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Intra-articular hyaluronic acid in knee osteoarthritis: clinical data for a product family (ARTHRUM), with comparative meta-analyses

Patrice Vincent, Engineer (ENSAM)*

R&D manager, LCA Pharmaceutical, 9 allée Prométhée, 28000 Chartres, France

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ABSTRACT

Introduction: Viscosupplementation is widely practiced, to reduce pain in osteoarthritis (OA), using intra articular (IA) injections of hyaluronic acid (HA). In Europe, these products are class III medical devices, for which the Medical Device Regulation (MDR) requires clinical assessment, based on specific studies and/or a bibliographical review of equivalent devices. The purpose of this article is to present a comparative review between a family of devices (ARTHRUM, from LCA Pharmaceuticals, Chartres, France) and an extensive group of presumed equivalent IA HA devices or their controls, whose results have been published in Scientific journals.

Methods: To meet the criteria used in most ARTHRUM studies, the Western Ontario and McMaster Universities' index sub-scores were selected for pain (WOMAC A), stiffness (WOMAC B) and function (WOMAC C). The main criterion was the variation of the WOMAC A score from T0 (date of inclusion) to T6 (6 months). The other WOMAC criteria were assessed at T1, T3, T6 and complemented by OMERACT-OARSI rates of responders to the treatment. Fifty articles were selected, containing treatment details on more than 12,000 patients. These were divided into three groups: ARTHRUM, EQUIVALENTS and CONTROLS. To get quantitative comparisons, meta-analyses were performed for each criterion individually. The 95% confidence interval of each difference from baseline, was used to assess the clinical relevance, with reference to a minimum validated in OA literature. Comparisons between groups and tolerance assessment completed the investigation.

Results: For the WOMAC A, B and C scores, the full 95% CI was always above the minimal perceptible clinical improvement (MPCI), in the ARTHRUM and EQUIVALENTS groups, but not for all criteria in the CONTROLS group. In the comparisons, both ARTHRUM and EQUIVALENTS groups were significantly better than the CONTROLS group for each criterion. The effect size (ES) on pain, for the ARTHRUM and EQUIVALENTS groups, varied from 0.28 to 0.56 and from 0.23 to 0.27, respectively. Overall, ARTHRUM was estimated always non-inferior to EQUIVALENTS, and sometimes statistically and clinically superior.

Conclusions: The comparison of ARTHRUM clinical studies, with studies selected through bibliographic research, leads to the conclusion that the clinical efficacy of the ARTHRUM medical devices, to reduce pain and improve the function in knee OA, during a six-month period, is at least as great as those of equivalent products. With good tolerance results (lowest rate of adverse events, and none of them serious), the risk benefit ratio favours using viscosupplementation with ARTHRUM.

Introduction

Osteoarthritis (OA) is a painful and handicapping disease, affecting a large part of the elderly population. OA is characterized by the loss of hyaluronic acid (HA) which is a major component

Abbreviations: AE, adverse event; CD, Cohen's D (effect size); CI, confidence interval (with probability %); CS, chondroitin sulfate; ES, effect size; GAG, glycosaminoglycan; HA, hyaluronic acid (sodium hyaluronate); IA, intra-articular; KL, Kellgren-Lawrence (radiological OA severity scale); MD, mean difference; MDR, Medical Device Regulation; MPCI, minimal perceptible clinical improvement; MSC, mesenchymal cells; Mw, molecular weight (average in weight); NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; OMERACT, Outcomes Measurements in Rheumatology (international network); PRP, platelet rich plasma; SD, standard deviation; SAE, serious adverse event; SE, standard error; SF, synovial fluid; SSD, smallest detectable difference; WOMAC, Western Ontario & Mac Master Universities (OA index).

* Correspondence author.
E-mail address: pvincent@lca-pharma.com

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of the cartilage, naturally present in the synovial fluid (SF) of a healthy joint. HA is a long molecular chain, belonging to the glycosaminoglycan (GAG) family. Its role in the joint is complex[1], giving viscoelasticity to SF to absorb shocks, lubricate, and protect the cartilage. HA is also involved in biological mechanisms inside the joint. Viscosupplementation of SF is one symptomatic treatment of knee OA, consisting of intra articular (IA) injections of solutions containing HA, to reduce pain in and restore mobility to the OA joint.

The purpose of this study is to assess the clinical results of a family of IA HA devices (ARTHRUM), and compare them to potentially 'equivalent' devices in accordance with the definition given in the Medical Device Regulation (MDR) for Europe ECC93/42 and its imminent replacement, 2017/745. This requires that the clinical evidence for class III devices, should be based first on the specific clinical results obtained for the device under evaluation and/or, on a comparison with other devices identified as 'equivalent'. These belong to the same generic group as they are basically similar, in formulation (same major HA ingredient), presentation, physical characteristics and primary indication. All these devices are used under the same conditions (intra articular injections), by the same medical doctors, on patients suffering from the same disease (knee OA, at the same stage). The available clinical results for these 'equivalent' devices are those published in Scientific Journals, preferably peer-reviewed, to ensure quality. To resume the rationale, it appeared relevant to consolidate the assessment of ARTHRUM, with a comparison to 'equivalent' devices.

Methods

Data base

For the renewal of the CE mark for ARTHRUM products, a systematic search of the relevant bibliography was undertaken. The clinical results obtained with ARTHRUM were compared with the results available from the literature, for products described as 'Equivalents' or for 'Controls'. The ARTHRUM products were identified as a family group, to give a sample size comparable with the two other groups. The small differences in formulation for two specific ARTHRUM devices were not taken into account, because most studies were carried out with the same product: ARTHRUM H 2% (3 injections). The first variant in the family was ARTHRUM visc 75 – the single-injection version – concentrating 75mg of the same HA, in one injection. The second variant, called ARTHRUM HCS, contains chondroitin sulfate (CS), added to the HA at same proportion (2%). This unique product is discussed at the end of this article.

The bibliographical research was carried on PubMed and Cochrane databases, using key words as "hyaluronate", "viscosupplement", "knee osteoarthritis", "intra articular" or "infiltration" as well as "ARTHRUM" and "SYNOVIUM", to detect any unknown publication on ARTHRUM devices. The word "Human" was used as a filter with PubMed. A control was also done on Clinical Trials, to identify ongoing studies. This research leading to 60 articles, was closed at the end of March 2020 and then it was supplemented with several articles identified in meta-analyses, including those treated with ARTHRUM (Figure 1).

The pain sub-score of the Western Ontario and McMaster Universities[2] (WOMAC A) index was chosen as the main criterion, as it was used for most of the clinical studies done with ARTHRUM. As secondary measures, the stiffness sub-score (WOMAC B), the function sub-score (WOMAC C) and the OMERACT-OARSI[3] rates of responders were also analyzed.

Data collection and treatment has fully been made at LCA. After removal of the articles containing none of above criteria, a comprehensive and complete data was obtained for a large population of 12,860 profiled patients. All patients were assessed, at least from one WOMAC index, or from their OMERACT-OARSI rate of responders (Figure 1). Observation times were those used for the majority of the studies: T0 (at inclusion) then T1, T3 and T6 (months). Separate analyses were performed for each index.

Groups

ARTHRUM devices were grouped-as a family as all were using the same basic ingredients and manufactured under identical strict conditions, including final sterilization. For CONTROLS, the IA placebos were selected, as well as injection shams and arthrocentesis (puncture of SF, without injection). Physical exercises and oral treatments (NSAIDs) were also included. Local active treatments such as IA injections of corticosteroids, platelet rich plasma (PRP) or mesenchymal cells (MSC) were excluded. The group of EQUIVALENTS devices, was the generic group of IA HA products indicated for knee OA symptomatic treatment, called viscosupplements. Any molecular weight (Mw) at any concentration was allowed for the HA, and the presence of an ancillary ingredient was accepted (cross linker agent, mannitol, sorbitol…). This was selected in this way to obtain a realistic representation of the IA HA market.

Statistics

To allow statistical analysis, continuous variables were defined by their mean (score), together with the standard deviation (SD) and the population involved for each observation time. If SD was not available, an estimation of it was made whenever possible (measuring the graph, or starting from the standard error (SE), the 95% CI, or from the p-value). Each score has been converted into a 0-100 base, and all data were treated using Excel (MicroSoft). For discrete variables, data needed to be available under the format of the sub-populations whether satisfying or not, the analyzed criterion.

For each studied data set, the score variation from baseline was assessed, at each available observation time. The result of each measure, has been expressed as a mean difference (MD) from the score at inclusion (baseline), positive in case of improvement for the patient, together with its 95% confidence interval (95% CI). This was done for each arm in individual studies: ARTHRUM devices, CONTROLS, or EQUIVALENTS devices.

Main and secondary criteria

The main criterion is the variation (MD) of the WOMAC pain sub-score (WOMAC A), from T0 (the baseline) to T6 (the final control time). This criterion is satisfied if the lower bound of the 95% CI for the group ARTHRUM, is greater than a clinically recognized minimum, accepted in the current state of the art of medicine. The secondary criteria, include the variations (MD) of the WOMAC A sub-score at other time Intervals, the same for the WOMAC B (stiffness) and WOMAC C (function) sub-scores, and the rates of patients responding to the treatment, according to OMERACT-OARSI criteria, at all available times.

