One-Year Efficacy and Safety of Single or One to Three Weekly Injections of Hylan G-F 20 for Knee Osteoarthritis: A Systematic Literature Review and Meta-Analysis

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## Supplemental Material

Table S0 PICO Eligibility Criteria

| PICO         | Inclusion Criteria                                                                 |
|--------------|------------------------------------------------------------------------------------|
| **Participants** | • Persons with knee osteoarthritis                                                |
| **Interventions** | • Hylan G-F 20 (single and 1-3 weekly injections)                                  |
| **Comparators** | • Any                                                                               |
|               | • None                                                                              |
| **Outcomes**  | • Response Rate                                                                     |
|               | • VAS Pain                                                                          |
|               | • WOMAC                                                                             |
|               | • SF-36                                                                             |
|               | • Adverse Events (Total, Serious, Severe, Treatment-Related, Target Knee)           |
|               | • Drug Discontinuation due to Adverse Events                                        |
|               | • Study Withdrawal due to Adverse Events                                            |
| **Timing**    | • 1 year                                                                            |
### Setting
- Any

### Study Design
- Randomized Controlled Trials
- Non-Randomized Clinical Trials
- Observational Studies

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**Table S1 MEDLINE (via PubMed) Search Strategy**

**Searched: October 18, 2018**

| Set # | Searches                                                                 | Results  |
|-------|---------------------------------------------------------------------------|----------|
| 1     | "Osteoarthritis, Knee"[Mesh]                                              | 16744    |
| 2     | "Knee Joint"[Mesh] OR "Knee"[Mesh] OR (Femoropatellar[tiab] OR femoro-patellar[tiab] OR knee[tiab] OR knees[tiab] OR kneecap[tiab] OR kneecaps[tiab] OR knee-cap[tiab] OR knee-caps[tiab] OR patella[tiab] OR patellas[tiab] OR patellar[tiab] OR patellofemoral[tiab] OR patello-femoral[tiab] OR tibiofemoral[tiab] OR tibia-femoral[tiab] OR tibio-femoral[tiab] OR tibiofibular[tiab] OR tibio-fibular[tiab]) | 155563   |
| 3     | "Osteoarthritis"[Mesh:NoExp] OR (arthriti*[tiab] OR degenerative arthro*[tiab] OR degenerative joint[tiab] OR degenerative joints[tiab] OR gonarthriti*[tiab] OR gonarthro*[tiab] OR osteoarthritis* OR osteo-arthritis* OR osteoarthros*[tiab] OR osteo-arthros*[tiab] OR OA[tiab]) | 247612   |
| 4     | 2 AND 3                                                                   | 40750    |
| 5     | 1 OR 4                                                                    | 42054    |
| 6     | "hylan" [Supplementary Concept] OR synvisc[tiab] OR hylan g f 20[tiab] OR hylan g-f 20[tiab] OR hylan gf:20[tiab] OR hylan gf:20[tiab] OR hylan gf 20[tiab] | 297      |
| 7     | Synvisc*[tiab] OR Synvisc-One[tiab]                                        | 108      |
| 8     | 6 OR 7                                                                    | 297      |
| 9     | 5 AND 8                                                                   | 205      |
| 10    | English[Language]                                                         | 24302437 |
| 11    | 9 AND 10                                                                  | 195      |
| 12    | "1995/01/01"[PDAT] : "3000/12/31"[PDAT]                                   | 17824460 |
| 13    | 11 AND 12                                                                | 194      |
Table S2 Embase (via OVID) Search Strategy

Searched: October 18, 2018

Embase Segment Used: 1974 to October 17, 2018

| Set # | Searches                                                                 | Results  |
|-------|--------------------------------------------------------------------------|----------|
| 1     | exp knee osteoarthritis/                                                | 27443    |
| 2     | exp knee/                                                               | 56537    |
| 3     | exp patella/                                                            | 8294     |
| 4     | exp patellofemoral joint/                                              | 3825     |
| 5     | (Femoropatellar or femoro-patellar or knee or knees or kneecap or kneecaps or knee-cap or knee-caps or patella or patellas or patellar or patellofemoral or patello-femoral or tibiofemoral or tibio-femoral or tibiofibular or tibio-fibular).ti,ab,kw. | 178810   |
| 6     | or/2-5                                                                 | 185851   |
| 7     | exp osteoarthritis/                                                    | 112888   |
| 8     | (arthriti$ or degenerative arthriti$ or degenerative arthro$ or degenerative joint or degenerative joints or gonorarthriti$ or gonarthro$ or osteoarthriti$ or osteo-arthriti$ or osteoarthros$ or osteo-arthros$ or OA).ti,ab,kw. | 321434   |
| 9     | 7 or 8                                                                  | 357680   |
| 10    | 6 and 9                                                                 | 57281    |
| 11    | 1 or 10                                                                 | 60727    |
| 12    | (Synvisc or Synvisc$ or Synvisc-One or Synvisc One or Synvisc-1 or Synvisc 1).mp. | 464      |
| 13    | (hylan g f 20 or hylan g-f 20 or hylan gf-20 or hylan gf 20).mp.         | 315      |
| 14    | 12 or 13                                                                | 599      |
| 15    | 11 and 14                                                               | 414      |
| 16    | (article or article in press or conference abstract or conference paper).pt. | 23978506 |
| 17    | 15 and 16                                                               | 307      |
| 18    | English.lg.                                                            | 26457670 |
| 19    | 17 and 18                                                               | 290      |
| 20    | limit 19 to yr="1995 -Current"                                          | 288      |
Table S3 Cochrane Central Database of Controlled Trials (via OVID) Search Strategy

Searched: October 18, 2018

| Set # | Searches                                                                                                                                                                                                 | Results |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| 1     | exp Osteoarthritis, Knee/                                                                                                                                                                             | 3216    |
| 2     | exp Knee/ or exp Knee Joint/ or exp Patella/ or exp patellofemoral joint/                                                                                                                                 | 3639    |
| 3     | knee$.ti,ab,kw,hw,sh.                                                                                                                                                                                | 20019   |
| 4     | (Femoropatellar or femoro-patellar or knee or knees or kneecap or kneecaps or knee-cap or knee-caps or patella or patellas or patellar or patellofemoral or patello-femoral or tibiofemoral or tibio-femoral or tibio-fibular).ti,ab,kw,hw,sh. | 20461   |
| 5     | or/2-4                                                                                                                                                                                               | 20563   |
| 6     | exp osteoarthritis/                                                                                                                                                                                   | 5941    |
| 7     | (arthriti$ or degenerative arthriti$ or degenerative arthros$ or degenerative joint or degenerative joints or gonarthriti$ or gonarthro$ or osteoarthriti$ or osteo-arthritis$ or osteoarthros$ or OA).ti,ab,kw,hw,sh. | 25241   |
| 8     | 6 or 7                                                                                                                                                                                               | 25241   |
| 9     | 5 and 8                                                                                                                                                                                               | 8283    |
| 10    | 1 or 9                                                                                                                                                                                                | 8283    |
| 11    | (synvisc or synvisc one).ti,ab,kw,hw,sh.                                                                                                                                                              | 53      |
| 12    | (hylan g f 20 or hylan g-f 20 or hylan gf-20 or hylan gf 20).ti,ab,kw,hw,sh.                                                                                                                        | 78      |
| 13    | 11 or 12                                                                                                                                                                                              | 105     |
| 14    | 10 and 13                                                                                                                                                                                             | 94      |
| 15    | English.lg.                                                                                                                                                                                            | 807813  |
| 16    | 14 and 15                                                                                                                                                                                              | 69      |
| 17    | limit 16 to yr="1995-2018"                                                                                                                                                                          | 69      |
Table S4 Study and patient characteristics

