvisc-One, the pivotal trial investigators recorded only mild and moderate local AEs, none of which were serious. Since Genzyme has been maintaining a safety database for hylan G-F 20, the spontaneous reporting rate for local AEs has been very low and stable across time.[25]

Benefit-Risk Analysis

Viscosupplement Class

Considering that OA is a disease of pain and disability, and is not life-threatening, extreme risks in exchange for clinical improvements are not well accepted by the medical community.

Bellamy et al. state in the Cochrane Review of the VS Class:

> …HA products generally appear superior to placebo on multiple efficacy variables, providing support for the use of those HA products for which the effect is not only statistically significant but also clinically important. These benefits appear to be achievable without attributable systemic adverse events but with occasional local reactions which tend, for the most part, to be relatively transient, resolving without sequelae either spontaneously or with simple intervention. It should be noted that this review is not the premier source of safety data, since sample sizes are relatively small in the trials reported, particularly for detecting less frequent or even rare adverse events. Readers are referred to the general literature and the surveillance literature for a more comprehensive appreciation of safety issues. Nevertheless, based on the evidence reviewed, HA products appear in general to be safe.[5]

There has been ongoing and recent controversy and acute interest surrounding systemic AEs for the widely used systemic medications to treat OA: acetaminophen and NSAIDs/COX-2 inhibitors. Although VIOXX® (rofecoxib) and BEXTRA® (valdecoxib) have been removed from the market, concerns remain about CELEBREX® (celecoxib).[19,26] Systemic AEs of note include: acetaminophen (liver toxicity), non-selective (ns) NSAIDs (gastric ulceration/perforation; lower GI effects; cardiovascular and renal effects), and CELEBREX (myocardial infarctions, other cardiovascular and renal AEs).[19,26] The American College of Rheumatology urges caution in the use of both ns-NSAIDs and CELEBREX.[26] Patients with risk factors for NSAID or acetaminophen toxicity need to consider other options with more acceptable safety profiles.

Accepting that there is currently no approved DMOAD in the US, all treatments for OA are thus for signs and symptoms. There are few hugely effective options except total joint replacement (a last resort), and OA is a chronic progressive disease. It follows that a desirable benefit-to-risk profile would include low or non-existent risk of serious systemic toxicity. The safety profile of the VS class, i.e., largely benign local events, fits well with this desirable benefit-risk equation.[24,27] This class should be considered for patients with NSAID risk factors, patients who do not wish to take or would have adherence issues with chronic oral medications, and patients who have failed NSAIDs/CELEBREX and who are not candidates for repeated corticosteroids (e.g., diabetics) or total knee arthroplasty.[27]

Please also see pgs. 25-26 of the Dossier.

Hylan G-F 20

Since SYNVISC and Synvisc-One are members of the VS class and have the same safety profile, all the statements and reasoning above related to the class applies equally to hylan G-F 20 products.

In fact, pre- and post-marketing studies have shown that SYNVISC use can lead to *reduced* utilization of the more systemically toxic NSAID class because pain in the locally treated knee is well controlled.[28,29]

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Viscosupplements Are Recommended by Professional Societies

The expert consensus guidelines for the treatment of knee OA from the following societies include VS:

- The American Pain Society
- The European League Against Rheumatism
- The Osteoarthritis Research Society International
- The American College of Rheumatology

Inclusion in such guidelines provides independent validation by non-industry experts. Please see pgs. 25-26 and related references in the Dossier.

Please note that since the Dossier was published, the American College of Rheumatology announced an update to their OA treatment guidelines at their 2009 Annual Meeting. The update still includes VS therapy. The manuscript has been submitted for publication; in the interim, the presentation made at the meeting has been posted on the ACR website (www.rheumatology.org).

The American Academy of Orthopaedic Surgeons recently updated their OA treatment guidelines, and therein changed their endorsement of VS to a category of "can recommend neither for nor against" VS therapy. This was not based on a new independent review by AAOS leadership, but rather a negative interpretation of the VS class review done by a US government agency, the Agency for Healthcare Research and Quality [found on the websites for each respective organization]. As we have communicated to AHRQ, its analysis was based solely on a systematic review of VS vs. placebo meta-analyses, much like the Divine et al. review discussed above. However, AHRQ had a less favorable conclusion from the class meta-analyses, potentially because they did not consider other evidence such as uncontrolled studies and studies vs. active control groups such as corticosteroids, usual care, and NSAIDs. (Please see p. 28 of the Dossier.) We have been in touch with AAOS about their reliance on the AHRQ report, and they have indicated to us that they are in the process of revising the guideline regarding VS based on their own independent review of the literature.

SUMMARY OF GENZYME CONCERNS RE VS SECTION OF AHRQ EVIDENCE REPORT ON TREATMENT OF KNEE OA

- Based solely on a systematic review of VS vs. placebo meta-analyses
- Did not consider evidence from other types of studies, such as
  - trials vs. corticosteroids
  - trials vs. usual care
  - trials vs. NSAIDs
  - HRQoL studies
  - cohort & other observational studies
  - other uncontrolled prospective trials
- Did not account for the fact that some of the meta-analyses reviewed excluded SYNVISC trials
- Did not account for heterogeneity in trial endpoints, observation periods, and sponsors who did not perform intent-to-treat (ITT) analyses
- The conclusions are more negative than the aggregated data would suggest, and do not convey much of the complexity and nuance contained in the body of the report
- Has the potential to narrow the already limited non-surgical treatment options for knee OA patients

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Effectiveness in Special Populations

Viscosupplement Class

To our knowledge, no group has published a class-level analysis of potential heterogeneity in response to VS by special population.