Meta-analyses of the WOMAC sub-scores results

To make a global and comparative assessment of ARTHRUM devices vs CONTROLS, and EQUIVALENTS groups, a meta-analysis has been done using Mix2.0 (BioStatXL), in the mode "random effect", to determine MD (95% CI) for each group, at times T1, T3 and T6. This has been repeated for each WOMAC sub-score. To complete the analysis, the results for each group were compared together. The result for the ARTHRUM group of devices was considered satisfactory when the average gain from baseline was:

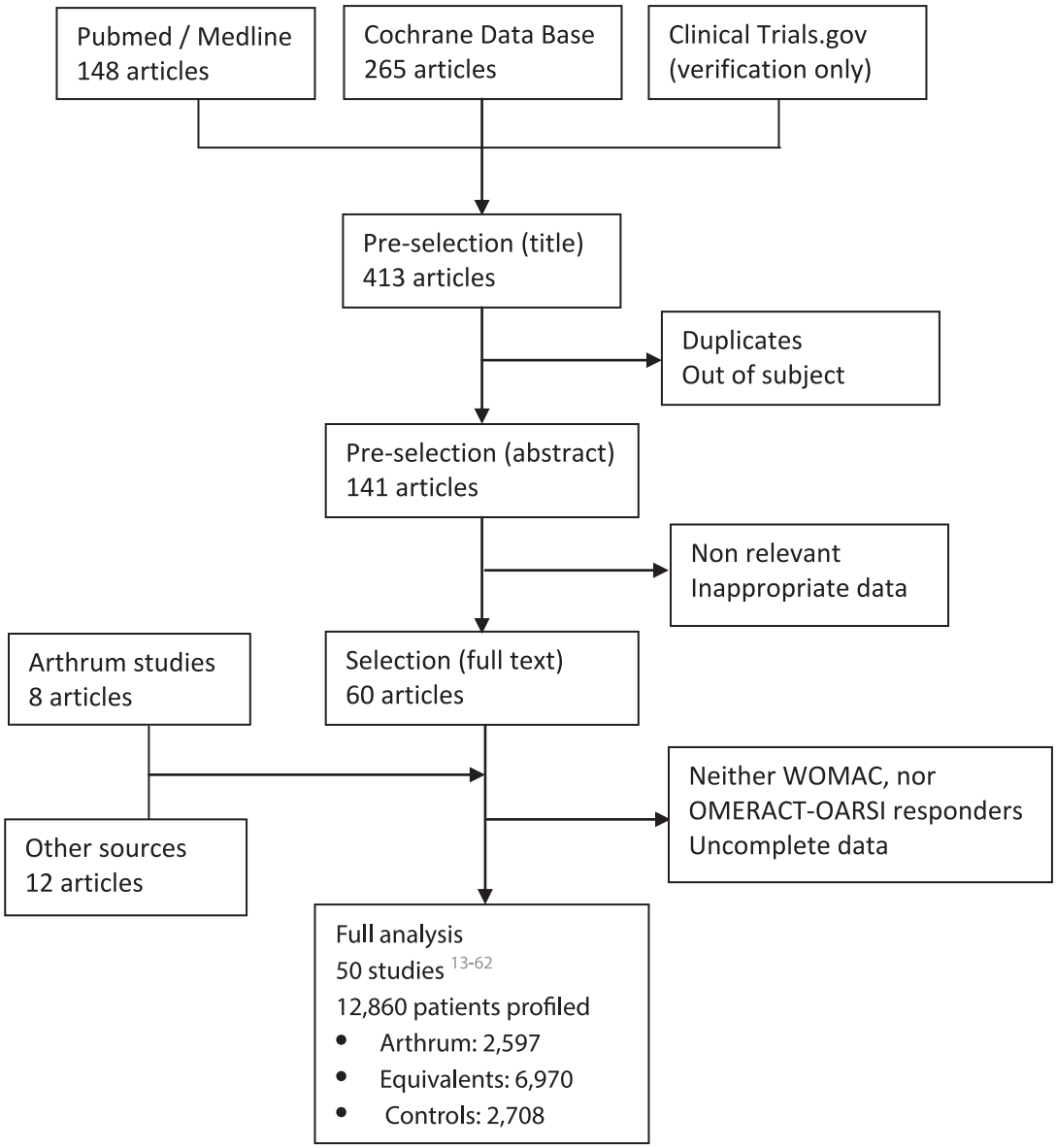

Figure 1. Data research and collection

- Greater – for its whole 95% CI – than the Minimum Perceptible Clinical Improvement (MPCI), defined by Ehrich[4], for the WOMAC A, B or C sub-scores.
- Clinically non-inferior to the EQUIVALENTS group, verifying that the lower bound of 95% CI for the ARTHRUM group, was above a non-inferiority limit. This limit was defined as MD for the EQUIVALENTS group, reduced by a non-inferiority margin, arbitrarily chosen to be equal to the SDD (Smallest Detectable Difference) defined by Angst et al[5], for each WOMAC sub-score.
- Statistically better than its homologues in the CONTROLS group ($p < 0,05$) and not worse than same in the EQUIVALENTS group.

Comparison between the groups was also made and, to give further confidence in the results, the effect size (ES) vs CONTROLS was calculated as defined by Cohen[6] (CD).

OMERACT-OARSI responders

The percentage of patients responding to OMERACT-OARSI criteria, has been re-assessed from the populations described in the studies, following two interpretation hypotheses:

- Definition "strict": base = population with sufficient criteria answered, to determine that patients were either certified responders, or certified non-responders.
- Definition "minimal": base = population with partial answers to the criteria, and for which a fraction of patients remains uncertain. In such cases, the percentage of responders is lower, as it is relative to a larger base (which can be up to the whole population included in the study). This is sometimes proposed, but is a matter for discussion, as some patients, potentially responders, may have been discarded, just because data were missing.

After re-evaluation or control of the rate of responders found in each study, a global assessment has been done for each group - ARTHRUM, EQUIVALENTS and CONTROLS. These results were then compared, using the chi^2 test and p-value.

Results

Patient profiles

The patient profiles described in the various studies (12,860 patients), were summarized to verify their representativeness regard-

Table 1
Selected studies for meta-analyses and synthesis of WOMAC results
The following tables, given per group, provide detailed results for the WOMAC A (pain sub-score)

WOMAC A			Baseline			T1			T3			T6		
AUTHOR	PUB	ARTHRUM	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD
Maravic (ART-QUALIVIE)[53]	**2019**	**Arthrum H 2%**	134	50,6	15,1				111	26,3	19,9	111	23,4	19,1
Baron (ART-ONE 75)[54]	**2018**	**Arthrum visc 75**	218	50,3	15,6	207	28	20	180	19,6	17,8	183	16,7	17,4
Thomas[55]	**2017**	**Arthrum H 2%**	202	49,9	17,2				202	33,5	17,9	202	27,6	18,2
Hilliquin (< 60 ANS)[56]	**2017**	**Arthrum H 2%**	182	32,4	18,4				182	17,7	15,6	182	12,3	13,0
Germonville[57]	**2015**	**Arthrum H 2%**	126	49,1	17,4				122	28,3	19,6	120	23,5	19,4
Hilliquin (DOULEUR & HANDICAP)[60]	**2021**	**Arthrum H 2%**	451	51,0	19,2				430	31,3	17,9	427	26,9	19,4
Vincent (LONG TERME)[58]	**2020**	**Arthrum H 2%**	1177	46,6	16,4				970	31,2	19,0	904	28,6	19,2
Rivera[59]	**2016**	**Arthrum HCS**	112	52,1	15,2	111	25,7	17,4	111	20,4	16,3	109	20,5	19,7
			2602			318			2308			2238		
AUTHOR	PUB	CONTROL	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD
Van Der Weegen[18]	**2015**	**Placebo IA**	97	44,4	15,0	97	33,0	22,5	97	25,5	24,6	96	30,5	21,8
Arden[22]	**2013**	**Placebo IA**	110	49,2	10,2	110	36,9	17,2						
Strand[24]	**2012**	**Placebo IA**	128	68,0	13,1	128	55,9	21,4	119	53,4	27,6			
DeCaria[25]	**2012**	**Placebo IA**	15	36,4	18,8	15	32,4	13,4	15	27,8	16,0	15	33,4	16,2
Huang[28]	**2011**	**Placebo IA**	100	45,4	13,1							98	23,9	19,4
Diraçoglu[29]	**2009**	**Placebo IA**	21	56,0	11,3	20	51,9	11,5						
Neustadt[37]	**2005**	**Arthrocentesis**	114	58,8	11,7				114	32,9	24,3	114	33,6	23,5
Altman[38]	**2004**	**Placebo IA**	174	52,1	11,4	139	35,2	19,1	139	35,0	20,5	139	37,7	20,9
Petrella[39]	**2002**	**NSAID**	26	42,2	32,5	26	28,6	27,5						
		Placebo IA	28	36,2	27,1	25	31,9	28,1						
Brandt[40]	**2001**	**Placebo IA**	112	81,5	13,5	69	62,3	9,0	69	62,3	22,5	69	65,3	21,2
Takamura[41]	**2018**	**Placebo IA**	159	63,5	9,2	159	48,0	22,9	159	47,0	25,5	159	48,7	23,3
Chevalier[49]	**2010**	**Placebo IA**	129	56,3	10,3	117	38,3	15,5	117	38,0	21,2	117	41,7	19,9
Cubukçu[50]	**2004**	**Placebo IA**	10	88,0	7,1	10	70,5	7,6						
Day[51]	**2004**	**Placebo IA**	115	43,4	18,6	115	22,9	16,0	115	23,2	15,8			
Baron (ART-ONE 75)[54]	**2018**	**Placebo IA**	326	61,4	11,5	326	43,5	19,6	326	42,2	24,3	198	40,4	21,6
Thomas (CELTIPHARM)[55]	**2017**	**NSAID**	199	50,4	16,1				199	46,5	17,3	199	43,5	18,1
			1863			1356			1469			1204		