| Author and Year | Study Design | Interventions | Number of Patients | Mean Age | OA Grade |
|-----------------|--------------|---------------|--------------------|----------|----------|
| Acharya KKV 2013<sup>27</sup> | RCT | Hylan G-F Single injection | 41 | NR | Osteoarthritis, Knee, Mild to Moderate - 82 (100%)  
Kellgren-Lawrence Classification, Grade 1-3 - 82 (100%) |
| | | Arthroscopy | 41 | | |
| Atamaz F 2006<sup>24</sup> | RCT | Hylan G-F 1-3 weekly injections | 20 | 60.4 yr (SD ± 9.3) | Kellgren-Lawrence Classification, Grade 2-3 - 82 (100%) |
| | | Sodium hyaluronate + sodium chloride (Orthovisc®) | 20 | 62.4 yr (SD ± 9) | |
| | | Physical Therapy Agents | 42 | 58.7 yr (SD ± 8.3) | |
| Bellamy N 2005a<sup>27</sup> | RCT | Hylan G-F 1-3 weekly injections | 127 | 62.6 yr (SD ± 9.4) | Osteoarthritis, Knee, Mild to Moderate - 127 (100%)  
Kellgren-Lawrence Classification, Grade, Not Reported - 0 (0%)  
Kellgren-Lawrence Classification, Grade 0 - 4 (3%)  
Kellgren-Lawrence Classification, Grade 1 - 17 (13%)  
Kellgren-Lawrence Classification, Grade 2 - 32 (25%)  
Kellgren-Lawrence Classification, Grade 3 - 49 (39%)  
Kellgren-Lawrence Classification, Grade 4 - 25 (20%) |
| | | Physical Therapy Agents | 128 | 63.5 yr (SD ± 10.5) | Osteoarthritis, Knee, Mild to Moderate - 128 (100%)  
Kellgren-Lawrence Classification, Grade, Not Reported - 1 (1%)  
Kellgren-Lawrence Classification, Grade 0 - 4 (3%)  
Kellgren-Lawrence Classification, Grade 1 - 11 (9%)  
Kellgren-Lawrence Classification, Grade 2 - 33 (26%)  
Kellgren-Lawrence Classification, Grade 3 - 37 (29%)  
Kellgren-Lawrence Classification, Grade 4 - 42 (33%) |
| Bellamy N 2005b<sup>30</sup> | RCT | Hylan G-F 1-3 weekly injections | 127 | 62.6 yr (SD ± 9.4) | Osteoarthritis, Knee, Mild to Moderate - 127 (100%)  
Kellgren-Lawrence Classification, Grade, Not Reported - 0 (0%)  
Kellgren-Lawrence Classification, Grade 0 - 4 (3%) |
| Author and Year | Study Design | Interventions | Number of Patients | Mean Age | OA Grade |
|-----------------|--------------|---------------|--------------------|----------|----------|
| Boutefnouchet T 2017<sup>49</sup> | Case Series | Hylan G-F Single injection | 77 | 58 yr (SD ± 11.9, Total: 32 – 88, 95% CI: 51.5 – 73.2) | NR |
| Clarke S 2005<sup>50</sup> | Non-Controlled Clinical Trial | Hylan G-F 1-3 weekly injections | 43 | 56 yr (SD ±10.6, Total: 36 – 82, 95% CI: 52.4 – 59) | NR |
| Cole BJ 2017<sup>51</sup> | RCT | Hylan G-F 1-3 weekly injections | 59 | 56.8 yr (SD ± 10.5) | Osteoarthritis, Knee, Mild to Moderate - 59 (100%) |
| | | | | | Kellgren-Lawrence Classification, Grade 1-4 - 59 (100%) |
| | | | | | Kellgren-Lawrence Classification, Grade, Unknown - 1 (2%) |
| | | | | | Kellgren-Lawrence Classification, Grade 1 - 0 (0%) |
| | | | | | Kellgren-Lawrence Classification, Grade 2 - 27 (54%) |
| | | | | | Kellgren-Lawrence Classification, Grade 3 - 22 (44%) |
| Platelet-Rich Plasma | | | 52 | 55.9 yr (SD ± 10.4) | Osteoarthritis, Knee, Mild to Moderate - 52 (100%) |
| | | | | | Kellgren-Lawrence Classification, Grade 1-4 - 52 (100%) |
| | | | | | Kellgren-Lawrence Classification, Grade, Unknown - 0 (0%) |
| | | | | | Kellgren-Lawrence Classification, Grade 1 - 3 (6.12%) |
| | | | | | Kellgren-Lawrence Classification, Grade 2 - 26 (53.06%) |
| Author and Year | Study Design | Interventions | Number of Patients | Mean Age | OA Grade |
|-----------------|--------------|---------------|--------------------|----------|----------|
| Daniel D 2011⁴⁶| Observational Non-Comparative | Hylan G-F Single injection | 451 | Kellgren-Lawrence Classification, Grade 3 - 22 (44%) - 20 (40.82%) |
| Huskin JP 2008⁴¹| Non-Controlled Clinical Trial | Hylan G-F 1-3 weekly injections | 62 | 55.4 yr (SD ± 11.35) | Osteoarthritis, Knee, Mild to Moderate - 62 (100%) - Kellgren-Lawrence Classification, Grade 1-2 - Kellgren-Lawrence Classification, Medial, Grade 1 - 36 (58%) - Kellgren-Lawrence Classification, Medial, Grade 2 - 25 (40%) - Kellgren-Lawrence Classification, Medial, Grade 3 - 1 (2%) - Kellgren-Lawrence Classification, Lateral, Grade 1 - 50 (80%) - Kellgren-Lawrence Classification, Lateral, Grade 2 - 12 (20%) - Kellgren-Lawrence Classification, Patellofemoral, Grade 1 - 52 (84%) - Kellgren-Lawrence Classification, Patellofemoral, Grade 2 - 10 (16%) |
| Juni P 2007⁳²| RCT | Hylan G-F 1-3 weekly injections | 222 | 63.3 yr (SD ± 12.3) | Osteoarthritis, Knee, Radiographic, Moderate - 126 (57%) - Osteoarthritis, Knee, Radiographic, Severe - 43 (19%) - Osteoarthritis, Knee, Clinical, Moderate - 42 (19%) - Osteoarthritis, Knee, Clinical, Severe - 143 (64%) - Kellgren-Lawrence Classification, Grade 2-4 - 222 (100%) |
|                | Medium Molecular Weight Hyaluronic Acid (Orthovisc⁶⁶) | 219 | 63.5 yr (SD ± 11.1) | Osteoarthritis, Knee, Radiographic, Moderate - 127 (58%) - Osteoarthritis, Knee, Radiographic, Severe - 48 (22%) - Osteoarthritis, Knee, Clinical, Moderate - 39 (18%) - Osteoarthritis, Knee, Clinical, Severe - 145 (66%) - Kellgren-Lawrence Classification, Grade 2-4 - 219 (100%) |
| Author and Year | Study Design | Interventions | Number of Patients | Mean Age | OA Grade |
|-----------------|--------------|---------------|--------------------|----------|----------|
| Non–cross-linked low molecular weight Hyaluronic Acid (Ostenil®) | RCT | Hylan G-F 1-3 weekly injections | 219 | 63.3 yr (SD ± 11.5) | Osteoarthritis, Knee, Radiographic, Moderate - 131 (60%) Osteoarthritis, Knee, Radiographic, Severe - 40 (18%) Osteoarthritis, Knee, Clinical, Moderate - 52 (24%) Osteoarthritis, Knee, Clinical, Severe - 138 (63%) Kellgren-Lawrence Classification, Grade 2-4 - 219 (100%) |
| Karatosun V 2005 | RCT | Hylan G-F 1-3 weekly injections | 46 | 60.5 yr (SD ± 9.5) | Osteoarthritis, Knee, Severe - 46 (100%) Kellgren-Lawrence Classification, Grade 3 - 46 (100%) Kellgren-Lawrence Classification, Grade 4 - 0 (0%) |
| Low-Molecular Weight Hyaluronic acid - 3 injections (Orthovisc®) | RCT | Hylan G-F 1-3 weekly injections | 46 | 60.6 yr (SD ± 9.6) | Osteoarthritis, Knee, Severe - 46 (100%) Kellgren-Lawrence Classification, Grade 3 - 46 (100%) Kellgren-Lawrence Classification, Grade 4 - 0 (0%) |
| Karlsson J 2002 | RCT | Hylan G-F 1-3 weekly injections | 88 | 70 yr (SD ± 7) | Ahlbäck Classification, Grade 1-2 - 88 (100%) Ahlbäck Classification, Grade 3-5 - 0 (0%) Ahlbäck Classification, Grade 1-52 (61%) Ahlbäck Classification, Grade 2 - 34 (39%) |
| 1% hyaluronan (Artzal®) – 3 injections per week | RCT | Placebo | 92 | 72 yr (SD ± 7) | Ahlbäck Classification, Grade 1-2 - 92 (100%) Ahlbäck Classification, Grade 3-5 - 0 (0%) Ahlbäck Classification, Grade 1 - 54 (60%) Ahlbäck Classification, Grade 2 - 36 (40%) |
| Placebo | RCT | Placebo | 66 | 71 yr (SD ± 6) | Ahlbäck Classification, Grade 1-2 - 66 (100%) Ahlbäck Classification, Grade 3-5 - 0 (0%) Ahlbäck Classification, Grade 1 - 38 (58%) Ahlbäck Classification, Grade 2 - 28 (42%) |
| Kearey P 2016 | Observational Non-Comparative | Hylan G-F Single injection | 131 | 60.2 yr (SD ± 11.3) | Kellgren-Lawrence Classification, Grade 1 - 7 (5.3%) Kellgren-Lawrence Classification, Grade 2 - 49 (37.4%) Kellgren-Lawrence Classification, Grade 3 - 68 (51.9%) |
| Author and Year | Study Design                  | Interventions                  | Number of Patients | Mean Age                  | OA Grade                                                                                       |
|-----------------|--------------------------------|-------------------------------|--------------------|---------------------------|------------------------------------------------------------------------------------------------|
| Lee S 2004⁴²    | Non-Controlled Clinical Trial  | Hylan G-F 1-3 weekly injections| 74                 | 68.27 yr (SD ± 12.7, Total: 31.9 – 92) | Kellgren-Lawrence Classification, Joint Space, Narrowing, Grade 2 - 67 (91%)<br>Kellgren-Lawrence Classification, Osteophytes, Grade 2 - 55 (74%) |
| Pal S 2014⁵¹    | Non-Controlled Clinical Trial  | Hylan G-F Single injection    | 394                | 57.6 yr (SD ± 9.8)        | Osteoarthritis, Knee, Mild to Moderate - 394 (100%)<br>Kellgren-Lawrence Classification, Grade 1-3 - 394 (100%)<br>Kellgren-Lawrence Classification, Tibiofemoral, Index Knee, Grade 1 - 20 (5.1%)<br>Kellgren-Lawrence Classification, Tibiofemoral, Index Knee, Grade 2 - 151 (38.3%)<br>Kellgren-Lawrence Classification, Tibiofemoral, Index Knee, Grade 3 - 223 (56.6%) |
| Pandey SK 2017⁶⁰| Observational Non-Comparative | Hylan G-F Single injection    | 352                | 59.1 yr (SD ± 4.39)      | Kellgren-Lawrence Classification, Grade 2-4 - 352 (100%) |
| Raman R 2008³⁶  | RCT                            | Hylan G-F 1-3 weekly injections| 199                | NR                       | Kellgren-Lawrence Classification, Grade 3 - 118 (61%)<br>Kellgren-Lawrence Classification, Grade 3 - 110 (59%) |
|                 |                                | Sodium Hyaluronate (Hyalgan®) | 193                |                           |                                                                                                   |
| Raynauld JP 2002²²| RCT                            | Hylan G-F 1-3 weekly injections| 127                | 62.6 yr (SD ± 9.4)       | Kellgren-Lawrence Classification, Grade, Not Reported - 0 (0%)<br>Kellgren-Lawrence Classification, Grade 0 - 4 (3%)<br>Kellgren-Lawrence Classification, Grade 1 - 17 (13%)<br>Kellgren-Lawrence Classification, Grade 2 - 32 (25%)<br>Kellgren-Lawrence Classification, Grade 3 - 49 (39%)<br>Kellgren-Lawrence Classification, Grade 4 - 25 (20%) |
|                 |                                | Appropriate Care              | 128                | 63.5 yr (SD ± 10.5)      | Kellgren-Lawrence Classification, Grade, Not Reported - 1 (0.78%)<br>Kellgren-Lawrence Classification, Grade 0 - 4 (3%)<br>Kellgren-Lawrence Classification, Grade 1 - 11 (9%)<br>Kellgren-Lawrence Classification, Grade 2 - 33 (26%)<br>Kellgren-Lawrence Classification, Grade 3 - 37 (29%)<br>Kellgren-Lawrence Classification, Grade 4 - 42 (33%) |
| Author and Year | Study Design | Interventions | Number of Patients | Mean Age | OA Grade |
|----------------|--------------|---------------|-------------------|----------|-----------|
| Raynauld JP 2005<sup>10</sup> | RCT | Hylan G-F (Single-Course) | 78 | 63.8 yr (SD ± 9.5) | Kellgren-Lawrence Classification, Grade 0 - 3 (3.9%)  
Kellgren-Lawrence Classification, Grade 1 - 12 (15.4%)  
Kellgren-Lawrence Classification, Grade 2 - 22 (28.2%)  
Kellgren-Lawrence Classification, Grade 3 - 26 (33.3%)  
Kellgren-Lawrence Classification, Grade 4 - 15 (19.2%) |
| | | Hylan G-F (Repeat-Course) | 48 | 60.8 yr (SD ± 9.2) | Kellgren-Lawrence Classification, Grade 0 - 1 (2.1%)  
Kellgren-Lawrence Classification, Grade 1 - 5 (10.4%)  
Kellgren-Lawrence Classification, Grade 2 - 9 (18.8%)  
Kellgren-Lawrence Classification, Grade 3 - 23 (47.9%)  
Kellgren-Lawrence Classification, Grade 4 - 10 (20.8%) |
| | | Appropriate Care | 128 | 63.5 yr (SD ± 10.5) | Kellgren-Lawrence Classification, Grade 0 - 4 (3.1%)  
Kellgren-Lawrence Classification, Grade 1 - 11 (8.6%)  
Kellgren-Lawrence Classification, Grade 2 - 33 (25.8%)  
Kellgren-Lawrence Classification, Grade 3 - 37 (28.9%)  
Kellgren-Lawrence Classification, Grade 4 - 42 (32.8%) |
| Rolf CG 2005<sup>30</sup> | RCT | Hylan G-F 1-3 weekly injections | 90 | 54.5 yr (SD ± 9.16) | Osteoarthritis, Knee, Severe, Symptomatic, Requiring Knee Replacement - 0 (0%)  
Ahlback Classification, Grade 0 - 36 (40%)  
Ahlback Classification, Grade 1 - 19 (21%)  
Ahlback Classification, Grade 2 - 11 (12%)  
Ahlback Classification, Grade 3 - 2 (2%) |
| | | Hylauron (Artzal<sup>28</sup>) | 91 | 53.9 yr (SD ± 9) | Osteoarthritis, Knee, Severe, Symptomatic, Requiring Knee Replacement - 0 (0%)  
Ahlback Classification, Grade 0 - 41 (46%)  
Ahlback Classification, Grade 1 - 20 (22%)  
Ahlback Classification, Grade 2 - 11 (12%) |
| Author and Year                  | Study Design                  | Interventions                          | Number of Patients | Mean Age         | OA Grade                                                                 |
|---------------------------------|-------------------------------|----------------------------------------|--------------------|------------------|--------------------------------------------------------------------------|
|                                 |                               |                                        |                    |                  | Ahlback Classification, Grade 3 - 1 (1%)                                  |
|                                 |                               | Placebo                                | 91                 | 53.1 yr (SD ± 10.08) | Osteoarthritis, Knee, Severe, Symptomatic, Requiring Knee Replacement - 0 (0%) |
|                                 |                               |                                        |                    |                  | Ahlback Classification, Grade 0 - 41 (47%)                                 |
|                                 |                               |                                        |                    |                  | Ahlback Classification, Grade 1 - 18 (20%)                                 |
|                                 |                               |                                        |                    |                  | Ahlback Classification, Grade 2 - 7 (8%)                                   |
|                                 |                               |                                        |                    |                  | Ahlback Classification, Grade 3 - 0 (0%)                                   |
| Trueba Vasavilbaso C 2017³³      | RCT                           | Hylan G-F 1-3 weekly injections         | 10                 | 56.9 yr (SD ± 9.8)    | Kellgren-Lawrence Classification, Grade 1-2 - 10 (100%)                  |
|                                 |                               |                                        |                    |                  | Kellgren-Lawrence Classification, Grade 1 - 8 (80%)                        |
|                                 |                               |                                        |                    |                  | Kellgren-Lawrence Classification, Grade 2 - 2 (20%)                        |
|                                 |                               | Hylauronic Acid (Orthovisc®) 4 injections | 10                 | 71.1 yr (SD ± 7)     | Kellgren-Lawrence Classification, Grade 1-2 - 10 (100%)                  |
|                                 |                               |                                        |                    |                  | Kellgren-Lawrence Classification, Grade 2 - 10 (100%)                     |
|                                 |                               | Hylauronic Acid (Suprahyl®/Adant®) 5 injections | 10                 | 66.3 yr (SD ± 9.6)    | Kellgren-Lawrence Classification, Grade 1-2 - 10 (100%)                  |
|                                 |                               |                                        |                    |                  | Kellgren-Lawrence Classification, Grade 2 - 6 (60%)                       |
|                                 |                               | Platelet Rich Plasma                   | 10                 | 60.3 yr (SD ± 9.5)    | Kellgren-Lawrence Classification, Grade 1-2 - 10 (100%)                  |
|                                 |                               |                                        |                    |                  | Kellgren-Lawrence Classification, Grade 2 - 6 (60%)                       |
|                                 |                               | Standard Care                          | 10                 | 67.5 yr (SD ± 7.8)    | Kellgren-Lawrence Classification, Grade 1-2 - 10 (100%)                  |
|                                 |                               |                                        |                    |                  | Kellgren-Lawrence Classification, Grade 2 - 9 (90%)                       |
| Vad VB 2003³⁰                    | Non-Randomized Controlled Clinical Trial | Hylan G-F 1-3 weekly injections         | 37                 | 64.8 yr (Total: 41 – 76) | Osteoarthritis, Patellofemoral, Moderate to Severe - 9 (24.32%)          |
|                                 |                               |                                        |                    |                  | Kellgren-Lawrence Classification, Grade 1 - 3 (8.11%)                     |
|                                 |                               |                                        |                    |                  | Kellgren-Lawrence Classification, Grade 2 - 6 (16.22%)                     |
|                                 |                               |                                        |                    |                  | Kellgren-Lawrence Classification, Grade 3 - 17 (45.95%)                    |
|                                 |                               |                                        |                    |                  | Kellgren-Lawrence Classification, Grade 4 - 11 (29.73%)                    |
|                                 |                               | Knee Lavage + Hylan G-F 1-3 weekly injections | 41                 | 63.9 yr (Total: 39 – 68) | Osteoarthritis, Patellofemoral, Moderate to Severe - 10 (22.73%)         |
|                                 |                               |                                        |                    |                  | Kellgren-Lawrence Classification, Grade 1 - 5 (11.36%)                     |
|                                 |                               |                                        |                    |                  | Kellgren-Lawrence Classification, Grade 2 - 6 (13.64%)                     |
|                                 |                               |                                        |                    |                  | Kellgren-Lawrence Classification, Grade 3 - 21 (47.73%)                    |
| Author and Year | Study Design | Interventions | Number of Patients | Mean Age | OA Grade |
|----------------|--------------|---------------|--------------------|----------|----------|
| Waddell DD 2005<sup>54</sup> | Non-Controlled Clinical Trial | Hylan G-F 1-3 weekly injections | 71 | 65.5 yr (SD ± 11.1, Total: 40 – 87) | Kellgren-Lawrence Classification, Grade 2 - 1 (1.4%) Kellgren-Lawrence Classification, Grade 3 - 18 (25.4%) Kellgren-Lawrence Classification, Grade 4 - 52 (73.2%) |
| Yan CH 2015<sup>55</sup> | Observational Non-Comparative | Hylan G-F Single injection | 95 | 62 yr (SD ± 9.8, Total: 33 – 86) | Kellgren-Lawrence Classification, Grade 1 - 5 (5.26%) Kellgren-Lawrence Classification, Grade 2 - 30 (31.58%) Kellgren-Lawrence Classification, Grade 3 - 38 (40%) Kellgren-Lawrence Classification, Grade 4 - 37 (38.95%) |

