Contents

Part I

Chondrosulf

1 Overview of chondrosulf

1.1 Included trials

A total of 3 randomized comparisons which enrolled 322 patients were identified. In all, 3 randomized comparisons concerned Chondrosulf 1200mg/d.
The detailed descriptions of trials and meta-analysis results is given in section **??** (page **??**) for Chondrosulf 1200mg/d.

The average study size was 107 patients (range 70 to 127). The first study was published in 1992, and the last study was published in 1999.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
The table **??** (page **??**) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

1.2 Summary of meta-analysis results

The meta-analysis of the available trials about chondrosulf provide the results listed in tables **??** to **??** (page **??**) and in the following graphs.

1.2.1 Chondrosulf 1200mg/d

Chondrosulf 1200mg/d was superior to **placebo** in terms of EVA (ES=-0.83, 95% CI -1.26 to -0.40, p=0.0000, 3 trials)with a random effect model in reason of a heterogeneity (Het. p=0.0372)(ES=-0.90, 95% CI -1.13 to -0.66, p=0.0000, 3 trials).

Table 1.1: *Main study characteristics - Chondrosulf*

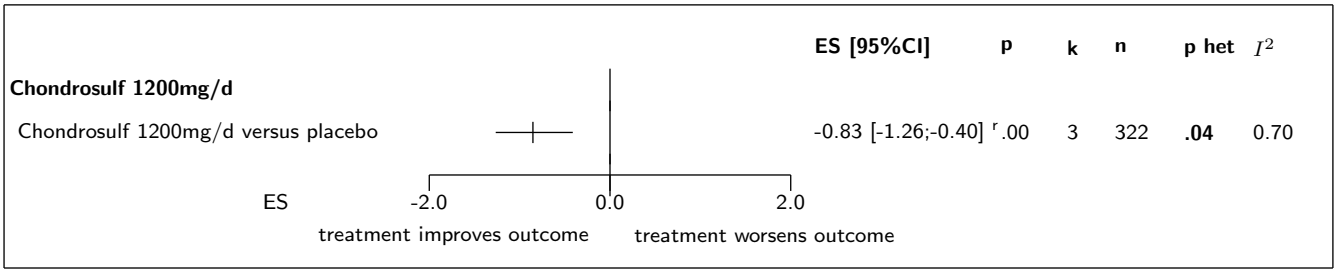
Trial	**Patients**	**Treatments**	**Trial design and method**
Chondrosulf 1200mg/d			
Chondrosulf 1200mg/d versus placebo			
LHirondel, 1992 [**?**] n = 63 vs. 62	patients with symptomatic knee osteoarthrosis	chondrosulf 1200mg/d for 6 months **versus** placebo	double-blind parallel groups multicentre,France
Bourgeois, 1998 [**?**] n = 83 vs. 44	patients with mono or bilateral knee osteoarthritis	chondrosulf 1200 mg/day oral gel **versus** placebo	double-blind parallel groups multicenter,
Pavelka 1200mg, 1999 [**?**] n = 35 vs. 35	patients with symptomatic knee osteoarthrosis	chondrosulf 400mg tid for 3 months **versus** placebo	double-blind parallel groups

Table 1.2: *Summary of all results for Chondrosulf 1200mg/d*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
Chondrosulf 1200mg/d versus placebo						
EVA	ES=-0.83 [1]	-1.26;-0.40	0.0000	0.0372 (0.70) †	3	322
AFI	ES=-0.90	-1.13;-0.66	0.0000	0.6421 (0.00)	3	322

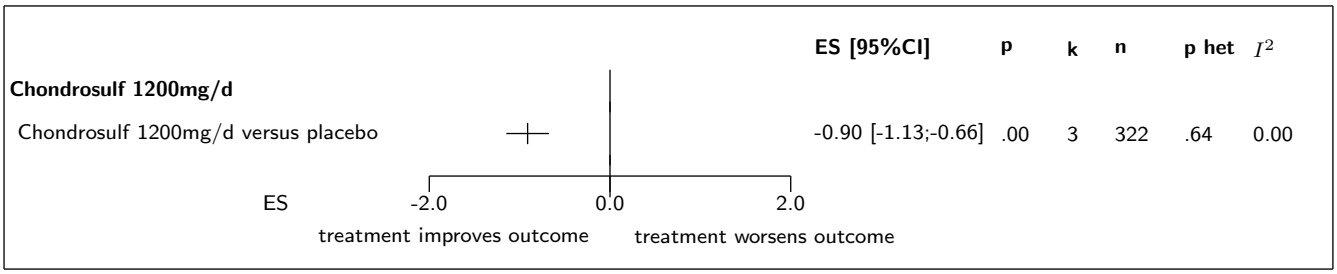
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 1.1: *Forest's plot for EVA*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; r: random effect model used