(*continued on next page*)

Table 1
(*continued*)

WOMAC A			Baseline			T1			T3			T6		
AUTHOR	PUB	EQUIVALENT	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD
Maheu E[14]	**2019**	**Ostenil Plus**	144	58,4	11,5	139	25,0	17,5	139	21,5	17,5	113	24,1	19,1
		Synvisc-One	148	58,3	12,0	141	27,0	20,0	141	22,5	20,0	112	22,1	22,2
Diraçoglu D[15]	**2016**	**Monovisc**	21	55,0	15,9	20	40,5	15,9	20	37,0	15,9	20	42,5	15,9
		Adant	20	52,5	17,7	20	37,5	17,7	20	34,5	17,7	20	35,0	17,7
Saccomanno MF[16]	**2016**	**Orthovisc**	55	48,2	20,4	53	35,4	19,6	53	35,5	20,1	53	36,3	19,6
Van Der Weegen[18]	**2015**	**Fermathron Plus**	99	40,2	17,6	99	30,0	22,5	99	23,5	24,6	97	32,0	21,8
Leighton R[21]	**2014**	**Durolane**	218	50,5	11,0	185	29,0	29,9	185	28,4	31,3	171	29,8	32,7
Arden NK[22]	**2013**	**Durolane**	108	49,9	10,5	103	37,1	19,0						
Berenbaum F[23]	**2012**	**Go-On**	217	47,5	14,3	217	27,0	18,8	217	28,0	18,9	217	24,6	21,0
		Hyalgan	209	48,8	14,9	209	31,0	16,5	209	29,5	18,6	209	30,4	20,4
Strand V[24]	**2012**	**Gel One**	247	70,7	14,4	247	50,5	21,4	231	49,7	27,7			
DeCaria JE[25]	**2012**	**Hyalgan**	15	26,0	17,2	15	16,0	13,3	15	15,0	14,2	15	16,6	10,7
Pavelka[27]	**2011**	**Sinovial**	192	55,2	10,8	183	25,4	18,9	183	22,7	21,1	183	22,7	22,8
		Synvisc	188	55,5	10,9	171	27,1	18,9	171	24,6	21,1	171	23,1	22,8
Huang T[28]	**2011**	**Hyalgan**	100	45,7	11,2							100	16,4	19,2
Diraçoglu D[29]	**2009**	**Synvisc**	42	58,4	13,2	40	41,8	14,2						
Onel E[30]	**2008**	**Euflexxa**	160	49,2	13,9	156	22,5	16,0	156	19,3	21,5			
		Synvisc	161	51,1	14,0	158	25,0	17,0	158	22,7	21,6			
Jüni P[32]	**2007**	**Synvisc**	222	45,0	18,0				221	34,0	30,4	219	35,0	22,6
		Orthovisc	219	46,0	19,0				218	31,0	34,0	215	35,0	22,5
		Ostenil	219	46,0	18,0				219	35,0	30,2	217	35,0	20,7
Mazières B[33]	**2007**	**Suplasyn**	294	48,5	15,5				285	35,5	19,5	275	30,0	19,5
Lee PB[35]	**2006**	**Hyruan-Plus**	75	47,5	20,0	75	30,0	21,3	75	30,0	25,0			
		Hyal	71	50,0	22,5	71	31,5	21,3	71	30,0	23,8			
Arensi F[36]	**2006**	**Go-On**	20	30,5	5,0	20	20,5	7,5	20	18,0	11,2			
		Hyalgan	20	23,5	4,5	20	14,5	7,5	20	13,5	11,2			
Neustadt D[37]	**2005**	**Orthovisc 3 inj**	107	57,8	10,1				107	33,6	24,1	107	36,1	24,9
Altman RD[38]	**2004**	**Durolane**	172	49,5	11,4	134	33,8	19,5	134	35,2	19,9	134	37,0	20,0
Petrella RJ[39]	**2002**	**Suplasyn**	25	33,2	24,2	25	24,2	23,4						
Brandt KD[40]	**2001**	**Orthovisc**	114	82,0	14,0	66	59,5	9,0	66	53,8	22,5	66	55,8	21,2
Takamura J[41]	**2018**	**Gel-One**	152	63,4	9,1	152	48,6	22,9	152	41,3	23,6	152	42,4	23,3
Tuan S[42]	**2018**	**Hya-joint Plus**	46	38,1	17,0	46	23,5	23,7	46	19,3	14,2	46	17,9	13,6
Ha CW[43]	**2017**	**Hyruan Plus**	146	52,8	16,6	111	36,8	15,8	111	31,7	18,5			
		Hyruan One	137	51,3	15,3	97	37,5	16,4	97	31,5	16,9			
Sun SF[44]	**2017**	**Hya-joint Plus**	66	49,5	17,0	62	32,0	20,0	62	29,0	13,5	62	28,5	13,5
		Synvisc-One	66	49,0	16,5	59	32,5	18,5	59	29,5	14,0	59	31,5	15,5
Conrozier T[45]	**2016**	**Happy Cross**	40	43,0	19,6				10	24,4	19,4	40	24,8	24,6
Pal S[47]	**2014**	**Synvisc-One**	394	55,5	13,6	380	37,9	16,2	380	32,4	17,7	380	29,8	18,6
Borras-Verdera A[48]	**2012**	**Ostenil Plus**	80	57,7	16,5	79	33,9	18,9	78	30,7	19,4	77	28,7	16,5
Chevalier X[49]	**2010**	**Synvisc**	124	57,5	11,0	115	36,3	15,2	115	35,6	20,8	115	38,4	20,4
Cubukçu D[50]	**2004**	**Synvisc**	30	78,6	12,9	30	57,0	11,2						
Day R[51]	**2004**	**Artz**	108	39,8	15,5	108	19,8	16,0	108	18,0	15,8			
Germonville T[57]	**2015**	**Hyalgan**	122	47,9	17,2				121	30,4	21,2	119	31,6	22,8
			5413			3806			4772			3764		

ing the target population for viscosupplementation, as it is recognized. Also, they were detailed and compared between groups, to ensure a minimal homogeneity. The profile assessment included following parameters: gender (%); age: mean (SD), [minimum-maximum]; OA anteriority: mean (SD); body mass index (BMI): mean (SD), [minimum-maximum]; and Kellgren & Lawrence[7] radiological grades, for the severity of the disease: KL I (%), KL II (%), KL III (%) and KL IV (%).

ARTHRUM group includes 2,597 patients: 61.8% women, aged 63.6 (10.4) years [20-97], anteriority 4.1 (4.2) years, BMI 27.3 (4.5) kg/m^2 [16.2-60.0], KL I (11.0%), KL II (39.7%), KL III (40.6%) and KL IV (8.7%)

EQUIVALENTS group includes 6,970 patients: 66.7% women, aged 63.3 (8.9) years [29-90], anteriority 4.9 (4.7) years, BMI 28.1 (4.2) kg/m^2 [18.0-61.1], KL I (4.8%), KL II (41.5%), KL III (47.6%) and KL IV (6.1%)

CONTROLS group includes 2,708 patients: 61.1% women, aged 63.3 (8.2) years [30-86], anteriority 5.1 (5.0) years, BMI 29.1 (4.5) kg/m^2 [18.4-54.6], KL I (5.6%), KL II (37.2%), KL III (50.3%) and KL IV (6.9%)

All these profiles meet those found in literature, and are close together, eliminating this potential cause of heterogeneity in the global comparisons. However, distribution of above parameters is wide in each group. Detailed tables for patients profiles are available (annexed to this article).

Data survey

A detailed and critical survey of the data[13-62], was undertaken to ensure full representation of the current practice of viscosupplementation for knee OA, according to the standard protocols. Following this, two studies and one arm have been rejected from their protocol. These were:

- Karlsson[52] (2002): only patients with an ultimately progressed OA (Ahlbäck grades), almost corresponding to the grade KL IV (indication for surgery with total knee replacement), leading to poor clinical results, outside the usual indication for viscosupplementation.
- Kearey[46] (2016): very high scores, due to a probable over-rating of the answers given by patients, assessed by phone at long distance (experimental protocol, in Australia). Also, this open study (no control group) was for a product already well represented in this analysis (Synvisc-One).
- Neustadt[37] (2005): one arm studying the effect of 4 successive injections of Orthovisc, has been removed from the analysis, as the product information suggests 3 injections.