NR= not reported, yr= year
| Author and Year | Interventions | WOMAC | VAS Pain | SF-36 MCS | SF-36 PCS |
|-----------------|--------------|--------|----------|-----------|-----------|
| Acharya KKV 2013 | Hylan G-F Single injection | WOMAC - 32 units | -- | -- | VAS, Pain, % Change - 87% | -- | -- |
| Arthroscopy     | WOMAC - 62 units | -- | -- | VAS, Pain, % Change - 42% | -- | -- |
| Atamaz F 2006  | Hylan G-F 1-3 weekly injections | WOMAC, Pain, Likert - 10.2 units (SD ± 2.9) | WOMAC, Physical Function, Likert - 38.9 units (SD ± 11.7) | VAS, Pain, Spontaneous - 49 mm (SD ± 13.3) | SF-36, Physical Functioning - 54 units (SD ± 25.9) |
| Sodium hyaluronate + sodium chloride (Orthovisc®) | WOMAC, Pain, Likert - 11.2 units (SD ± 3.5) | WOMAC, Physical Function, Likert - 37.6 units (SD ± 13.6) | VAS, Pain, Spontaneous - 56.7 mm (SD ± 23) | SF-36, Physical Functioning - 31 units (SD ± 14.3) |
| Physical Therapy Agents | WOMAC, Pain, Likert - 15.5 units (SD ± 4.1) | WOMAC, Physical Function, Likert - 38.2 units (SD ± 12.6) | VAS, Pain, Spontaneous - 59.5 mm (SD ± 21.2) | SF-36, Physical Functioning - 53 units (SD ± 22.7) |
| Clarke S 2005  | Hylan G-F 1-3 weekly injections | WOMAC, Pain, VAS - 205 mm (SD ± 133.24, 95% CI: 150 – 260) | WOMAC, Physical Function, VAS - 700 mm (SD ± 462.69, 95% CI: 509 – 891) | VAS, Stiffness, VAS - 89 mm (SD ± 60.56, 95% CI: 64 – 114) | -- | -- |
| Cole BJ 2017  | Hylan G-F 1-3 weekly injections | WOMAC, Pain - 4 units (SD ± 4.24, SE ± 0.6) | WOMAC, Physical Function, VAS - 4 units (SE ± 4.24) | VAS, Pain - 57.3 mm (SD ± 26.87, SE ± 3.8) | -- | -- |
| Platelet-Rich Plasma | WOMAC, Pain - 3.02 units (SD ± 3.36, SE ± 0.48) | WOMAC, Physical Function, VAS - 3.02 units (SE ± 0.48) | VAS, Pain - 44 mm (SD ± 32.2, SE ± 4.6) | -- | -- |
| Author and Year | Interventions | WOMAC | VAS Pain | SF-36 MCS | SF-36 PCS |
|----------------|--------------|-------|----------|-----------|-----------|
| Daniel D 2011[^45] | Hylan G-F Single injection | -- | -- | -- | -- |
| Huskin JP 2008[^46] | Hylan G-F 1-3 weekly injections | WOMAC - 20.6 units | WOMAC, Pain - 3.8 units | WOMAC, Physical Function - 14.2 units | WOMAC, Stiffness - 1.4 units | VAS, Pain, Walking - 26.8 mm | -- | -- |
| Karlsson J 2002[^44] | Hylan G-F 1-3 weekly injections | -- | -- | -- | -- | VAS, Pain, Maximum, Change - -22.3 mm | -- | -- |
| 1% hyaluronan (Artzal[^5]) – 3 injections per week | -- | -- | -- | -- | VAS, Pain, Maximum, Change - -23.5 mm | -- | -- |
| Placebo | -- | -- | -- | -- | VAS, Pain, Maximum, Change - Baseline - -21.9 mm | -- | -- |
| Kearey P 2016[^46] | Hylan G-F Single injection | WOMAC, Change - 18.19 units (SD ± 23.6) | WOMAC, Pain, % Change - 36.77% | WOMAC, Physical Function, Change - 17.55 units (SD ± 23.9) | WOMAC, Stiffness, Change - -20.25 units (SD ± 26.18) | SF-36, Mental Component - 45.79 units (SD ± 13.84) | SF-36, Physical Component - 35.47 units (SD ± 10.29) |
| Pal S 2014[^47] | Hylan G-F Single injection | -- | WOMAC, Pain, VAS - 27 mm (SD ± 17.1) | WOMAC, Physical Function, VAS - 28.7 mm (SD ± 17.8) | WOMAC, Stiffness, VAS - 27 mm (SD ± 18.6) | SF-36, Mental Component, Change - 3 units (SD ± 10.17) | SF-36, Physical Component, % Change - 9.24% | SF-36, Physical Component, % Change - 9.24% |
| Author and Year | Interventions | WOMAC | VAS Pain | SF-36 MCS | SF-36 PCS |
|-----------------|---------------|--------|-----------|-----------|-----------|
| Pandey SK 2017<sup>37</sup> | Hylan G-F Single injection | WOMAC, Likert - 36 units (SD ± 11.65) | -- | -- | -- |
| Raman R 2008<sup>38</sup> | Hylan G-F 1-3 weekly injections | WOMAC, Physical Function, Likert - 15 units | VAS, Pain - 3.5 cm | -- | -- |
| Sodium Hyaluronate (Hyalgan<sup>6</sup>) | WOMAC, Physical Function, Likert - 33.3 units | VAS, Pain - 6.4 cm | -- | -- |
| Raynault JP 2002<sup>32</sup> | Hylan G-F 1-3 weekly injections | WOMAC, Physical Function, Likert - 24.26 units (SD ± 12.95) | SF-36, Mental Component - 55.29 units (SD ± 10.45) | SF-36, Physical Component - 33.24 units (SD ± 10.16) |
| Appropriate Care | WOMAC, Physical Function, Likert - 33.87 units (SD ± 13.88) | SF-36, Mental Component - 52.65 units (SD ± 11.56) | SF-36, Physical Component - 27.78 units (SD ± 8.9) | SF-36, Physical Component - 20.31% (SD ± 37.43) |
| Author and Year | Interventions | WOMAC | VAS Pain | SF-36 MCS | SF-36 PCS |
|-----------------|---------------|-------|----------|-----------|----------|
|                 |               | Total | Pain     | Physical Function | Stiffness |
| Raynault JP 2005 | Hylan G-F (Single-Course) | -- | WOMAC, Pain - 6.71 units | WOMAC, Physical Function - -39.6% | WOMAC, Stiffness, % Change - -35.8% | -- | SF-36, Mental Component, % Change - 9.8% | SF-36, Physical Component, % Change - 19.7% |
|                 | Hylan G-F (Repeat-Course) | -- | WOMAC, Pain - 7.44 units | WOMAC, Physical Function - -35% | WOMAC, Stiffness, % Change - -33% | -- | SF-36, Mental Component, % Change - 14.3% | SF-36, Physical Component, % Change - 21.3% |
|                 | Appropriate Care | -- | WOMAC, Pain - 10.1 units | WOMAC, Physical Function - -14.5% | WOMAC, Stiffness, % Change - -10.4% | -- | SF-36, Mental Component, % Change - 5.4% | SF-36, Physical Component, % Change - 1.1% |
| Trueba Vasavilbaso C 2017 | Hylan G-F 1-3 weekly injections | WOMAC, Likert - 18.6 units (SD ± 8.55) | WOMAC, Pain, Likert, % Change - -48.48% | WOMAC, Physical Function, Likert, % Change - -72.82% | WOMAC, Stiffness, Likert, % Change - -50% | -- | -- | -- |
|                 | Hylauroinic Acid (Orthovisc®) 4 injections | WOMAC, Likert - 51.4 units (SD ± 27.46) | WOMAC, Pain, Likert, % Change - -21.71% | WOMAC, Physical Function, Likert, % Change - -23.59% | WOMAC, Stiffness, Likert, % Change - 39% | -- | -- | -- |
|                 | Hylauroinic Acid (Suprahyal®/Adant®) 5 injections | WOMAC, Likert - 17.2 units (SD ± 13.07) | WOMAC, Pain, Likert, % Change - -71.07% | WOMAC, Physical Function, Likert, % Change - -71.06% | WOMAC, Stiffness, Likert, % Change - 80% | -- | -- | -- |
|                 | Platelet Rich Plasma | WOMAC, Likert - 30 units (SD ± 35.11) | WOMAC, Pain, Likert, % Change - -32.42% | WOMAC, Physical Function, Likert, % Change - -51.13% | WOMAC, Stiffness, Likert, % Change - 35% | -- | -- | -- |
| Author and Year | Interventions | WOMAC | VAS Pain | SF-36 MCS | SF-36 PCS |
|-----------------|---------------|--------|----------|-----------|-----------|
|                 |               | Total  | Pain     | Physical Function | Stiffness |          |          |          |
| Standard Care   | WOMAC, Likert -- 53.5 units (SD ± 16.5) WOMAC, Likert, % Change --10.28% (± 50.08) | WOMAC, Pain, Likert, % Change - 29.44% WOMAC, Physical Function, Likert, % Change - -41.46% WOMAC, Stiffness, Likert, % Change - 55% | -- | -- | -- |
| Vad VB 2003^1)  | Hylan G-F 1-3 weekly injections | -- | -- | -- | VAS, Pain - 3.2 cm (± 1.2) | -- | -- |
|                 | Knee Lavage + Hylan G-F 1-3 weekly injections | -- | -- | -- | VAS, Pain - 2.1 cm (± 1.4) | -- | -- |
| Waddell DD 2005^4 | Hylan G-F 1-3 weekly injections | WOMAC, Change - 19.8 units (SD ± 15.21, SE ± 2.13) WOMAC, Pain, Walking - 1.25 units (SD ± 0.79, SE ± 0.11) WOMAC, Pain, Walking, Change - 1.1 units (SD ± 0.86, SE ± 0.12) | WOMAC, Physical Function, Change - -13.69 units (SD ± 11, SE ± 1.54) | -- | -- | -- |
| Yan CH 2015^6   | Hylan G-F Single injection | -- | -- | -- | VAS, Pain - 48 mm (SD ± 20.6, Total: 0 – 85) | -- | -- |
### Table S6 Safety outcomes