One of the class meta-analyses has made general statements about this topic.

Wang et al. noted: "We found that the patients who were older than sixty-five years of age and those with the most advanced radiographic stage of osteoarthritis (complete loss of joint space) were less likely to benefit from intra-articular injection of hyaluronic acid. Understanding the differences in hyaluronic acid efficacy among different patient populations is important when selecting patients for this therapy."[6]

We are not sure about the basis for the age group remark by these authors. Per approved labeling, pivotal clinical trials for approved VS included patient age ranges of:

- Synvisc-One: 42-83
- Hyalgan: 41-90

For those products not including age ranges in their labels, the mean ages of trial participants were:

- SYNVISC: 62, 60, 63
- Supartz: 62, 65, 64, 62, 59, 61
- Orthovisc: 65, 59, 59
- Euflexxa: 63

To our knowledge, there are no publications that have definitively proven that older patients or patients with advanced radiographic have a reduced VS analgesic effect. Inclusion in Synvisc-One and Hyalgan pivotal trials of patients as old as 83 or 90 suggests this would not be the case. In addition, we are unaware of any published study in which the authors have been able to predict, via demographic factors alone, which patients will respond to VS.

Hylan G-F 20

The Prescribing Information for hylan G-F 20 products is silent on the issue of special populations. No diminution in effect or safety issues were found to be associated with any special population.[25]

In fact, two of the registration trials for SYNVISC found that patients responded equally well regardless of X-ray grade, a surrogate for disease severity.[28,33]

A large, clinical practice-based post-marketing study included a secondary analysis of potential predictive factors for short-term effectiveness. The authors found that the following factors were associated with a higher likelihood of response: being underweight, male gender, shorter time since diagnosis, and severe baseline pain.[30] In a study of potential factors associated with long-term effectiveness, the authors stated: "Factors significantly ($P < 0.05$) associated with a good

outcome were a moderate effusion, injection lateral to the patella, joint space loss in a single compartment, and radiological meniscal calcinosis."[31]

All the above findings were from hypothesis-generating analyses and would need to be confirmed in an appropriate prospective study.

Cost Effectiveness

Viscosupplement Class

The cost-effectiveness of the VS class has been reviewed by Waddell.[32] In general, VS products relieve pain, and the cost to the healthcare system includes the acquisition price for the product, the cost of the diagnostic and treatment office visits, the cost of the injection procedure(s), and costs for treatment of any AEs. Potential offsets to these costs include reduction in use of other treatments for OA of the knee (e.g., systemic and topical NSAIDs, arthroscopy, arthroplasty), associated reduction in costs of follow-up visits for treatment failures (e.g. NSAID turnover, revision arthroplasty) and systemic AEs, and reduced costs for treatment of systemic AEs (e.g., GI and cardiovascular events, infections, thrombi/emboli, etc.).

Dr. Waddell summarized his analysis as follows:

> "The cost effectiveness of intra-articular hyaluronan has been demonstrated, but only in a limited number of studies. Cost savings with intra-articular hyaluronan can also be realised with reduction of NSAID medication use and the possibility of delaying total knee replacement, which can reduce the need for costly revision procedures. Because different intra-articular hyaluronan formulations require different numbers of injections and office visits, are associated with variable treatment costs, and provide varying degrees of efficacy, not all intra-articular hyaluronan formulations may be equally cost effective over time."[32]

Hylan G-F 20

Genzyme's economic and value analyses related to SYNVISC and Synvisc-One are found in Sections III and IV of the Dossier, pgs. 118-130. Total costs to the health care system to achieve 6 months of analgesia with each of the approved VS are summarized in Figure III-2 on page 122. Total costs are found to be lower with SYNVISC and Synvisc-One.

The following is a brief summary of those sections of the Dossier. Please note that the citation numbers here refer to references contained in Dossier Section V.

Osteoarthritis of the knee and its accompanying disability are associated with substantial public health burden – both in terms of personal suffering and use of health resources (4). Direct medical costs associated with disability due to osteoarthritis of the knee include surgical procedures, visits to health care providers, diagnostic procedures, physical therapy, pharmacologic therapy and intra-articular therapy (33,69,78,88). Indirect costs such as time lost from employment and unpaid informal care provided by family or friends also account for a substantial portion of the economic burden associated with osteoarthritis of the knee (87).

Viscosupplementation with SYNVISC is associated with significant improvements in pain, quality of life, activity, and function relative to other treatments (e.g., NSAIDs and intra-articular steroids). Several studies have reported substantial reductions in the use of corticosteroid intra-articular injections, NSAIDs and their associated complications, analgesics, physical therapy,

and assistive devices in patients receiving Synvisc (37, 42, 44, 47, 49). Additionally, SYNVISC may delay the need for total knee replacement in patients who were candidates for this surgery (56-58). A major potential medical and economic benefit of treatment with SYNVISC is that the delay of an index procedure could avoid the need for a revision during a patient's lifetime. Revision knee replacements are associated with greater complication rates than index surgeries.