A search for outlier studies, providing inconsistent results and heterogeneity, was done on the whole selected population. Preliminary meta-analysis tests were carried out, using funnel plots to assess MD and ES (CD), that must remain coherent (Figure 2). This yielded:

- Petrella[34] (2006): uncertain results (very low precision) and risk of bias
- Davalillo[19] (2015): absurd results, and very important bias
- Zhang[20] (2015): under-rated SD (and SE) giving abnormally high results for ES (CD), and risk of bias

Following the removal of these doubtful studies, the remaining selected studies were split into three groups, ARTHRUM, CONTROLS and EQUIVALENTS for each criterion WOMAC A, B or C. All details are given for WOMAC A (Table 1). Completed data (mostly SD) are highlighted using a gray background, in these tables.

Representativeness of selected studies

With more than 12,000 patients included in the studies, this review and meta-analyses compare favorably in size with other large meta-analyses carried out for viscosupplementation. Another necessary aspect was to verify that the EQUIVALENTS group was truly representative of the market. This was done for the main criterion population (base 5,413 patients):

Synvisc 915, Durolane 498, Orthovisc 495, Hyalgan 466, Synvisc One 460, Gel-One 399, Suplasyn 319, GoOn 237, Ostenil Plus 224, Hyruan Plus 221, Ostenil 219, Sinovial 192, Euflexxa 160, Hyruan One 137, Hya Joint Plus 112, Artz 108, Fermathron Plus 99, Hyal 71, Happy-Cross 40, Monovisc 21, Adant 20

More than 20 devices are represented. With the advantage of more published studies, Synvisc devices comprise 25% of patients in the EQUIVALENTS group. Some products present on other markets (USA or Asia), have also been included here (16% of patients), but their presence on the European market has not been established or confirmed. In this group, single injection devices have been used for 33% of the patients, showing the expansion of this regime.

About heterogeneity

It is generally recognized that heterogeneity is important in most meta-analyses[8-12] made on clinical studies about viscosupplementation, showing all difficulties. Beyond the internal heterogeneity of the studies (wide distribution of patient's profiles and variations between patient's responses…), there are big differences between studies (greater differences between patient profiles at inclusion, different investigators, and possible variations depending on country, approach or education). Moreover, the risks of bias exist, and could be important in their influence on final results. Research for and exclusion of outlier studies, was therefore essential.

For the WOMAC A at T6 (main criterion), the true heterogeneity index (inside studies) varied from $I^2 = 95\%$ for all studies before exclusions, to $I^2 = 93\%$ for the EQUIVALENTS group, $I^2 = 86\%$ for the CONTROLS group, and $I^2 = 93\%$ for the ARTHRUM group. Despite this slight improvement, heterogeneity remained important. In the same conditions for the WOMAC A at T6, the heterogeneity index τ^2 (between studies, and dimensionless) was clearly improved, moving from $\tau^2 = 0.34$ for all studies, to $\tau^2 = 0.24$ for the EQUIVALENTS group, $\tau^2 = 0.11$ for the CONTROLS group, and $\tau^2 = 0.14$ for the ARTHRUM group. This greater improvement is clearly the result of the exclusion of these divergent protocol and outlier studies.

Forest plots

The following forest plots (Figures 3–5) represent the score variations from baseline (scale 0-100). For each study arm, the mean difference (MD) is represented by a square, and its 95% CI is represented by the associated horizontal bar. Synthesis is given by the vertical dark red bar (mean) and the horizontal width of the lozenge below represents 95% CI, for the group. The table to the left of each plot gives the numerical results, with product identity (ID), weighting (%) used to calculate the overall mean (inverse variance, random effects). These results are given at T6, respectively for WOMAC A (Figure 3), WOMAC B (Figure 4) and WOMAC C (Figure 5).

Results interpretation

All the combined results (MD 95%CI) of the meta-analyses are detailed by group and WOMAC sub-score at times T1, T3 and T6 (Table 2). Populations are given at inclusion (N0) and at the observation time (N). To assess the importance of the gain obtained

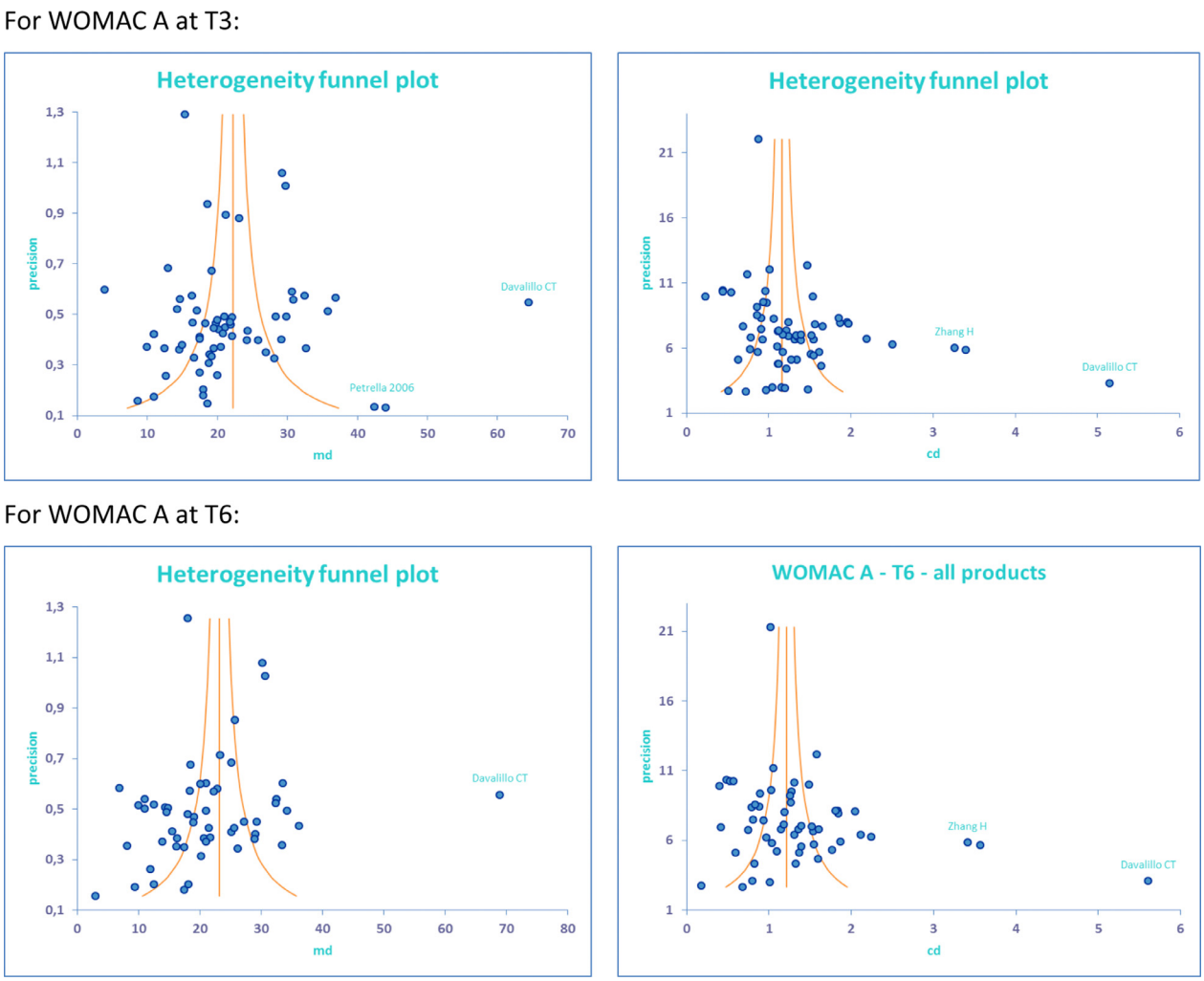

Figure 2. Funnel plots to identify doubtful studies.
In these graphs, each study result is represented by a point function of gain for MD or CD (x axis) and of study precision (y axis). The average mean is represented by a vertical line. The surrounding curves represent the 95% CI, which reduces as precision is increased (higher population, smaller SE). Abnormally high effect sizes (CD) in contradiction with MD (as for Zhang), demonstrate the under-rating of SD and SE.
Note: 2 points below an author's name, describe 2 products (device and/or control)

from inclusion (baseline), the minimal perceptible clinical improvement (MPCI) from Ehrich[4] has been used: 9.7 for the WOMAC A, 10.0 for the WOMAC B and 9.3 for the WOMAC C (scale 0-100). When these values are exceeded, the answer "Yes" is given on the table.

For the main criterion WOMAC A at T6:

- Each lower bound of the 95% CI, for individual studies in the ARTHRUM group, demonstrates an important gain, higher than the MPCI (= 9.7). This, *a fortiori*, also applies to the lower bound of the 95% CI estimated at 21.02 for the group as a whole.
- In the EQUIVALENTS group, the lower bounds of 95% CIs are below the MPCI for 35% of individual studies. However, the lower bound of the 95% CI, estimated at 17.50 for the group as a whole, is above the MPCI.
- For the CONTROLS group, the results are similar to the EQUIVALENTS group with clinical efficacy of the IA placebo being observed. The lower bound of the 95% CI for the group as a whole, estimated at 12.02 is also above the MPCI.