Figure 1.2: *Forest's plot for AFI*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; r: random effect model used

[1] with a random model ($\tau^2 = 0.100$). The results with a fixed effect model was RRFE=-0.78 95% CI -1.01;-0.54

2 Details

2.1 Available trials

A total of 3 RCTs which randomized 322 patients were identified: all compared Chondrosulf 1200mg/d with placebo.
The average study size was 107 patients (range 70 to 127). The first study was published in 1992, and the last study was published in 1999.
All trials were double blind in design. All included studies were reported in English language. We did not found any unpublished trial.
AFI data was reported in 4 trials; and 3 trials reported data on EVA.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of Chondrosulf 1200mg/d.

Table 2.1: *Treatment description - Chondrosulf - Chondrosulf 1200mg/d*

Trial	Studied treatment	Control treatment
Chondrosulf 1200mg/d versus placebo		
LHirondel (1992) [**?**]	Chondrosulf 1200mg/d for 6 months	placebo
Bourgeois (1998) [**?**]	Chondrosulf 1200 mg/day oral gel	placebo
Pavelka 1200mg (1999) [**?**] [c]	Chondrosulf 400mg tid for 3 months	placebo

c) Chondrosulf at 200, 800 or 1200 mg/d

Table 2.2: *Descriptions of participants - Chondrosulf - Chondrosulf 1200mg/d*

Trial	Patients
Chondrosulf 1200mg/d versus placebo	
LHirondel (1992) [**?**]	Patients with symptomatic knee osteoarthrosis
Bourgeois (1998) [**?**]	Patients with mono or bilateral knee osteoarthritis
Pavelka 1200mg (1999) [**?**]	Patients with symptomatic knee osteoarthrosis

Table 2.3: *Main patients characteristics - Chondrosulf - Chondrosulf 1200mg/d*

Trial	Characteristics
Chondrosulf 1200mg/d versus placebo	
LHirondel, 1992 [?]	joint affected: knee
Bourgeois, 1998 [?]	joint affected: knee
Pavelka 1200mg, 1999 [?]	joint affected: knee

Table 2.4: *Design and methodological quality of trials - Chondrosulf - Chondrosulf 1200mg/d*

Trial	Design	Duration	Centre	Primary endpoint
Chondrosulf 1200mg/d versus placebo				
LHirondel, 1992 [?] n=125	Parallel groups double-blind	6 months	France multicentre	
Bourgeois, 1998 [?] n=127	Parallel groups double-blind confirmatory trial at low risk of bias	3 months	multicenter	
Pavelka 1200mg, 1999 [?] n=70	Parallel groups double-blind	3 months		

2.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Chondrosulf 1200mg/d versus placebo

All the 3 studies had extractable data about the number of participants with **EVA**. The analysis detected a statistically significant difference in favor of Chondrosulf 1200mg/d in EVA, with a ES of -0.83 (95% CI -1.26 to -0.40, p=0.0000). A random effect model was used because there was a substantial statistical heterogeneity detected between the studies (p = 0.0372, I^2 = 0.70%).
All the 3 studies had extractable data about the number of participants with **AFI**. The analysis detected a statistically significant difference in favor of Chondrosulf 1200mg/d in AFI, with a ES of -0.90 (95% CI -1.13 to -0.66, p=0.0000). No heterogeneity was detected (p = 0.6421, I^2 = 0.00%).