Several studies have evaluated the economic impact of SYNVISC. Among them, Waddell and Bricker evaluated the costs of SYNVISC therapy relative to the costs of treatment without SYNVISC over a three year period. They found that costs were substantially reduced with SYNVISC treatment due to the expected reductions in total knee replacements (TKR). The average cost per knee to delay TKR by a median of 2.1 years was $1,419.76 (56). Also, Torrance et al conducted an economic analysis of usual care plus SYNVISC compared to usual care alone. They found that although SYNVISC was associated with additional costs over appropriate care, these costs were diffused by significant improvements in pain and health related quality of life with SYNVISC. The resulting incremental cost-effectiveness ratio of $10,000 per quality adjusted life year (QALY) gained falls into the decision sector of "strong evidence for adoption" under widely accepted guidelines (146).

In addition, with the arrival of Synvisc-One to the US market, there is opportunity for further cost savings through fewer injection and office visit claims.

Summary

- Despite heterogeneity among meta-analyses, products and individual clinical trials, VS have in the aggregate been shown to be effective in reducing pain and improving function in patients with knee OA.
- The pivotal clinical trials for SYNVISC and Synvisc-One have consistently shown evidence of clinically-meaningful efficacy. In particular, the observed pooled treatment effect for SYNVISC has been shown to be greater than that for pooled non-cross-linked viscosupplements on the US market.
- No DMOAD is currently FDA approved. Preclinical evidence for both hylan G-F 20 and other VS agents suggests the ability to protect cartilage in OA, potentially through inhibition of catabolic enzyme activity.
- VS products, in the aggregate, have a similar effect size for relief of OA pain to NSAIDs as a class.
- VS products have a safer systemic toxicity profile than ns-NSAIDs and CELEBREX. There are rare systemic allergic reactions, mostly in the form of rashes. Local AEs associated with use of VS consist of local injection site reactions, and pain and/or swelling within the injected knee. These events typically are mild to moderate and resolve with no or minimal intervention. More severe events consist of swelling and associated pain; these events usually resolve with aspiration of the effusion, potentially along with rest, icing, and intra-articular corticosteroid. The GI, cardiovascular and renal AEs than can occur with NSAIDs and CELEBREX do not happen with VS. It would benefit patients to consider VS products for those who have failed NSAID therapy or who have risk factors for it, especially when such patients are not candidates for intra-articular corticosteroids or total knee arthroplasty.
- Hylan G-F 20 products have a similar overall safety profile to other VS products.

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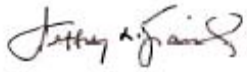
- Multiple professional societies include VS in their current OA treatment guidelines.
- Neither registration trials nor post-marketing studies have revealed any substantial variance in the efficacy or safety profiles of VS products in special populations. There are certain demographic characteristics that have been associated with VS effect/lack of effect; however these factors need to be tested in controlled trials.
- Viscosupplements benefit society by reducing pain and improving mobility in appropriate patients, with a cost per QALY-gained well within acceptable guidelines.
- Among US VS, total system costs to achieve 6 months of analgesia are lowest with SYNVISC and Synvisc-One.
- SYNVISC in particular has been shown to delay the decision to have total knee arthroplasty, which could benefit society in the long run.
- Synvisc-One is the only single-injection VS product currently approved by the FDA, and permits even greater efficiency for medical practices and patients.

If you have further questions after reviewing this information, please feel free to contact me at 617-591-5547. We also plan to reach out to your office to discuss a meeting on VS in general and hylan G-F 20-based products in particular, to address any remaining concerns and help your office make decisions based on the best and most complete information. We look forward to that dialog.

Sincerely,



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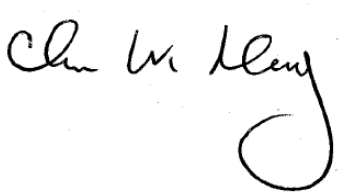

Christopher W. Murray, Ph.D.
Senior Director, Medical Affairs

Enclosures

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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

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ABSTRACT

Objectives: The primary objective was to compare a single, 6 ml, intra-articular injection of hylan G-F 20 with placebo in patients with symptomatic knee osteoarthritis. The safety of a repeat injection of hylan G-F 20 was also assessed.

Methods: Patients with primary osteoarthritis knee pain were randomly assigned to arthrocentesis plus a 6 ml intra-articular injection of either hylan G-F 20 or placebo in a prospective, double-blind (one injector/one blinded observer) study. Results were evaluated at 4, 8, 12, 18 and 26 weeks post-injection. The primary outcome criterion was change from baseline over 26 weeks in Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index A pain. Secondary outcome measures included WOMAC A1 and C, patient global assessment (PGA) and clinical observer global assessment (COGA) and Outcome Measures in Rheumatology, Osteoarthritis Research Society International responder rates. A 4-week, open, repeat treatment phase evaluated safety only.