For the secondary criterion WOMAC C at T6, the same observations can be made, as the MPCI (= 9.3) is below each lower bound for each individual study for the ARTHRUM group, and below the lower bound of the overall 95% CI, for each group. For the other criteria at any time, the MPCI is always below the 95% CI for the ARTRUM and EQUIVALENTS groups. However, for the CONTROLS groups, there are several cases with the MPCI greater than the 95% CI lower bound (Table 2), demonstrating that an IA placebo, does not always attain the minimum efficacy to be clinically relevant.

Inter groups comparisons

The Inter group comparisons have been done on two groups at a time, giving three comparisons (Table 3). Results are presented for each WOMAC sub-score, at each observation time. The differences between the score variations (MD) from baseline, are given with SD_{pooled} and SE_{pooled}, allowing the t-test, to determine whether the differences are significant ($p<0.05$). The non-inferiority of ARTHRUM vs EQUIVALENTS, was determined using SDD[5] as non-inferiority margin, converted into a 0-100 base, giving -8.1 for the WOMAC A, -9.6 for the WOMAC B and -7.8 for the WOMAC C. The lowest bound of 95% CI (kept at the same size as in Table 2) was always above this limit, confirming the non-inferiority of ARTHRUM. In the comparisons vs CONTROLS, ES was calculated.

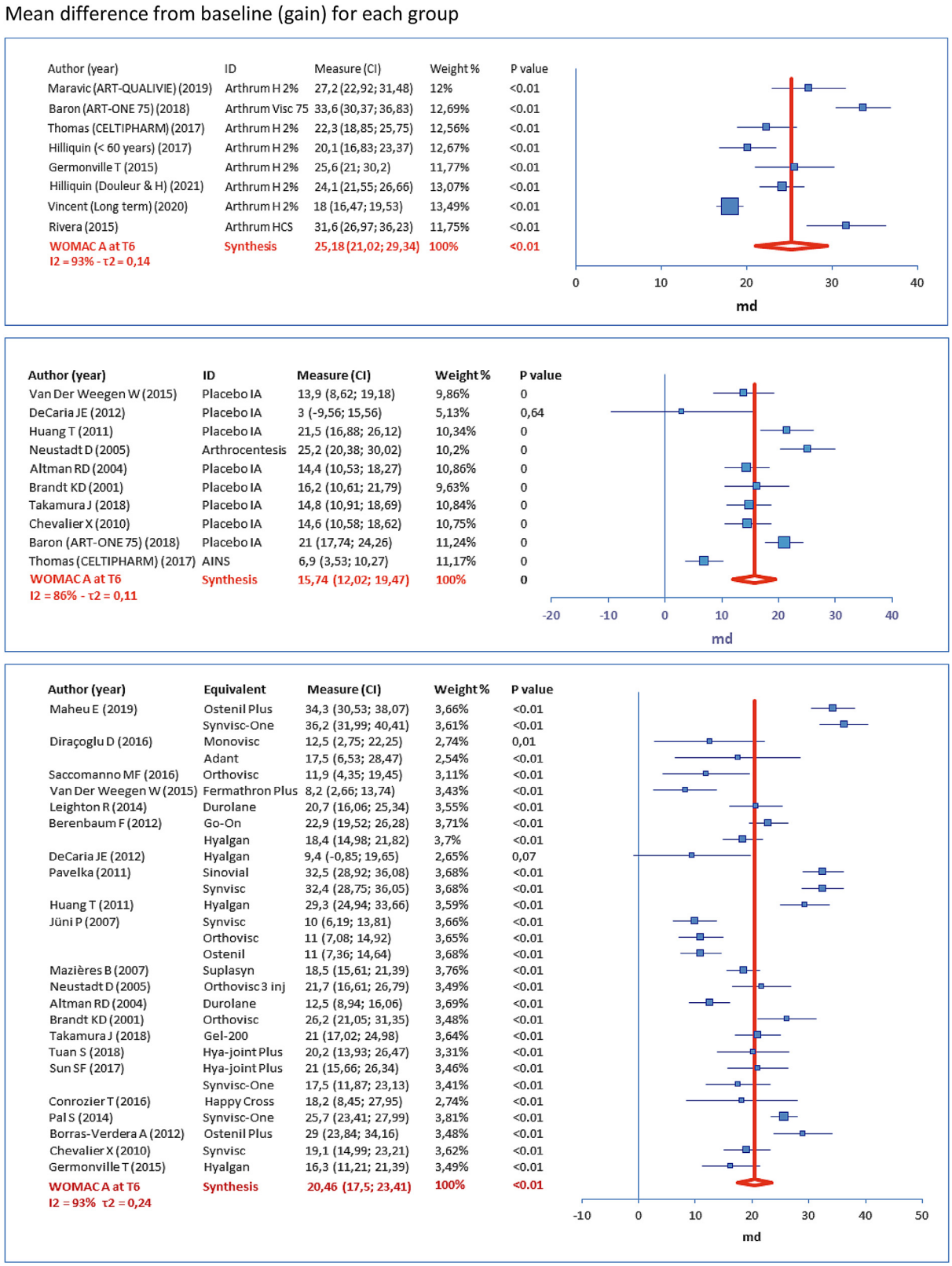

Figure 3. Results for the main criterion (WOMAC A at T6)

Table 2
Consolidated WOMAC results

ARTHRUM	Time	N0	N	MD	SD	MPCI	< 95% CI
WOMAC A	**T1**	330	318	**24.14 (20.14; 28.13)**	17.0	9.7	Yes
	T3	2602	2308	**21.61 (17.15; 26.07)**	17.3	9.7	Yes
	T6	2602	2238	**25.18 (21.02; 29.34)**	17.5	9.7	Yes
WOMAC B	**T1**	218	208	**21.20 (17.02; 25.38)**	22.1	10.0	Yes
	T3	1179	1117	**20.02 (13.62; 26.41)**	20.2	10.0	Yes
	T6	1179	1113	**23.55 (18.55; 28.54)**	19.8	10.0	Yes
WOMAC C	**T1**	218	185	**18.30 (14.70; 21.90)**	18.3	9.3	Yes
	T3	2356	2066	**16.72 (12.45; 21.00)**	18.4	9.3	Yes
	T6	2356	2000	**20.93 (16.61; 25.25)**	18.2	9.3	Yes
EQUIVALENTS	Time	N0	N	MD	SD	MPCI	< 95% CI
WOMAC A	**T1**	4090	3806	**18.97 (16.75; 21.19)**	15.5	9.7	Yes
	T3	4682	4346	**20.91 (18.38; 23.44)**	17.3	9.7	Yes
	T6	4063	3764	**20.46 (17.50; 23.41)**	17.3	9.7	Yes
WOMAC B	**T1**	2069	1874	**15.29 (13.11; 17.48)**	19.9	10.0	Yes
	T3	2461	2249	**18.73 (16.35; 21.12)**	20.6	10.0	Yes
	T6	1987	1799	**17.99 (14.62; 21.36)**	21.4	10.0	Yes
WOMAC C	**T1**	2671	2462	**14.09 (12.16; 16.03)**	16.2	9.3	Yes
	T3	3242	3011	**17.62 (15.4; 19.85)**	17.3	9.3	Yes
	T6	2994	2731	**17.61 (15.38; 19.85)**	17.8	9.3	Yes
CONTROLS	Time	N0	N	MD	SD	MPCI	< 95% CI
WOMAC A	**T1**	1450	1356	**14.97 (12.76; 17.17)**	16.3	9.7	Yes
	T3	1568	1469	**16.84 (13.03; 20.65)**	18.1	9.7	Yes
	T6	1425	1204	**15.74 (12.02; 19.47)**	16.9	9.7	Yes
WOMAC B	**T1**	596	557	**10.20 (6.98; 13.41)**	20.0	10.0	No
	T3	712	634	**11.27 (5.38; 17.15)**	20.1	10.0	No
	T6	597	518	**8.18 (4.59; 11.78)**	20.0	10.0	No
WOMAC C	**T1**	1090	1032	**12.26 (9.18; 15.34)**	15.5	9.3	No
	T3	1094	1028	**14.98 (9.83; 20.13)**	17.6	9.3	Yes
	T6	1208	1108	**13.51 (9.89; 17.12)**	18.0	9.3	Yes