Table 2.5: *Results details - Chondrosulf - Chondrosulf 1200mg/d*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
Chondrosulf 1200mg/d versus placebo						
EVA	ES=-0.83	[-1.26;-0.40]	0.0000	0.0372 (I^2=0.70)	3	322
AFI	ES=-0.90	[-1.13;-0.66]	0.0000	0.6421 (I^2=0.00)	3	322

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 2.1: *Forest's plot for EVA*

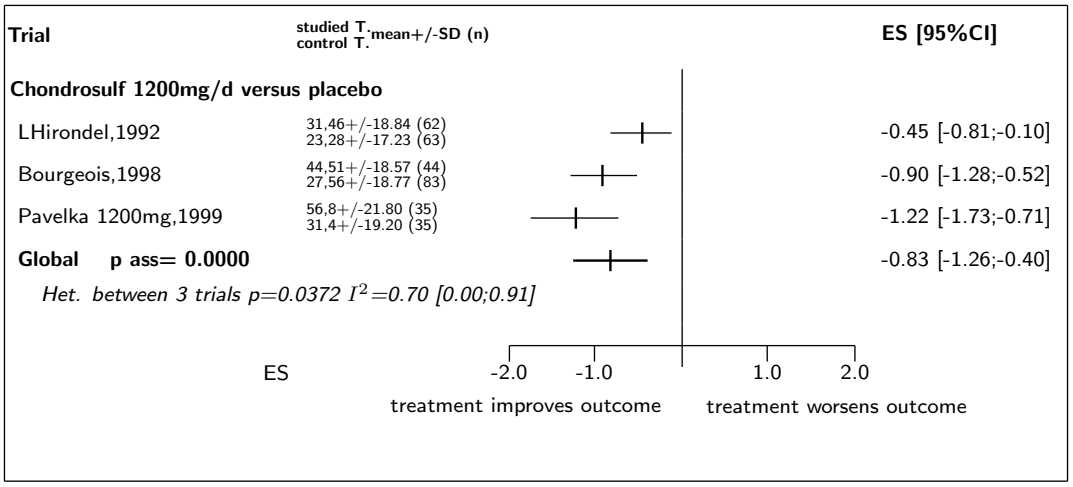
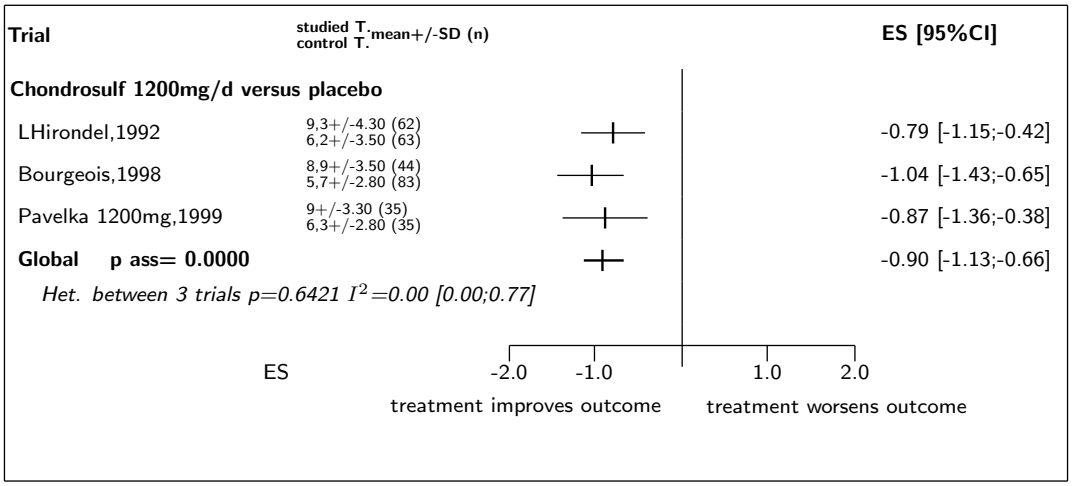


Figure 2.2: *Forest's plot for AFI*



References

[1] LHirondel JL. Klinische Doppelblind-Studie mit oral verabreichtem Chondroitinsulfatgegen Placebo bei der tibiofemoralen Gonarthrose (125 patients).. Litera Rheumatologica. 1992;14:77-84.

[2] Bourgeois P, Chales G, Dehais J, Delcambre B, Kuntz JL, Rozenberg S. Efficacy and tolerability of chondroitin sulfate 1200 mg/day vs chondroitin sulfate 3 x 400 mg/day vs placebo. Osteoarthritis Cartilage 1998;6 Suppl A:25-30. [PMID=9743816]

[3] Pavelka K, Manopulo R, Busci L. Double-blind, dose-effect study of oralchondroitin 4 & 6 sulfate 1200 mg, 800 mg, 200 mg, and placebo in thetreatment of knee osteoarthritis. Litera Rhumatologica. 1999;24:21-30..