| Author and Year | Interventions | Adverse Events | Drug Discontinuation due to AE | Study Withdrawal due to AE |
|-----------------|---------------|----------------|------------------------------|---------------------------|
| Atamaz F 2006<sup>28</sup> | Hylan G-F 1-3 weekly injections | -- | -- | -- |
| | Sodium hyaluronate + sodium chloride (Orthovisc<sup>®</sup>) | -- | -- | -- |
| | Physical Therapy Agents | -- | -- | -- |
| Boutefnouchet T 2017<sup>49</sup> | Hylan G-F Single injection | -- | -- | -- |
| Clarke S 2005<sup>50</sup> | Hylan G-F 1-3 weekly injections | -- | -- | -- |
| Daniel D 2011<sup>48</sup> | Hylan G-F Single injection | Adverse Events - 15 (2.63%) | Adverse Events, Treatment-Related - 0 (0%) | -- |
| Huskin JP 2008<sup>41</sup> | Hylan G-F 1-3 weekly injections | -- | -- | -- |
| Karatosun V 2005<sup>53</sup> | Hylan G-F 1-3 weekly injections | -- | -- | -- |
| | Low-Molecular Weight Hyaluronic acid - 3 injections (Orthovisc<sup>®</sup>) | -- | -- | -- |
| Author and Year | Interventions | Adverse Events | Drug Discontinuation due to AE | Study Withdrawal due to AE |
|-----------------|---------------|---------------|---------------------------------|---------------------------|
|                 |               | Total | Serious | Treatment-Related | Target Knee |                |                |
| Karlsson J 2002 | Hylan G-F 1-3 weekly injections | -- | -- | Adverse Events, Treatment-Related, Serious - 0 (0%) | -- | Drug Discontinuation, Adverse Events - 1 (1.16%) | -- |
|                 | 1% hyaluronan (Artzal®) – 3 injections per week | -- | -- | Adverse Events, Treatment-Related, Serious - 0 (0%) | -- | Drug Discontinuation, Adverse Events - 2 (2.22%) | -- |
|                 | Placebo       | -- | -- | Adverse Events, Treatment-Related, Serious - 0 (0%) | -- | Drug Discontinuation, Adverse Events - 2 (3.03%) | -- |
| Kearey P 2016   | Hylan G-F Single injection | Adverse Events - 37 (28%) | -- | -- | -- | -- | -- |
| Lee S 2004      | Hylan G-F 1-3 weekly injections | -- | -- | Adverse Events, Treatment-Related, Localized - 3 (4%) | -- | -- | -- |
| Pal S 2014      | Hylan G-F Single injection | -- | Adverse Events, Serious - 6 (2%) | Adverse Events, Treatment-Related - 10 (3%) | Adverse Events, Target Knee - 23 (5.8%) | -- | Study Withdrawal, Adverse Events - Baseline – 52 1 (0.25%) |
| Raman R 2008    | Hylan G-F 1-3 weekly injections | -- | Adverse Events, Serious - 1 (0.52%) | Adverse Events, Treatment-Related - 39 (20.1%) | -- | -- | Study Withdrawal, Adverse Events - 0 (0%) |
|                 | Sodium Hyaluronate (Hyalgan®) | -- | Adverse Events, Serious - 1 (0.52%) | Adverse Events, Treatment-Related - 30 (16.13%) | -- | -- | Study Withdrawal, Adverse Events - 0 (0%) |
| Raynauld JP 2002 | Hylan G-F 1-3 weekly injections | Adverse Events - 122 (96%) | Adverse Events, Serious - 1 (0.52%) | -- | -- | -- | -- |
|                 | Appropriate Care | Adverse Events - 115 (90%) | Adverse Events, Serious - 1 (0.52%) | -- | -- | -- | -- |
| Raynauld JP 2005 | Hylan G-F(Single-Course) | -- | -- | Adverse Events, Treatment-Related, Target Knee - 1 (1.28%) | -- | -- | -- |