Results: A total of 253 patients (Kellgren–Lawrence grade II or III) was randomly assigned. Patients receiving hylan G-F 20 experienced statistically significantly greater improvements in WOMAC A pain scores (−0.15, SE 0.076, $p = 0.047$), and several of the secondary outcome measures (WOMAC A1, PGA and COGA), than patients receiving placebo. There was no difference between the safety results of the two groups. No increased risk of local adverse events was observed in the open, repeat treatment phase.

Conclusions: This placebo-controlled study demonstrated that, in patients with knee osteoarthritis, a single 6 ml intra-articular injection of hylan G-F 20 is safe and effective in providing statistically significant, clinically relevant pain relief over 26 weeks, with a modest difference versus placebo.

Trial registration number: NCT00131352.

Osteoarthritis is the most common joint disease and one of the most frequent causes of physical impairment.[1] Osteoarthritis of the knee has been associated with a decrease in the elasticity and viscosity of the synovial fluid,[2–4] which may alter the transmission of mechanical forces to the cartilage, possibly increasing its susceptibility to mechanical damage, or wear and tear. Viscosupplementation addresses the degradation of hyaluronic acid (HA) in the synovial fluid of patients with knee osteoarthritis by the addition of exogenous HA, or its derivatives, by intra-articular injection and is cited for the treatment of knee osteoarthritis in the guidelines of several professional societies.[5–10]

Hylan G-F 20 (Synvisc) is a high molecular weight (average 6000 kDa) HA product consisting of two cross-linked components. Approved in several countries for the treatment of pain associated with knee osteoarthritis, the recommended treatment regimen for the treatment of knee osteoarthritis pain is one 2 ml intra-articular injection per week for three consecutive weeks.[11 12]

In order to reduce the number of intra-articular injections (and potential related side effects) a pilot study was conducted, and the results suggested that at 6 months post-injection, one 6 ml injection performed at least as well as three 2 ml injections.[13] A single 6 ml injection may represent an attractive alternative to the current treatment regimen, reducing the number of intra-articular injections required and thereby offering potential comfort and safety benefits to patients.

The current study was designed to assess the efficacy and safety of one 6 ml injection of hylan G-F 20 in a 26-week, pivotal, prospective, multicentre, double-blind, randomised, placebo controlled clinical trial.

METHODS

Ethics

The study was performed in accordance with the principles of good clinical practice guidelines. Ethics committee approvals and informed patient consents were obtained. The study was registered in the ClinicalTrials.gov National Institutes of Health trial register under the identification number NCT00131352.

Study design

At the screening visit patients gave their written, informed consent and a physical examination was performed on the knee to be treated (''target knee''). A radiographic assessment was also performed if no valid *x* ray had been taken within 3 months before screening was available. Demographic data and medical history information were collected.

Before commencing the study, a washout period of prohibited pain and osteoarthritis medications (analgesics and non-steroidal anti-inflammatory

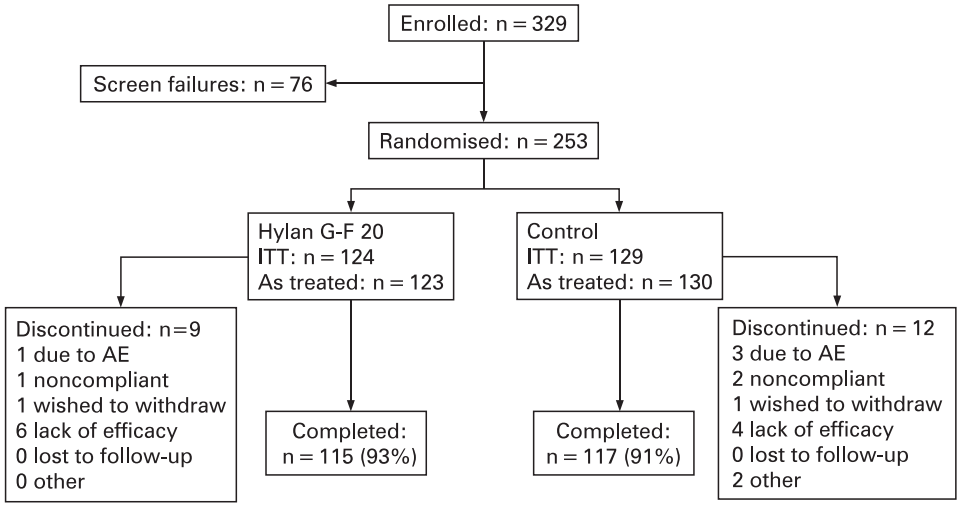

Figure 1 Study flow chart. AE, adverse event; ITT, intent-to-treat.

drugs with half lives of ⩾5 h and systemic corticosteroids) was required.

Patients were randomly assigned to receive arthrocentesis plus a 6 ml intra-articular injection of either hylan G-F 20 or buffered physiological sodium chloride solution (PBS) (placebo) on day 0.

Patients completed the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index Likert and patient global assessment (PGA) questionnaires and a blinded evaluator completed the clinical observer global assessment (COGA).