3 Global meta-analysis: all Chondrosulf

3.1 Global meta-analysis: all Chondrosulf versus placebo

Table 3.1: *All Chondrosulfversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
EVA	ES=-0.83 [1]	-1.26;-0.40	0.0000	0.0372 (0.70) †	3	322
AFI	ES=-0.90	-1.13;-0.66	0.0000	0.6421 (0.00)	3	322

legend B

4 Ongoing studies of Chondrosulf

No ongoing trial was identified.

[1] with a random model ($\tau^2 = 0.100$). The results with a fixed effect model was RRFE=-0.78 95% CI -1.01;-0.54

5 Excluded studies for Chondrosulf

A total of studies were not eligible for this systematic review. A list of these excluded studies with the reason of their exclusion is given table **??**.

Table 5.1: *Excluded studies of Chondrosulf*

Study	**Exclusion reason**
Morreale (1996) [**?**]	not uncounfounded comparison of CS versus placebo
Bucsi and Poor (1998) [**?**]	inadequate dose
Bourgeois 1200 od (1998)	pas le bon schma posologique (1200mg en une seule fois la place de en 3 prise)
Uebelhart (1998) [**?**]	inadequate dose
Pavelka 800 mg/d (1999)	inadequate dose
Malaise (1999) [**?**]	inadequate dose
Uebelhart (2004) [**?**]	inadequate dose

Part II

Structum

6 Overview of structum

6.1 Included trials

A total of 4 randomized comparisons which enrolled 1425 patients were identified. In all, 4 randomized comparisons concerned Structum 1g daily.
The detailed descriptions of trials and meta-analysis results is given in section **??** (page **??**) for Structum 1g daily.

The average study size was 356 patients (range 132 to 837). The first study was published in 2001, and the last study was published in 2007.
All trials were double blind in design. All included studies were reported in English language. We found 2 unpublished trials.
The table **??** (page **??**) summmarizes the main characteristics of all the included trials. More detailed description is given in the following section.

6.2 Summary of meta-analysis results

The meta-analysis of the available trials about structum provide the results listed in tables **??** to **??** (page **??**) and in the following graphs.

6.2.1 Structum 1g daily

Structum 1g daily was superior to **placebo** in terms of NSAID consumption (ES=-0.42, 95% CI -0.76 to -0.09, p=0.0122, 1 trial), EVA (ES=-0.21, 95% CI -0.38 to -0.04, p=0.0146, 3 trials)and AFI (ES=-0.18, 95% CI -0.35 to -0.02, p=0.0316, 3 trials).
But Structum 1g daily worsened algo-functional Index (AFI) (ES=-0.21, 95% CI -0.38 to -0.05, p=0.0102, 3 trials), pain during activity (VAS) (ES=-0.23, 95% CI -0.40 to -0.07, p=0.0051, 3 trials)and pain during activity at 6 months (ES=-0.22, 95% CI -0.41 to -0.04, p=0.0189, 2 trials).
However, no significant difference was found on pain at rest (VAS) (ES=-0.09, 95% CI -0.30 to 0.11, p=0.3752, 3 trials), WOMAC index (ES=-0.14, 95% CI -0.48 to 0.19, p=0.4031, 1 trial)and pain during activity at 3 months (ES=-0.14, 95% CI -0.30 to 0.03, p=0.1101, 3 trials).

No significant difference was found between **Structum 1g daily** and **Chondrosulf 1200mg/d** in terms of algo-functional Index (AFI) (ES=0.06, 95% CI -0.09 to 0.21, p=0.4482, 1 trial), pain at rest (VAS) (ES=0.00, 95% CI -0.15 to 0.15, p=0.9940, 1 trial), pain during activity (VAS) (ES=0.00, 95% CI -0.15 to 0.15, p=0.9940, 1 trial), EVA (ES=-0.05, 95% CI -0.19 to 0.10, p=0.5533, 1 trial)and AFI (ES=-0.04, 95% CI -0.19 to 0.11, p=0.6099, 1 trial).