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| Author and Year | Interventions | Adverse Events | Drug Discontinuation due to AE | Study Withdrawal due to AE |
|-----------------|---------------|----------------|-------------------------------|--------------------------|
|                 |               | **Total**      | **Serious**                  | **Target Knee**          |
|                 |               | **Treatment-Related** | **Adverse Events, Treatment-Related, Target Knee - 5** (10.42%) | **Adverse Events, First Course, Target Knee - 11 (22.92%)** |
|                 |               |                | **Adverse Events, Treatment-Related, First Course, Target Knee - 2** (4.17%) | **Adverse Events, Second Course, Target Knee - 13 (27.08%)** |
|                 |               |                | **Adverse Events, Treatment-Related, Second Course, Target Knee - 3** (6.25%) | --                       |
| Hylan G-F (Repeat-Course) | -- | -- | -- | -- |
| Hylan G-F (Repeat-Course) | -- | -- | -- | -- |
| Appropriate Care | -- | -- | -- | -- |
| Rolf CG 2005 | Hylan G-F 1-3 weekly injections | Adverse Events - 53 (59%) | -- | -- |
|                 | Adverse Events, Treatment-Related, Severe - 1 (1.11%) | -- | -- | -- |
|                 | Adverse Events, Treatment-Related, Serious - 0 (0%) | -- | -- | -- |
| Hylan G-F 1-3 weekly injections | Adverse Events - 53 (59%) | -- | -- | -- |
| Hylauron (Artzal®) | Adverse Events - 55 (60%) | -- | -- | -- |
| Placebo | Adverse Events - 55 (60%) | -- | -- | -- |
| Trueba Vasavilbaso C 2017 | Hylan G-F 1-3 weekly injections | -- | -- | -- |
| Hylan G-F 1-3 weekly injections | -- | -- | -- | -- |
| Hylauronic Acid (Orthovisc®) 4 injections | -- | -- | -- | -- |
| Author and Year   | Interventions                          | Adverse Events                                                                 | Drug Discontinuation due to AE | Study Withdrawal due to AE |
|------------------|----------------------------------------|--------------------------------------------------------------------------------|--------------------------------|---------------------------|
|                  |                                        | Total | Serious | Treatment-Related | Target Knee |                                            |                                              |
| Hylauronic Acid (Suprahyal®/Adant®) 5 injections | -- | -- | Adverse Events, Treatment-Related - 0 (0%) |-- |-- |-- |-- |
| Platelet Rich Plasma | -- | -- | Adverse Events, Treatment-Related - 0 (0%) |-- |-- |-- |-- |
| Standard Care    | -- | -- | Adverse Events, Treatment-Related - 0 (0%) |-- |-- |-- |-- |
| Waddell DD 200564 | Hylan G-F 1-3 weekly injections | -- | -- | Adverse Events, Treatment-Related, Possible - 3 (4.2%) |-- |-- |Study Withdrawal, Adverse Events, Treatment-Related - 0 (0%) |
| Yan CH 201556    | Hylan G-F Single injection              | Adverse Events - 18 (16.4%) | -- | -- | -- | -- |
Table S7 Cochrane Collaboration tool