Safety assessments (including physical examination findings), usage of concomitant medications and treatments and vital signs were recorded until study completion. It was left to the judgement of the clinical evaluator to decide whether each target knee adverse event (AE) was related to the study procedure (ie, expected with any intra-articular injection procedure) or to the study material.

Patients were followed up 1, 4, 8, 12, 18 and 26 weeks after injection.

To assess the safety of a repeat injection of 6 ml hylan G-F 20, patients from both groups were permitted to enter a 4-week open-label repeat treatment phase 26 weeks after their initial injection if they had no major safety concerns during the first course of treatment and an average WOMAC A score of at least 1.

Patient selection

Patients were required to meet the American College of Rheumatology criteria for osteoarthritis (knee pain for most days of the previous month and osteophyte(s) at the joint margin visible on *x* ray).[14]

Table 1 Baseline characteristics for all randomly assigned patients (ITT population)

	Hylan G-F 20 (N = 124)	Placebo (N = 129)
Mean age, years (SD)	63.6 (9.64)	62.5 (9.17)
Mean BMI, kg/m^2 (SD)	29.08 (4.81)	29.77 (5.74)
Gender (M/F)	32/92	41/88
Tibiofemoral compartment with the most severe features of osteoarthritis, N* (%)		
Medial	93 (75.6)	103 (79.2)
Lateral	30 (24.4)	27 (20.8)
Modified Kellgren–Lawrence grade in most severe tibiofemoral compartment, N* (%)		
Grade II	63 (51.2)	51 (39.2)
Grade III	60 (48.8)	78 (60.0)
Grade IV	0	1 (0.8)
Previous corticosteroids in the target knee, N* (%)	40 (32)	31 (24)
Previous arthroscopy in the target knee, N* (%)	26 (21)	28 (22)
Total WOMAC score (0–4), mean (SD)	2.30 (0.44)	2.28 (0.39)
WOMAC A score (0–4), mean (SD)	2.30 (0.43)	2.25 (0.41)
Symptomatic osteoarthritis that was responsive to paracetamol and did not require other therapy, N* (%)		
In the contralateral knee	68 (55.3)	76 (58.5)
In either hip	12 (9.8)	18 (13.8)
Mean time since osteoarthritis diagnosis, months* (SD) (median, range)	77.38 (76.44) (51.94, 3.1–350.9)	70.01 (64.43) (47.34, 3.6–241.9)

*Safety population.
BMI, body mass index; ITT, intent-to-treat; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Main inclusion criteria were: age 40 years or greater; diagnosis of primary osteoarthritis of the target knee; radiographic evidence of osteoarthritis in the medial and/or lateral tibiofemoral compartment (one or more osteophyte(s) and a measurable joint space on a standard radiograph taken within 3 months before screening); continued osteoarthritis pain in the target knee despite conservative treatments. Patients were required to have a score of 2 or 3 (0 to 4 scale) on question 1 of the WOMAC (Likert version 3.1) pain (A) subscale (pain while walking on a flat surface) as this is the most commonly reported symptom in clinical practice and the protocol was designed to weight this symptom more heavily. Included patients required a mean score of 1.5–3.5 on the WOMAC A (total pain) subscore.[15]

Main exclusion criteria were: secondary osteoarthritis in the target knee; grade IV radiographic stage osteoarthritis (Kellgren–Lawrence grading system);[16] clinically apparent tense effusion of the target knee; significant valgus/varus deformities; viscosupplementation in any joint in the past 9 months; surgery in the knee within the past 6 months; symptomatic osteoarthritis of the contralateral knee or either hip unresponsive to paracetamol; systemic or intra-articular injection of corticosteroids in any joint within 3 months before screening.

Study treatments

Hylan G-F 20 (Synvisc-One, Genzyme Corporation, Ridgefield, New Jersey, USA), was supplied in 6 ml PBS. Placebo was 6 ml PBS. Both hylan G-F 20 and placebo were packaged identically in order to maintain the study blind.

The injection approach was left to the unblinded injector's clinical discretion. Arthrocentesis was performed before injecting hylan or PBS.

Concomitant medications and treatments

Paracetamol (⩽4000 mg/day) was permitted as rescue medication for the target knee. Other permitted medications were analgesics/non-steroidal anti-inflammatory drugs with a half-life of 5 h or less for indications other than osteoarthritis pain (not to be taken for more than five consecutive days or >10 days/month) and aspirin (⩽325 mg/day). However, for 48 h before a study visit, patients were required to abstain from any paracetamol, pain or osteoarthritis medications.

Other permitted treatments may be reviewed in supplementary material 1 available online only.