Table 6.1: *Main study characteristics - Structum*

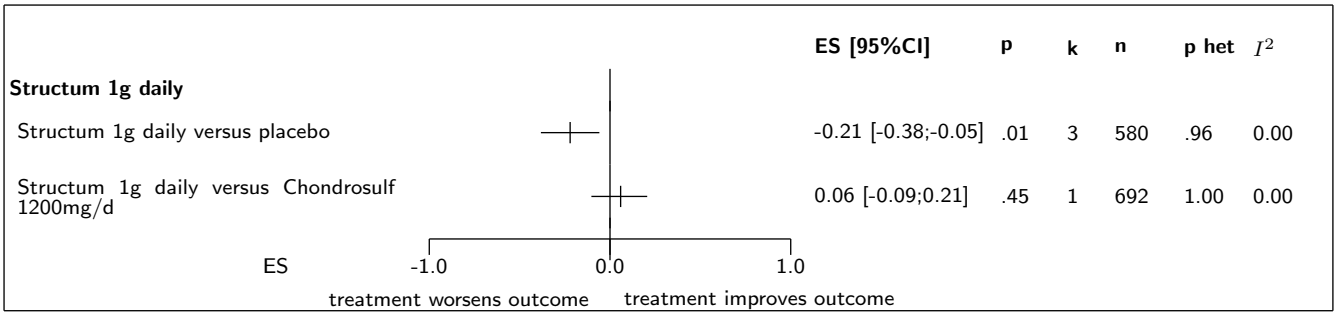
Trial	Patients	Treatments	Trial design and method
Structum 1g daily			
Structum 1g daily versus placebo			
GE 301 (Uebelhart), 0 [**?**] n = 72 vs. 73	patients with symptomatic knee osteoarthrosis	structum 500mg twice daily for 6 months **versus** placebo	double-blind parallel groups Primary endpoint: algo-functional Index (AFI) 25 centres,Switzerland ITT analysis: yes
GE 301 1 (Mazires), 2001 [**?**] n = 64 vs. 68	patients with symptomatic femorotibial osteoarthritis	structum 500mg twice daily for 3 months **versus** placebo	double-blind parallel groups Primary endpoint: algo-functional Index (AFI) 47 centres,France ITT analysis: yes
GE 402 (Mazires), 2007 [**?**] n = 155 vs. 156	patients with symptomatic knee osteoarthritis	structum 500mg twice daily for 6 months **versus** placebo	double-blind parallel groups Primary endpoint: pain on activity and Lequesnes Index Score 99 centres,France, Switzerland ITT analysis: yes
Structum 1g daily versus Chondrosulf 1200mg/d			
GE 409 (Fardellone), [**?**] n = 412 vs. 425	patients with symptomatic knee osteoarthrosis	structum 500mg twice daily **versus** chondrosulf 1200 mg/d (400mg tid)	double-blind parallel groups 126 centres,

Table 6.2: *Summary of all results for Structum 1g daily*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
Structum 1g daily versus placebo						
algo-functional Index (AFI)	ES=-0.21	-0.38;-0.05	0.0102	0.9621 (0.00)	3	580
NSAID consumption	ES=-0.42	-0.76;-0.09	0.0122	1.0000 (0.00)	1	143
pain at rest (VAS)	ES=-0.09	-0.30;0.11	0.3752	0.2165 (0.35)	3	580
pain during activity (VAS)	ES=-0.23	-0.40;-0.07	0.0051	0.8264 (0.00)	3	580
OMERACT-OARSI responders	RR=1.20	1.06;1.36	0.0030	0.5117 (0.00)	3	580
WOMAC index	ES=-0.14	-0.48;0.19	0.4031	1.0000 (0.00)	1	134
pain during activity at 3 months	ES=-0.14	-0.30;0.03	0.1101	0.6084 (0.00)	3	557
pain during activity at 6 months	ES=-0.22	-0.41;-0.04	0.0189	0.5718 (0.00)	2	450
EVA	ES=-0.21	-0.38;-0.04	0.0146	0.8702 (0.00)	3	552
AFI	ES=-0.18	-0.35;-0.02	0.0316	0.8404 (0.00)	3	552
Structum 1g daily versus Chondrosulf 1200mg/d						
algo-functional Index (AFI)	ES=0.06	-0.09;0.21	0.4482	1.0000 (0.00)	1	692
pain at rest (VAS)	ES=0.00	-0.15;0.15	0.9940	1.0000 (0.00)	1	692
pain during activity (VAS)	ES=0.00	-0.15;0.15	0.9940	1.0000 (0.00)	1	692
EVA	ES=-0.05	-0.19;0.10	0.5533	1.0000 (0.00)	1	692
AFI	ES=-0.04	-0.19;0.11	0.6099	1.0000 (0.00)	1	692