| Domain                           | Support for judgment                                                                 | Review authors' judgement                                                                 |
|----------------------------------|---------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| **Selection bias**               |                                                                                       |                                                                                           |
| Random sequence                  | Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. | Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence. |
| generation.                      |                                                                                       |                                                                                           |
| Allocation concealment.          | Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. | Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment. |
| **Performance bias**             |                                                                                       |                                                                                           |
| Blinding of participants and personnel | Assessments should be made for each main outcome (or class of outcomes).              |                                                                                           |
| Assessment                       | Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective. | Performance bias due to knowledge of the allocated interventions by participants and personnel during the study. |
| **Detection bias**               |                                                                                       |                                                                                           |
| Blinding of outcome assessment   | Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective. | Detection bias due to knowledge of the allocated interventions by outcome assessors.        |
| Assessment                       |                                                                                       |                                                                                           |
| Attribition bias                 | Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors. | Attribition bias due to amount, nature or handling of incomplete outcome data.               |
| **Reporting bias**               |                                                                                       |                                                                                           |
| Selective reporting              | State how the possibility of selective outcome reporting was examined by the review authors, and what was found. | Reporting bias due to selective outcome reporting.                                          |
| **Other bias**                   |                                                                                       |                                                                                           |
| Other sources of bias            | State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review’s protocol, responses should be provided for each question/entry. | Bias due to problems not covered elsewhere in the table.                                   |
Table S8 Cochrane quality assessment summary