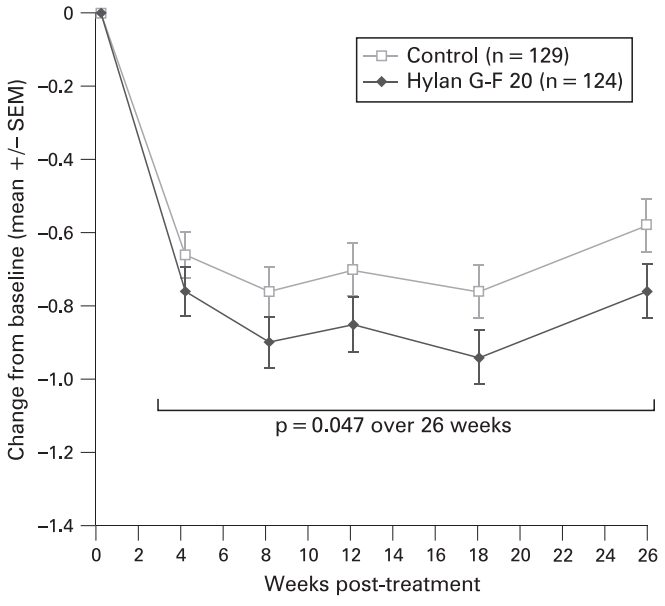

Figure 2 Mean change from baseline in the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index A (pain), intent-to-treat population.

Randomisation

Randomisation was performed by a centralised, interactive, voice-response system and was done by site in computer-generated blocks of four. Unblinded injectors were strictly forbidden from discussing treatment allocation with patients and clinical observers.

Power and sample size

The sample size estimation was based on the mean intergroup difference in the WOMAC A pain subscale change from baseline over 26 weeks. The following assumptions were made to compute the sample size: anticipated overall treatment difference of 0.297; common SD of 0.725; dropout rate of 25%; two-sided significance level of 5%. A resulting sample size of approximately 250 patients (125 patients per group) provided greater than 80% power to detect a difference between the hylan G-F 20 and placebo groups over 26 weeks.

Efficacy analyses

The primary efficacy analysis was performed on the intent-to-treat (ITT) population (all randomly assigned patients), based on a repeated-measures analysis of covariance that was used to test for intergroup differences in the WOMAC A (pain) subscore over 26 weeks. The analysis of covariance model included terms for treatment, site, time and time-by-treatment interaction, as well as the baseline WOMAC A score as a covariate.

Secondary efficacy outcomes were analysed using generalised estimating equations for a proportional odds logistic regression. The generalised estimating equations model was fitted to the observed data and included terms for baseline measure, site, visit, treatment group and a visit-by-treatment group interaction. These analyses included the difference between the groups from baseline at week 26 in WOMAC A and the differences from baseline over and at 26 weeks in WOMAC A1, WOMAC subscale C, PGA, COGA, and the responders to treatment per the Outcome Measures in Rheumatology, Osteoarthritis Research Society International (OMERACT–OARSI) responder criteria.[17]

For the WOMAC A1 responder analysis, patients were classified at each post-baseline visit into a responder category (yes/no). Those patients with at least a one-point category improvement from baseline who did not withdraw due to lack of efficacy were considered responders.

Safety analyses

The safety analyses were performed on the safety population (all patients who received at least one injection of hylan G-F 20 or placebo).

RESULTS

Disposition of patients, baseline data

Patients were enrolled at 21 sites in the UK, France, the Czech Republic, Germany, Belgium and The Netherlands. A total of 329 patients enrolled; 76 patients (23.1%) were screening failures; 253 patients (73 men, 180 women) were randomly assigned and analysed: 124 to receive hylan G-F 20 and 129 to receive placebo. All 253 randomly assigned patients were included in the safety population (hylan G-F 20 123 patients;

Table 2 Primary efficacy endpoint—WOMAC A (pain) change over 26 weeks (ITT population)

	Baseline mean (SE)	26-Week mean (SE)	Estimated change (SE)	Estimated difference between groups (SE)	p Value
Hylan G-F 20 (n = 124)	2.30 (0.038)	1.43 (0.060)	−0.84 (0.060)	−0.15 (0.076)	0.047
Placebo (n = 129)	2.25 (0.036)	1.59 (0.058)	−0.69 (0.058)		

ITT, intent-to-treat; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

placebo 130 patients). One patient was randomly assigned to the hylan G-F 20 group but received placebo in error and was therefore counted in the placebo group for safety and the hylan G-F 20 group for ITT efficacy.

A total of 232 patients (91.7%) completed the study. Nine patients (7.3%) randomly assigned to hylan G-F 20 and 12 patients (9.2%) randomly assigned to placebo failed to complete the study schedule as planned (fig 1).

There were no statistically significant, or clinically meaningful, differences between treatment groups in any baseline or demographic parameter (table 1).

Treatment efficacy

The treatment effect with hylan G-F 20 was statistically significantly superior to placebo for the primary endpoint, change in WOMAC A (pain) over 26 weeks (table 2 and fig 2).

Hylan G-F 20 demonstrated an estimated change (absolute change, adjusted for values, time and treatment) from baseline over 26 weeks of −0.84, a mean percentage change in pain from baseline of 36%. Patients in the placebo group had an estimated change from baseline over 26 weeks of −0.69, a mean percentage change in pain from baseline of 29%. The estimated treatment difference between the two treatment groups over the 26-week study was statistically significant (p = 0.047).

Some, but not all, of the secondary endpoints, including WOMAC A1 (walking pain), PGA and COGA, showed statistically significant differences between the two groups favouring hylan G-F 20 treatment (tables 3 and 4).