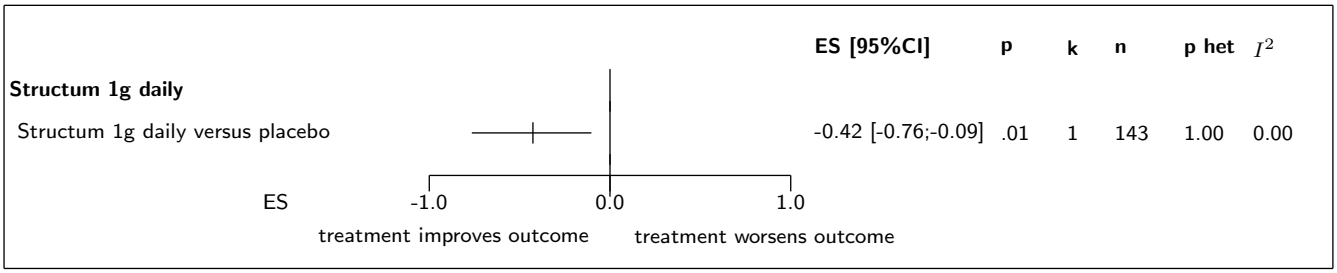
CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients

Figure 6.1: *Forest's plot for algo-functional Index (AFI)*



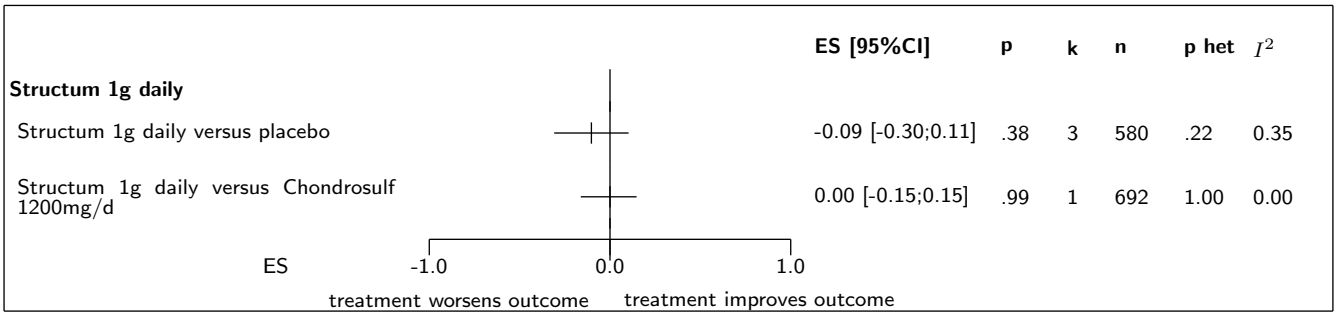
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 6.2: *Forest's plot for NSAID consumption*



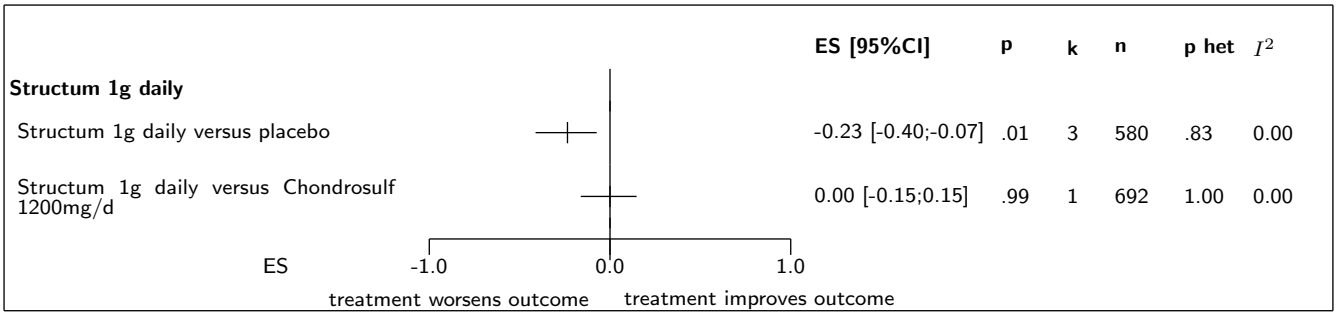
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 6.3: *Forest's plot for pain at rest (VAS)*