| Author & Year           | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Other Bias | Other Source of Bias |
|-------------------------|----------------|------------------|----------------|----------------|----------------|------------|----------------------|
|                         | Random Sequence Generation | Allocation Concealment | Blinding of Participants and Personnel | Blinding of Outcome Assessment | Incomplete Outcome Data | Selective Outcome Reporting | Source of Bias |
| Acharya KKV 201327      | Unclear        | Unclear          | Unclear        | Unclear        | Unclear        | Low        | Low                  |
| Atamaz F 200628         | Unclear        | Unclear          | High           | High           | High           | Low        | High                 |
| Cole BJ 201731          | Unclear        | Unclear          | Low            | Low            | High           | Low        | Low                  |
| Juni P 200725           | Low            | Low              | High           | Low            | Low            | Low        | High                 |
| Karatosun V 200533      | Low            | Low              | Low            | Low            | High           | Low        | Low                  |
| Karlsson J 200234       | Low            | Low              | Low            | High           | Low            | High       | Low                  |
| Raman R 200836          | Low            | Low              | High           | Low            | High           | Low        | Low                  |
| Raynauld JP 200232      | Low            | Low              | High           | High           | High           | Low        | High                 |
| Rolf CG 200538          | Unclear        | Unclear          | Low            | High           | Low            | Low        | High                 |
| Trueba Vasavilbaso C 201739 | Low            | Unclear          | High           | Low            | High           | Low        | Low                  |
## Table S9 Newcastle-Ottawa Scale

| Study Design | Selection | Comparability | Outcome/Exposure |
|--------------|-----------|---------------|-----------------|
| **Cohort**   | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of the design or analysis | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow-up of cohorts |
| **Case Control** | Is the case definition adequate | Representativeness of the cases | Selection of controls | Definition of controls | Comparability of cases and controls on the basis of the design or analysis | Ascertainment of exposure | Same method of ascertainment of cases and controls | Non-response rate |
Table S10 Newcastle-Ottawa Scale quality assessment

| Author & Year | Selection | Comparability | Exposure or Outcome | Final Score |
|---------------|-----------|---------------|---------------------|-------------|
| Clarke S 2005 | **        | *             |                     | 3           |
| Daniel D 2011 | **        | *             |                     | 3           |
| Huskin JP 2008| **        | *             |                     | 3           |
| Kearey P 2016 | **        | **            | *                   | 5           |
| Lee S 2004   | ***       | *             |                     | 4           |
| Pal S 2014   | ***       | **            | **                  | 7           |
| Pandey SK 2017| *         | *             | *                   | 3           |
| Vad VB 2003  | ***       | *             | **                  | 6           |
| Waddell DD 2005| **       | **            | *                   | 5           |
| Yan CH 2015  | **        | **            |                     | 4           |

The Newcastle-Ottawa Scale is an instrument that is used to evaluate three domains of bias: selection of study groups, comparability of the groups, and assessment of outcome/exposure (Table S9). Each high-quality item was allocated with a star. A maximum of one star can be designated for each item within the “Selection” and “Outcome/Exposure” and a maximum of two stars for “Comparability.” The sum of stars for each study can range from 0 to 9 stars. Studies are rated as low (0-3 stars), moderate (4-6 stars), or high (7-9 stars) quality.

The quality of 10 non-RCT studies were assessed with the Newcastle-Ottawa Scale (Table S10). Boutefnouchet et al. 2017 is a case series and was not assessed using the Newcastle-Ottawa Scale as the scale is designed for cohort and case control studies. Overall, studies were mainly rated as moderate quality. Nine studies (90%) were rated as moderate quality, with 6 studies (60%) receiving a final score of 4, 6,8,9,14,16,24 1 study (10%) receiving a final score of 5, 23 and 2 studies (20%) receiving a final score of 6. 13,22 One study (10%) was rated as high quality with a final score of 7. 15 For the Selection criteria, the majority of studies (7 studies, 70%) were allocated 3 stars. 6,8,9,13-15,22 Three studies (30%) were allocated 2 stars. 16,23,24 For the Comparability criteria, the majority of the studies (5 studies, 50%) were allocated 0 stars. 6,8,9,14,24

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Two studies (20%) were allocated 1 star\textsuperscript{16} and three studies (30%) were allocated 2 stars.\textsuperscript{15,23} For the Exposure/Outcome criteria, the majority of the studies (7 studies, 70%) were allocated 1 star\textsuperscript{6,8,9,13,14,16,23} and the remaining three studies were allocated 2 stars.\textsuperscript{15,22,24}
| Type of Adverse Event                                      | Studies Reporting AE |
|----------------------------------------------------------|----------------------|
| Adverse Events, Overall                                  | 2,5,6,8,12,13,18,20,24 |
| Adverse Events, Treatment Related                        | 11,12,13,17,21       |
| Anaphylactic shock                                       | 10                   |
| Arthralgia                                               | 8,15,20,23           |
| Arthritis                                                | 23                   |
| Arthropathy                                              | 20                   |
| Arthrosis                                                | 23                   |
| Asthmatic Crisis                                         | 8                    |
| Back Pain                                                | 20                   |
| Bacterial Infection                                      | 20                   |
| Burning Sensation                                        | 8                    |
| Bursitis                                                 | 15                   |
| Cerebrovascular Accident                                 | 6                    |
| Chills                                                   | 8                    |
| CNS Disorders                                            | 8,10,20              |
| Coryzal Symptoms                                         | 6                    |
| Effusion                                                 | 10                   |
| Endocrine and Metabolic Disorders                        | 10                   |
| Flare                                                    | 10                   |
| Flushing                                                 | 8                    |
| Foot Pain                                                | 6                    |
| General Disorders and Administration Site Conditions     | 8,10                 |
| GI                                                       | 8,10,18,20           |
| GI, Severe                                               | 18                   |
| GI, Severe, Treatment Related                            | 18                   |
| Headache                                                 | 20                   |
| Hypersensitivity                                         | 8                    |
| Hyperventilation                                         | 8                    |
| Hypotension                                              | 8                    |
| Immune System Disorders                                  | 8                    |
| Infected toenail                                         | 6                    |
| Infection                                                | 20                   |
| Influenza-like Symptoms                                  | 20                   |
| Type of Adverse Event                                      | Studies Reporting AE |
|-----------------------------------------------------------|----------------------|
| Injection Site Reaction (total)                           | 2,6,14,15,20         |
| Injection Site Reaction, Mild                             | 6                    |
| Injection Site Reaction, Moderate or Severe               | 6                    |
| Joint Effusion                                            | 8                    |
| Joint or Musculoskeletal Stiffness                        | 6,8,15               |
| Joint Swelling                                            | 8,24                 |
| Local AE, Requiring Additional Treatment                  | 10                   |
| Local or Target Knee AE, Moderate to Severe               | 15                   |
| Local or Target Knee AE                                  | 10,13,15,18,19,22    |
| Local or Target Knee AE, Treatment Related               | 8,9,13,15,18,19,23   |
| Mental and Behavioral Disorders                          | 10                   |
| Mild Adverse Events                                       | 8,17,24              |
| Mild Adverse Events, Treatment Related                    | 13                   |
| Moderate Adverse Events                                   | 8                    |
| Moderate Adverse Events, Treatment Related                | 13                   |
| MSK Disorders                                             | 8,10,20              |
| Myalgia                                                   | 8                    |
| Nausea                                                    | 6,8                  |
| Neck pain                                                 | 6                    |
| Neoplasms                                                 | 10                   |
| Pain                                                      | 8,20,24              |
| Pain in Contralateral Knee                                | 6                    |
| Polycythaemia rubra vera                                  | 6                    |
| Respiratory System Disorder                               | 8,10,20              |
| Rheumatoid Arthritis                                      | 6                    |
| Rhinitis                                                  | 20                   |
| Septic Arthritis                                          | 10                   |
| Severe/Serious Adverse Events                            | 2,8,10,12,13,15,17,18,24 |
| Severe/Serious Adverse Events, Treatment-Related         | 10,13,20             |
| Sinusitis                                                  | 20                   |
| Skeletal Pain                                             | 20                   |
| Syncope                                                   | 8                    |
| Synovitis                                                 | 8,9,15               |
| Systemic Adverse Events                                   | 2,14,15,17,20        |
| Type of Adverse Event                          | Studies Reporting AE |
|-----------------------------------------------|----------------------|
| Systemic Adverse Events, Treatment Related    | 15                   |
| Target Knee AE, Mild or Moderate, Treatment Related | 9,13,19,23           |
| Target Knee AE, Severe, Treatment Related     | 9,13,23              |
| Toothache                                     | 20                   |
| Urinary System Disorder                       | 10,20                |
| UTI                                           | 20                   |
| Vascular Disorders                            | 8,10                 |
| Vascular Disorders                            | 8                    |
| Vertigo                                       | 8                    |
| Viral Infection                               | 20                   |
Figure S1 PRISMA diagram