Seventy-one per cent (88/124) of the patients were WOMAC A1 (walking pain) responders at week 18 in the hylan G-F 20 group compared with 53% (69/129) in the placebo group (p = 0.003). At week 26, 64% (79/124) of patients in the hylan G-F 20 group were WOMAC A1 responders compared with 50% (64/129) in the placebo group (p = 0.028).

The change in WOMAC C (function) scores did not reach statistical significance. Further exploratory analyses of predefined covariates were carried out to understand better the lack of effect of hylan G-F 20 on the WOMAC C endpoint. In patients without any other lower limb osteoarthritis (defined as hip or contralateral knee involvement), those treated with Synvisc experienced a greater change in WOMAC C than those treated with placebo (−0.71 and −0.55, respectively).

The OMERACT–-OARSI responder analysis over 26 weeks approached statistical significance (p = 0.059). At week 26, 73 patients (59%) in the hylan G-F 20 group and 66 patients (51%) in the placebo group were responders.

Overall, patients consumed a mean daily dose of 0.26 g (SD 0.654 g) of paracetamol in the hylan G-F 20 group, and 0.28 g (SD 0.570 g) in the placebo group. Throughout the study there was no statistically significant difference in paracetamol consumption between the two groups (p = 0.370).

AE and safety

There were no target knee serious AE and no serious AE that were related to the study treatment or the study procedure. The overall frequency of AE was comparable between the two treatment groups (hylan G-F 20, n = 70, 56.9%; placebo, n = 79, 60.8%).

The most commonly reported AE were pain in the target knee (coded as ''arthralgia''), joint stiffness, joint effusion and joint swelling. The incidence of AE was slightly higher in the hylan G-F 20 group (n = 7, 5.7%) than in the placebo group (n = 4, 3.1%) but this was not statistically significant (p = 0.366) (table 5). In addition, there were no statistically significant differences between the groups in treatment-related (p = 0.203)

Table 3 Secondary efficacy endpoints (ITT population): estimated between-group differences

	Baseline mean (SE)	Week 26 mean/overall mean (SE)	Estimated change (SE)	Estimated between-group difference	p Value
WOMAC A (pain) change from baseline at 26 weeks*					
Hylan G-F 20	2.30 (0.04)	1.51 (0.074)	−0.76 (0.07)	−0.18 (0.097)	0.064
Placebo	2.25 (0.04)	1.69 (0.073)	−0.58 (0.07)		
WOMAC C (function) change from baseline over 26 weeks†					
Hylan G-F 20	2.29 (0.04)	1.62 (0.061)	−0.66 (0.061)	−0.03 (0.077)	0.679
Placebo	2.28 (0.04)	1.66 (0.059)	−0.63 (0.059)		
WOMAC C (function) change from baseline at 26 weeks†					
Hylan G-F 20	2.29 (0.04)	1.69 (0.076)	−0.59 (0.076)	−0.11 (0.100)	0.266
Placebo	2.28 (0.04)	1.80 (0.074)	−0.48 (0.074)		

*Week 26 mean in column 3; †overall mean in column 3. ITT, intent-to-treat; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 4 Secondary efficacy endpoints (ITT population): estimates of odds ratios

	Week 26 subscore		Estimate of OR (placebo/hylan G-F 20) (95% CI)	
	Hylan G-F 20 n (%)	Placebo n (%)	At week 26	Over 26 weeks
WOMAC A1 (walking pain) subscore				
None	17 (13.7)	13 (10.1)	0.56 (0.35 to 0.92) p = 0.022	0.64 (0.45 to 0.91) p = 0.013
Mild	45 (36.3)	39 (30.2)		
Moderate	41 (33.1)	42 (32.6)		
Severe	11 (8.9)	19 (14.7)		
Extreme	1 (0.8)	4 (3.1)		
Patient global assessment				
Very well	9 (7.3)	2 (1.6)	0.51 (0.31 to 0.82) p = 0.005	0.69 (0.50 to 0.96) p = 0.029
Well	33 (26.6)	27 (20.9)		
Fair	50 (40.3)	54 (41.9)		
Poor	21 (16.9)	31 (24.0)		
Very poor	2 (1.6)	3 (2.3)		
Clinician observer global assessment				
Very well	13 (10.5)	8 (6.2)	0.56 (0.34 to 0.93) p = 0.025	0.71 (0.50 to 0.99) p = 0.041
Well	37 (29.8)	31 (24.0)		
Fair	38 (30.6)	38 (29.5)		
Poor	22 (17.7)	34 (26.4)		
Very poor	5 (4.0)	6 (4.7)		
OMERACT–OARSI responders				
Responder	73 (58.9)	66 (51.2)	0.69 (0.41 to 1.16) p = 0.156	0.66 (0.44 to 1.02) p = 0.059
Non-responder	50 (40.3)	63 (48.8)		
Based on OMERACT–OARSI responder criteria	43 (34.7)	52 (40.3)		
Due to withdrawal before study completion	7 (5.6)	11 (8.5)		

ITT, intent-to-treat; OMERACT–OARSI, Outcome Measures in Rheumatology, Osteoarthritis Research Society International; OR, odds ratio; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

or procedure-related (p = 0.531) target knee AE, all of which were of mild or moderate severity.