Table 3
WOMAC comparisons between groups

Criterium	Time	Difference	NI limit	NI	SD_{pooled}	SE_{pooled}	P-value	ES
ARTHRUM vs EQUIVALENTS								
WOMAC A	T1	5.17 (1.18; 9.17)	-8.1	Yes	15.67	0.91	< 0.001	NA
	T3	0.70 (-3.76; 5.16)	-8.1	Yes	17.28	0.45	0.12	NA
	T6	4.72 (0.56; 8.88)	-8.1	Yes	17.39	0.46	< 0.001	NA
WOMAC B	T1	5.91 (1.73; 10.09)	-9.6	Yes	20.09	1.47	< 0.001	NA
	T3	1.29 (-5.11; 7.69)	-9.6	Yes	20.46	0.75	0.085	NA
	T6	5.56 (0.57; 10.56)	-9.6	Yes	20.81	0.79	< 0.001	NA
WOMAC C	T1	4.21 (0.61; 7.81)	-7.8	Yes	16.35	1.25	< 0.001	NA
	T3	-0.90 (-5.18; 3.38)	-7.8	Yes	17.73	0.51	0.076	NA
	T6	3.32 (-1.00; 7.64)	-7.8	Yes	17.96	0.53	< 0.001	NA
ARTHRUM vs CONTROLS								
WOMAC A	T1	9.17	NA	NA	16.41	1.02	< 0.001	**0.56**
	T3	4.77	NA	NA	17.61	0.59	< 0.001	**0.27**
	T6	9.44	NA	NA	17.29	0.62	< 0.001	**0.55**
WOMAC B	T1	11.00	NA	NA	20.59	1.67	< 0.001	**0.53**
	T3	8.75	NA	NA	20.19	1.00	< 0.001	**0.43**
	T6	15.37	NA	NA	19.84	1.06	< 0.001	**0.77**
WOMAC C	T1	6.04	NA	NA	15.97	1.28	< 0.001	**0.38**
	T3	1.74	NA	NA	18.13	0.69	0.012	**0.10**
	T6	7.42	NA	NA	18.13	0.68	< 0.001	**0.41**
EQUIVALENTS vs CONTROLS								
WOMAC A	T1	4.00	NA	NA	15.74	0.50	< 0.001	**0.25**
	T3	4.07	NA	NA	17.49	0.53	< 0.001	**0.23**
	T6	4.72	NA	NA	17.24	0.57	< 0.001	**0.27**
WOMAC B	T1	5.09	NA	NA	19.89	0.96	< 0.001	**0.26**
	T3	7.46	NA	NA	20.48	0.92	< 0.001	**0.36**
	T6	9.81	NA	NA	21.10	1.05	< 0.001	**0.46**
WOMAC C	T1	1.83	NA	NA	16.00	0.59	0.002	**0.11**
	T3	2.64	NA	NA	17.36	0.63	< 0.001	**0.15**
	T6	4.10	NA	NA	17.85	0.64	< 0.001	**0.23**

NI limit = - SDD (Angst)

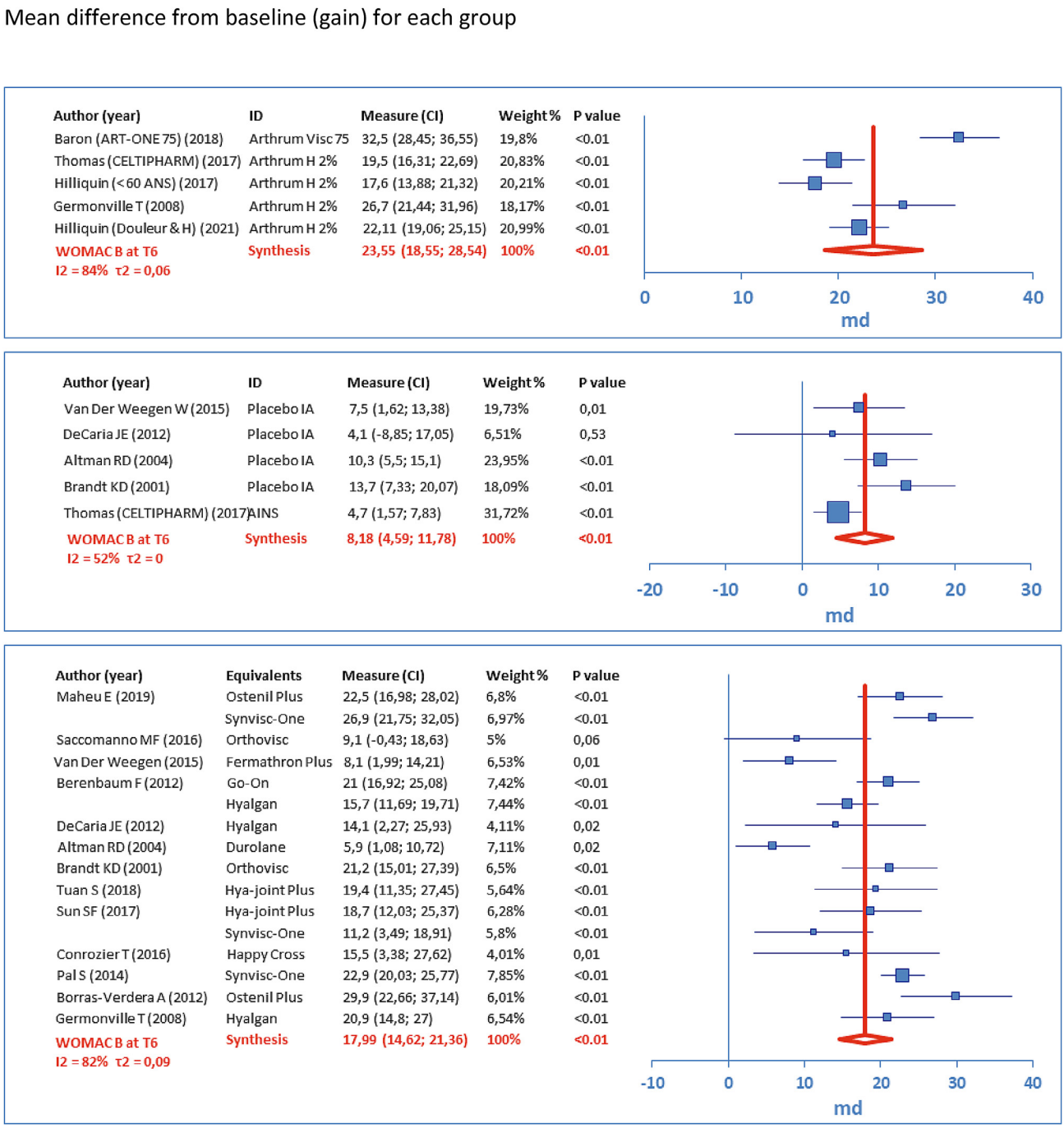

Figure 4. Results for a secondary criterion (WOMAC B at T6)

The analyses demonstrated that ARTHRUM and EQUIVALENTS were significantly better than CONTROLS for each measurement time, for all criteria. For the WOMAC A at T3 and T6, ES was respectively 0.28 and 0.56 for ARTHRUM vs 0.23 and 0.27 for EQUIVALENTS. This difference in favour of ARTHRUM was significant at T6. Similar results were observed for the other WOMAC sub-scores.

OMERACT-OARSI responders

Results for OMERACT-OARSI responders (Table 4), have been collected from 13 studies (3 for ARTHRUM). Data were insufficient at T1 or T2. Results at T3 and T4 have been pooled when it appeared relevant. The rates of patients who were strictly responders, according to OMERACT-OARSI, varied from:

- 63.4% to 88.6% at T3-4 and 64.7% to 91.2% at T6, for the ARTHRUM group
- 49.5% to 71.3% at T3-4 and 52.4% to 85.7% at T6, for the EQUIVALENTS group
- 54.6% to 60.9% at T3-4 and 41.8% to 58.7% at T6, for the CONTROLS group

At T3-4 and T6 respectively, the average "strict" rates were better for ARTHRUM, 68.4% - 76.8%, vs 63.2% - 67.8% for EQUIVALENTS, and 59.0% - 55.1% for CONTROLS. With the "minimum" concept, these rates at T3-4 and T6, were respectively 66.2% -