Gap search results from October 18, 2018 to August 17, 2020
The Cochrane Collaboration’s tool is an instrument that is used to evaluate seven domains of bias: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other sources of bias (other bias) (Table S7).26

Risk of bias assessments were conducted on 10 trials (13 publications) (Table S8 and Figure S2). The risk of selection bias was mostly low risk for random sequence generation (60%, 6 trials) and unclear risk for allocation concealment (50%, 5 trials); there were no trials assessed as high risk. For performance bias, pertaining to the blinding of participants and personnel, 50% (5 trials) were assessed as high risk as they were single-blinded or open-label studies, 40% (4 trials) were assessed as low risk, and 20% (2 trials) were assessed as unclear risk. The risk of detection bias, pertaining to the blinding of outcome assessment was mainly low (70%, 7 studies); however, 20% (2 trials) were assessed as high risk as they were single-blinded or open-label studies. For attrition bias, pertaining to incomplete outcome data, 80% (8 trials) were assessed...
as high risk as studies had high rates of dropouts, differential rates of dropouts between groups, and/or missing data have not been imputed using appropriate methods; 10% (1 trial) was assessed as low risk and 10% (1 trial) was assessed as unclear risk. The risk of reporting bias, pertaining to selective outcome reporting, was mainly low (90%, 9 studies) and there were no trials assessed as high risk. The risk of other bias was mainly low (50%, 5 trials); however, 50% (5 trials) were assessed as high risk as the studies allowed retreatment and/or concomitant medication, which may have skewed the outcome estimates.
Figure S3 WOMAC Stiffness (non-RCTs)

| Author (Year) Scale | SMCC [95% CI] |
|---------------------|---------------|
| **Synvisc-One**     |               |
| Pal S (2014) 0-200  | -1.17 [-1.29, -1.04] |
| Kearey P (2016) 0-20| -0.77 [0.97, -0.56]  |
| REML Model for Synvisc-One I^2 = 90.36% |               |
| **Synvisc**         |               |
| Clarke S (2000) 0-200| -0.35 [0.65, -0.04]  |
| Huskin JP (2008) 0-8 | -1.52 [1.88, -1.19]  |
| REML Model for Synvisc I^2 = 95.65% |               |

RE Model (Q 36,11 df = 3, p = 0.00, I^2 = 94.3%) | -0.99 [-1.42, -0.47] |

Standardized Mean Change

Figure S4 WOMAC Stiffness (RCTs)

| Author (Year) Scale | SMCC [95% CI] |
|---------------------|---------------|
| **Synvisc**         |               |
| Raynauld JP (2002) 0-0| -1.05 [-1.27, -0.83] |
| Trueba Vasavilbaso C (2017) 0-8 | -1.26 [-2.12, -0.44] |

RE Model (Q 9,27 df = 1, p = 0.60, I^2 = 0.0%) | -1.07 [-1.28, -0.86] |

Standardized Mean Change
Figure S5 VAS Pain (non-RCTs)

| Author (Year) Scale          | SMCC [95% CI] |
|------------------------------|---------------|
| Synvisc-One                  |               |
| Yan CH (2015) 0-100          | -0.54 [-0.75, -.32] |
| Synvisc                      |               |
| Vad VB (2003) 0-10           | -4.39 [-5.44, -.34] |
| RE Model (Q = 69, df = 6, p < 0.00, I² = 98.8%) | -2.42 [-6.20, 1.35] |

Figure S6 VAS Pain (RCTs)

| Author (Year) Scale          | SMCC [95% CI] |
|------------------------------|---------------|
| Synvisc                      |               |
| Raman R (2008) 0-10          | -2.45 [-2.73, -.17] |
| Cole BL (2017) 0-100         | -0.23 [-0.49, 0.03] |
| Atanazi F (2006) 0-100       | -2.12 [-2.91, -1.33] |
| REML Model for Synvisc I² = 97.62% | -1.58 [-2.97, -.19] |
| RE Model (Q = 136.25, df = 2, p = 0.00, I² = 97.8%) | -1.58 [-2.97, -.19] |
Across 3 non-RCT studies with 812 participants, 11% (95% CI 3, 38; p=0.0101) of those that used single Hylan G-F injection experienced an adverse event.8,13,24

Across 2 RCTs with 217 participants, 85% (95% CI 26, 99; p=0.2174) of those that used Hylan G-F 1-3 weekly injections experienced an adverse event.18,20
Across 2 non-RCT studies with 965 participants, 1% (95% CI 0, 7; p=0.0002) of those that used single Hylan G-F injection experienced a serious adverse event.\(^8,15\)

Across 2 RCTs with 321 participants, 0% (95% CI 0, 2; p<0.0001) of those that used Hylan G-F 1-3 weekly injections or experienced a serious adverse event.\(^17,18\)

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**Figure S9 Serious Adverse Events (Non-RCTs)**

| Author (Year) Scale | PRO [95% CI] |
|---------------------|-------------|
| Hylan G-F Single Injection |
| Pal S (2014)         | 0.02 [0.01, 0.03] |
| Daniel D (2011)      | 0.00 [0.00, 0.01] |
| RE Model (Q < 0.00 df = 1, p = 0.05) \(P^2 = 73.7\%\) | 0.01 [0.00, 0.07] |

**Figure S10 Serious Adverse Events (RCTs)**

| Author (Year) Scale | PRO [95% CI] |
|---------------------|-------------|
| Hylan G-F 1-3 Injections |
| Raynaud JP (2002)   | 0.00 [0.00, 0.06] |
| Raman R (2006)      | 0.01 [0.00, 0.04] |
| RE Model (Q < 0.03 df = 1, p = 0.67) \(P^2 = 0.0\%\) | 0.00 [0.00, 0.02] |
Across 2 non-RCT studies with 471 participants, 2% (95% CI 1, 4; p<0.0001) of those that used single Hylan G-F injection experienced a treatment-related adverse event.$^5,15$
Across 3 RCTs with 236 participants, 8% (95% CI 1, 35; p=0.0088) of those that used Hylan G-F 1-3 weekly injections experienced a treatment-related adverse event.\textsuperscript{11,17,21}