Repeat treatment phase

A total of 160 patients was treated in the open, repeat treatment phase, of which 77 received a second injection of hylan G-F 20 and 83 received a first injection of hylan G-F 20, having received placebo during the initial treatment phase. There were no target knee serious AE. In the group receiving a second injection of hylan G-F 20 one patient (1.3%) experienced target knee AE related to the study treatment and four patients (5.2%) experienced target knee AE related to the study procedure.

Patients who developed target knee AE during the initial phase of the study, and who subsequently received repeat treatment, did not experience target knee AE on repeat exposure to hylan G-F 20. All treatment-related and procedure-related target knee AE were of mild or moderate severity.

DISCUSSION

This study demonstrates that a single intra-articular injection of hylan G-F 20 is safe and effective in providing statistically

Table 5 Target knee adverse events: safety population

Preferred term	Hylan G-F 20 N = 123 n (% of patients)	Placebo N = 130 n (% of patients)
Any treatment-emergent target knee AE	44 (35.8)	44 (33.8)
Any treatment and/or procedure-related target knee AE	7 (5.7)	4 (3.1)
Arthralgia	2 (1.6)	3 (2.3)
Joint effusion	2 (1.6)	0 (0)
Arthritis	1* (0.8)	0 (0)
Arthropathy	1 (0.8)	0 (0)
Injection site pain	1 (0.8)	1 (0.8)
Any treatment-related target knee AE	4 (3.3)	1 (0.8)
Any procedure-related target knee AE	6 (4.9)	4 (3.1)

Related to treatment refers to unknown relationship to, or possibly, probably, or definitely related to treatment. Patients are counted once for each unique adverse event (AE) and may have had more than one unique AE. If a patient had more than one occurrence of the same AE, the strongest relationship to study treatment or injection procedure was included. Treatment groups reflect the actual treatment received, not the randomised treatment. Patients may be counted in more than one category. *Patient withdrew from the study due to target knee arthritis of moderate severity.

significant, clinically relevant pain relief, as measured by WOMAC A1 (walking pain) over 26 weeks, with a modest difference compared with placebo. Several secondary efficacy results also show the superiority of hylan G-F 20 over placebo. Pain while walking is particularly medically relevant for the assessment of symptomatic relief and has been selected as the primary efficacy measure in other studies of hylan G-F 20 or other hyaluronans.[18–20] The OMERACT–OARSI responder analysis also favoured hylan G-F 20 although statistical significance was not reached ($p = 0.059$).

This trial had a large placebo effect (−0.69 change in mean WOMAC A score over 26 weeks), which may explain why the observed overall treatment difference (0.15) was weaker than anticipated (0.297). The placebo effect in osteoarthritis treatment has been re-evaluated in a recent meta-analysis showing that it induces significant pain relief, especially in trials involving intra-articular injections.[21] Furthermore, because the actual therapeutic effect of arthrocentesis (with synovial fluid aspiration if needed) has never been assessed, it is possible that this contributed to the robust response in patients receiving placebo. However, hylan G-F 20 was still significantly superior to placebo in the primary and several of the secondary endpoints.

Effect size is a way to measure effectiveness and to compare clinical interventions.[22] The effect size of hylan G-F 20 versus control in this study was −0.23 for WOMAC A at week 26. In chronic pain conditions such as osteoarthritis, this modest effect size should be interpreted as clinically relevant on an individual patient basis as recommended by the IMMPACT consensus.[23 24]

In addition, the accepted threshold for a minimum clinically important improvement in osteoarthritis (12–18% improvement in WOMAC A from baseline)[25] was exceeded in this study. Patients treated with one 6 ml injection of hylan G-F 20 experienced a 31.3% improvement in WOMAC A from baseline ($p<0.001$) at week 26.

The WOMAC C (function) subscale findings in the current study are inconsistent with those from previous controlled studies of hylan G-F 20.[18 26] However, our post-hoc analysis showed that WOMAC C scores were improved in a subgroup of patients without any other lower limb joint involvement, suggesting that osteoarthritis occurring in other lower limbs may contribute to substantial functional impairment, and may confound the patient's ability to detect improvement in the target knee in a clinical trial setting.

Evaluation of the safety profile for the higher injected volume (6 ml) of hylan G-F 20 was also a major objective of this study. The similarity in the safety profiles of hylan G-F 20 and placebo (PBS) is reassuring. No new, unrecognised AE were identified during this study. The safety profile of hylan G-F 20 was confirmed during the repeat treatment phase of the study, indicating no increase in the risk of AE in the patients receiving a second injection of hylan G-F 20. This finding contrasts with previous reports of post-marketing studies, which suggest an approximate threefold increased risk of local target knee AE with a repeat course of hylan G-F 20.[19] The excellent safety profile of the increased 6 ml dose translates to an improved benefit-to-risk ratio for the patient.

CONCLUSIONS

This placebo-controlled study demonstrated that, in patients with knee osteoarthritis, a single 6 ml intra-articular injection of hylan G-F 20 is safe and effective in providing statistically significant, clinically relevant pain relief over 26 weeks, with a modest difference compared with placebo.

In daily practice the favourable benefit/risk profile of a single injection of 6 ml hylan G-F 20 has the major advantage of decreasing the number of injections from three to five to only one.

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