Mean difference from baseline (gain) for each group

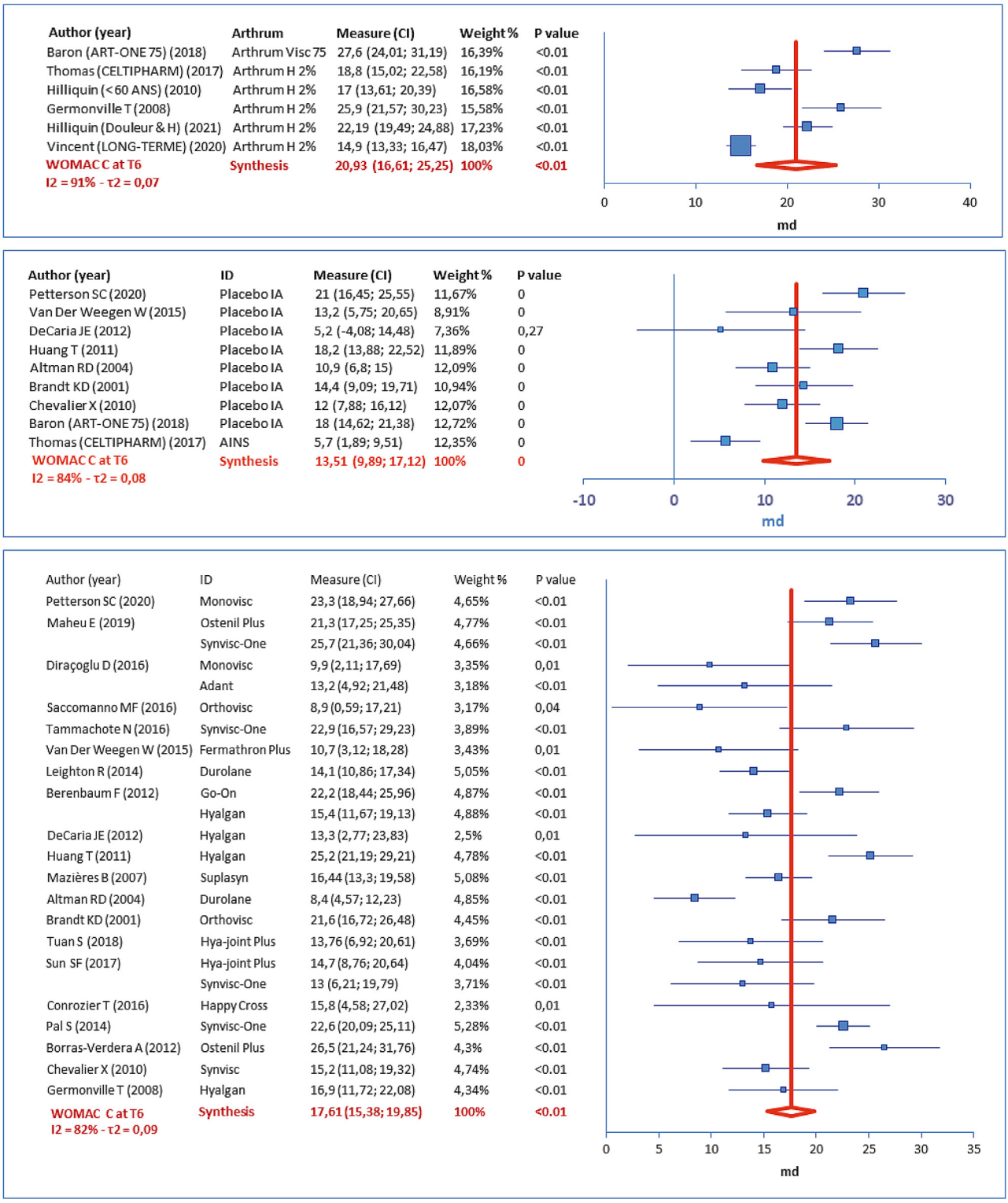

Figure 5. Results for a secondary criterion (WOMAC C at T6)

74.4% for ARTHRUM, vs 61.6% - 63.9% for EQUIVALENTS, and 54.8% - 50.5% for CONTROLS. Statistical comparisons were made with the chi[2] test (Table 5). Significantly better rates for OMERACT-OARSI responders were obtained with ARTHRUM devices ($p<0.01$).

Tolerance

Tolerance was not a target for this meta-analysis. However, the tolerance results recorded from the bibliographical research have been evaluated for 59 articles, representing 7,031 EQUIVALENTS

Table 4
Results for OMERACT-OARSI responders

OMERACT-OARSI			T3-4					T6				
AUTHOR	PUB	PRODUCT	N	NR	NNR	% Min	% Strict	N	NR	NNR	Min	% Strict
Maheu[14]	**2019**	**Ostenil Plus**						134	93	19	69.4	83.0
		Synvisc-One						132	96	16	72.7	85.7
Berenbaum[23]	**2012**	**Go-On**	217	151	66	69.6	69.6	217	159	58	73.3	73.3
		Hyalgan	209	126	83	60.3	60.3	209	122	87	58.4	58.4
Strand[24]	**2012**	**Gel One**	247	141	90	57.1	61.0					
		Placebo	128	65	54	50.8	54.6					
Kawasaki[26]	**2009**	**Artz**						42	22	20	52.4	52.4
		Exercices						45	25	20	55.6	55.6
Onel[30]	**2008**	**Euflexxa**	157	112	45	71.3	71.3					
		Synvisc	158	99	59	62.7	62.7					
Lundsgaard[31]	**2008**	**Hyalgan**						84	50	32	59.5	61.0
		Placebo						84	33	46	39.3	41.8
Ha[43]	**2017**	**Hyruan**	111	55	56	49.5	49.5					
		Hyruan Plus	97	57	40	58.8	58.8					
Maheu[61]	**2011**	**Structovial**	119	76	43	63.9	63.9	119	77	42	64.7	64.7
		Synvisc	117	70	47	59.8	59.8	117	79	38	67.5	67.5
Chevalier[49]	**2010**	**Synvisc**						124	73	43	58.9	62.9
		Placebo						129	66	52	51.2	55.9
Altman[62]	**2009**	**Euflexxa**	291	173	90	59.5	65.8	291	169	85	58.1	66.5
		Placebo	295	167	107	56.6	60.9	295	155	109	52.5	58.7
Baron[54]	**2018**	**Arthrum visc 75**	214	156	20	72.9	88.6	214	165	16	77.1	91.2
Germonville[57]	**2008**	**Arthrum H 2%**	126	96	26	76.2	78.7	126	102	18	81.0	85.0
		Hyalgan	122	77	44	63.1	63.6	122	77	42	63.1	64.7
Vincent[58]	**2020**	**Arthrum H 2%**	970	615	355	63.4	63.4	904	658	246	72.8	72.8
TOTAL		**ARTHRUM**	**1310**	**867**	**401**	**66.2**	**68.4**	**1244**	**925**	**280**	**74.4**	**76.8**
		EQUIVALENTS	**1845**	**1137**	**663**	**61.6**	**63.2**	**1591**	**1017**	**482**	**63.9**	**67.8**
		CONTROLS	**423**	**232**	**161**	**54.8**	**59.0**	**553**	**279**	**227**	**50.5**	**55.1**

N Population studied for OMERACT-OARSI responders
NR Number of patient responders
NNR Number of patient non-responders

Table 5
Comparative statistics for OMERACT-OARSI responders

OMERACT-OARSI	Time	Calculation	chi^2	P-value	Conclusion
ARTHRUM vs CONTROLS	T3-4	Strict	11.7	0.0006	ARTHRUM better
		Mini	17.7	< 0.0001	
	T6	Strict	79.9	< 0.0001	
		Mini	98.9	< 0.0001	
ARTHRUM vs EQUIVALENTS	T3-4	Strict	8.92	0.0028	ARTHRUM better
		Mini	6.86	0.0088	
	T6	Strict	26.3	< 0.0001	
		Mini	35.2	< 0.0001	
EQUIVALENTS vs CONTROLS	T3-4	Strict	2.36	0.12	unclear
		Mini	6.62	0.010	EQUIVALENTS better
	T6	Strict	761	< 0.0001	
		Mini	31.1	< 0.0001	

patients, 2,959 CONTROLS patients and 5,831 ARTHRUM patients. For the CONTROLS group, any comparator was accepted, except for IA HA patients, that were included in the EQUIVALENTS group, even when other treatments were associated. For this total population of 15,821 patients, no serious adverse event (SAE) has been reported.

The Assessment of lower grade adverse events – possibly related to the treatment – was more delicate, because transient minor events (almost all at the site of injection), were unequally reported in the various studies. By limiting the investigation to the comparative studies (including those comparing several treatments from the same group), the results became more consistent. The rates of these minor adverse events (AE) were 13.2% for EQUIVALENTS (6,481 patients), 12.5% for CONTROLS (2,959 patients) and 6.5% for ARTHRUM (718 patients). Overall, one can conclude that the tolerance of IA HA is good, as the rate of AE was similar between the EQUIVALENTS and the CONTROLS group (most with IA placebo). Looking in greater detail, the presence of 29% patients receiving a modified (cross-linked) HA – Synvisc, Synvisc-One, Durolane, Monovisc or Gel-One – show two differentiated subgroups within the EQUIVALENTS group: for the cross-linked fraction (1,896 patients) the rate of AE became 18.8%, whereas for the non-cross-linked devices the rate was 10.8%.

Discussion

Equivalence between devices

According to MDR, a strictly equivalent device should be identical to the one which is assessed in all aspects: formulation, ingredients, presentation and all physical, chemical and biological properties. For the main active ingredient (HA) contained in viscosupplements, this should include the molecular weight (Mw), the nature of the molecule (native or modified by cross-linking), and their impact upon rheology or residence time. This should also include the whole manufacturing process, and therefore it could be difficult to achieve apart from within the same device family.

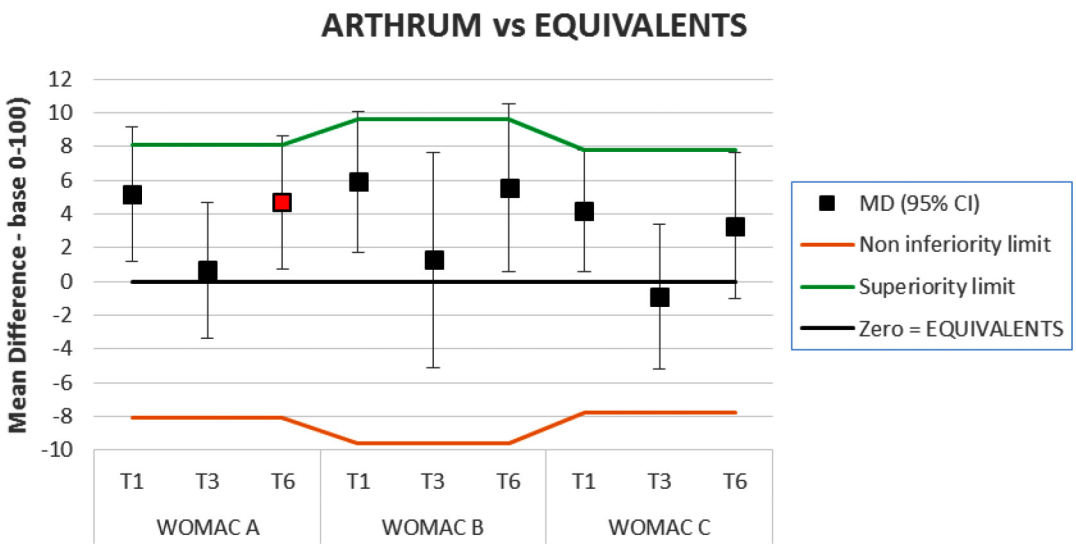

Figure 6. Non inferiority or clinical equivalence.
The graph illustrates the difference between the ARTHRUM and the EQUIVALENTS groups, for each WOMAC sub-score, at all observation times. Positive results are in favour of ARTHRUM. The squares represent the mean difference (MD) – filled in red for the main criterion – and the vertical bars represent the 95% CI. The orange and green lines respectively represent the non-inferiority limit for ARTHRUM (which is always observed) and its superiority limit. When the 95% CI intervals are totally between these two limits, it is reasonable to infer clinical equivalence between ARTHRUM and EQUIVALENTS devices. But when the upper bound of the CI interval is above the green limit, one can assume a combined non-inferiority and superiority of ARTHRUM. Also, when the lower bound of CI is above zero. a statistical superiority of ARTHRUM over EQUIVALENTS is observed ($p<0.05$).

Inside the ARTHRUM group, two devices present slight differences from the original ARTHRUM H 2%: a single-injection product (ARTHRUM visc 75) containing 75mg of the same HA (in a 3 mL syringe), and a device containing 40 mg chondroitin sulfate (ARTHRUM HCS) in addition to the 40 mg HA (in each 2 mL syringe). These differences were considered as minor, in relation to the general properties of the devices.

On the clinical side, 'equivalence' is defined as non-inferiority combined with non-superiority. This was assessed when comparative results were available. In this study, the smallest detectable difference (SDD) from Angst[5], was used as non-inferiority and superiority margins as in the Results chapter. Thus, for clinical equivalence, the whole 95% CI must remain between the 2 limits (Figure 6), which was observed at T3 for all scores and for the WOMAC C at T6. In other cases, ARTHRUM was non-inferior and superior.

About the method

Our approach may certainly be questioned for several elements, notably for the design of the CONTROLS group, which is heterogenous. From this, it was impossible to make one-to-one comparisons with individual IA HA arms of the studies. However, the method works "globally" as our quantitative results meet those described in the literature, and in particular from Bannuru[10] (ES = 0.20 à 0.46), and from Rutjes[11] (ES = 0.37), confirming our results for the groups ARTHRUM and EQUIVALENTS.

About results

Compared with the baseline, the improvements observed over time for the ARTHRUM group are statistically significant and clinically relevant for each WOMAC sub-score, at all time points. Compared with the CONTROLS group, these improvements are also significantly in favor of ARTHRUM group, for the same criteria, at all time points. Based on ES (dimensionless value), these improvements are low to moderate at T3 (ES = 0.10 to 0.43), then clearly better at T6 (ES = 0.41 to 0.77). From Cohen[6], ES is low at 0.2, medium at 0.5 and high at 0.8. Overall, these ES results for pain, match those published by authors of other major meta-analyses[8-11]. At T6, there is some clinical superiority in favor of ARTHRUM for the WOMAC A and B sub-scores (Figure 6). The clinical superiority of ARTHRUM compared with EQUIVALENTS, is also observed ($p<0.01$) from the rates of OMERACT-OARSI responders (Table 5). The results for ARTHRUM at T1, should be treated with some caution as they are based on only two studies, although both gave excellent results (Baron[54] and Rivera[59]). One can conclude that long term clinical efficacy is demonstrated for the ARTHRUM family of devices.

About intra-articular placebo

The importance of the therapeutic efficacy of the IA placebo, can be clearly seen from this study, as the gain on pain index is greater than the MPCI from Ehrich[4], for its pooled 95% CI (Table 2). Such a gain is greater than a simple placebo effect: in an OA joint, the injection of a physiological liquid (pH balanced) has a certain beneficial effect that may persist three months or more. Expert authors such as Altman[12] or Bannuru[9] have observed this phenomenon. It is therefore a positive benefit of IA HA, that an improvement (even modest ES = 0.23 to 0.56) over an IA placebo is obtained. The position of the IA placebo in OA visco-supplementation studies should therefore be considered. For the patient an improvement is perceived from the baseline, and this should be considered as relevant. This supports the use of such indicators as the rates of OMERACT-OARSI responders, in real live studies.

About ARTHRUM HCS

The original formulation of ARTHRUM HCS (2% HA + 2% CS), was only represented in this meta-analysis by the study made by Rivera[59], giving results for the WOMAC A at T1, T3 and T6. A graph (Figure 7) allows comparison of the evolution of the WOMAC A (pain) score for ARTHRUM HCS, with those of the other ARTHRUM devices (based on HA alone), represented as a scatter plot (with associated tendency curve). This representation of the advantage of ARTHRUM HCS, is somewhat biased because of the relatively high

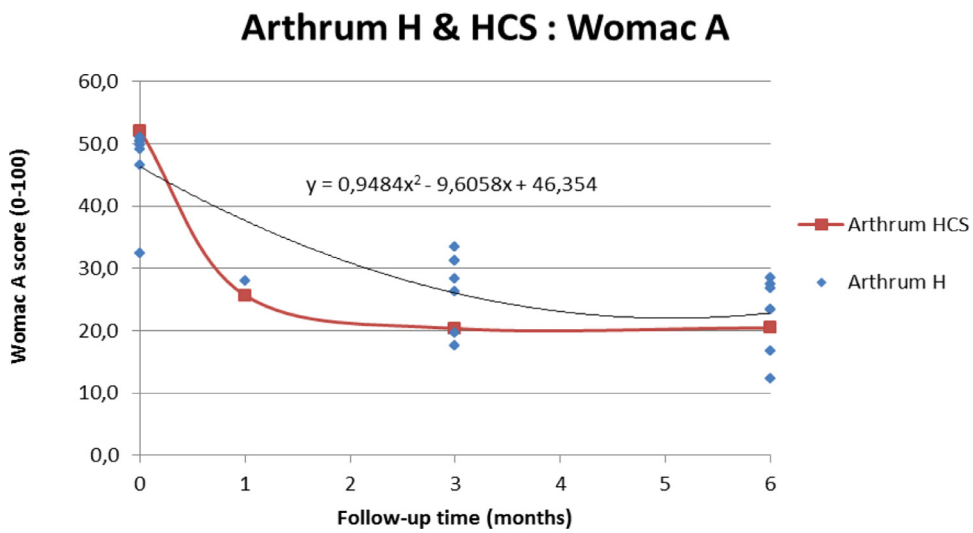

Figure 7. ARTHRUM HCS compared to other ARTHRUM devices.
The WOMAC A (pain) scores are represented: ARTHRUM HCS (red curve) vs other ARTHRUM (scatter plots completed with the tendency curve and its equation): the lack of data at T1 explains the difference in the overall curve shape.

heterogeneity of ARTHRUM H trials, which include a large diversity of patients, some with a limited potential for improvement: some with ultimate radiological grades (KL IV) and conversely, young patients with early OA symptoms. Therefore, other comparison tests were made between Rivera[59] and Baron[54] studies, both of which gave consistent results. The difference (base 0-100, positive in favor of ARTHRUM HCS in the score variation of MD (SD) from baseline, for the WOMAC A (pain sub-score) were: 4.1(17.4) at T1, 1.0(16.3) at T3 and -2.0(16.9) at T6. As in the main results, the improvement was significantly better at T1 (p=0.045) with ARTHRUM HCS. At times T3 and T6, the differences were not significant. This confirms the feed-back information given by doctors prescribing ARTHRUM HCS, that a very fast response on pain is obtained. This presence of CS is beneficial from the beginning of the treatment (as seen at T1), and should be recommended if the OA is painful at the time of treatment.

Conclusions

The comparison of ARTHRUM clinical studies (all devices), with studies selected after systematic bibliographical research (LCA, 2020), leads to the conclusion that the clinical efficacy of the ARTHRUM medical devices, in reducing pain and improving function, in knee osteoarthritis, for a period of up to 6 months has been demonstrated. Non inferiority and also superiority to equivalent IA HA devices, present on the market, were observed. With good tolerance results (lowest rate of AE, and none of them serious), the risk benefit ratio clearly favors viscosupplementation with ARTHRUM.

Conflicts of Interest

As share-holder and employee of LCA Pharmaceutical (Chartres, France), I have interest in the family of the medical devices “ARTHRUM”, intended for the viscosupplementation of osteoarthritic joints.

I am the sole author of this review article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.curtheres.2021.100637.

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