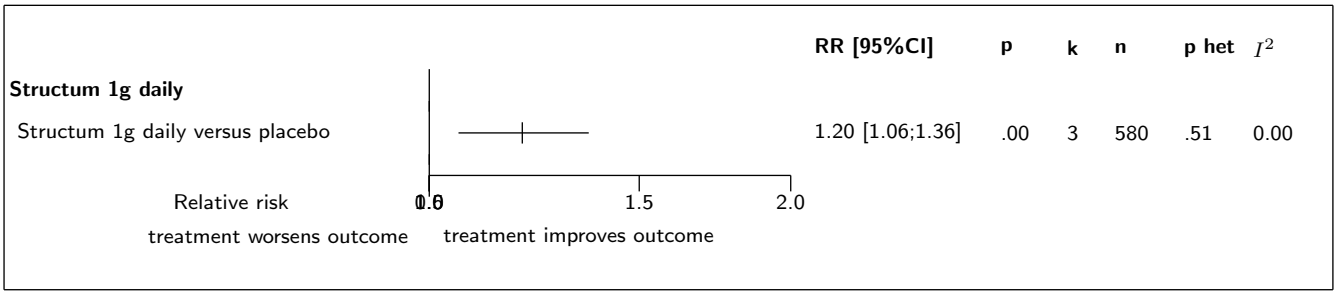
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 6.4: *Forest's plot for pain during activity (VAS)*



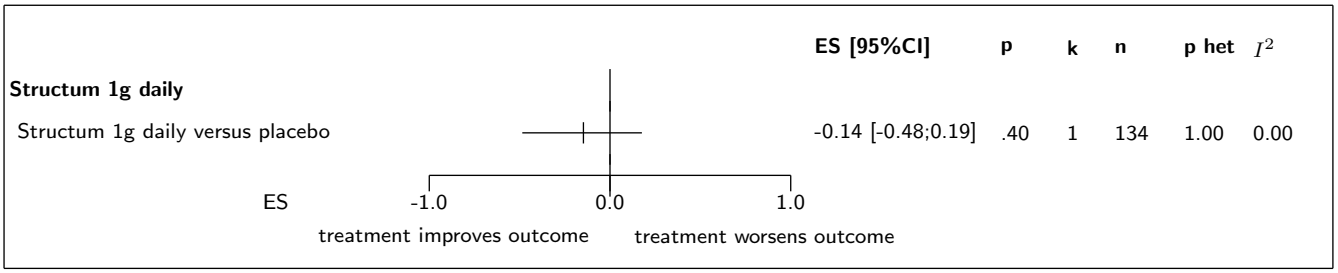
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 6.5: *Forest's plot for OMERACT-OARSI responders*



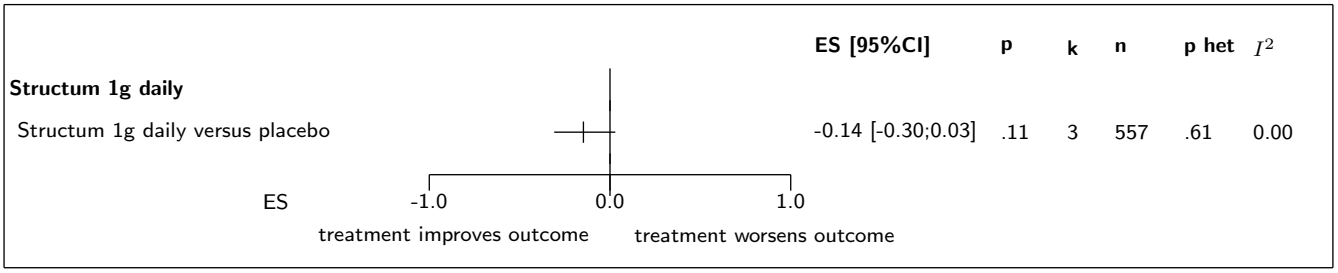
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
RR: relative risk; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; ^{r}: random effect model used

Figure 6.6: *Forest's plot for WOMAC index*



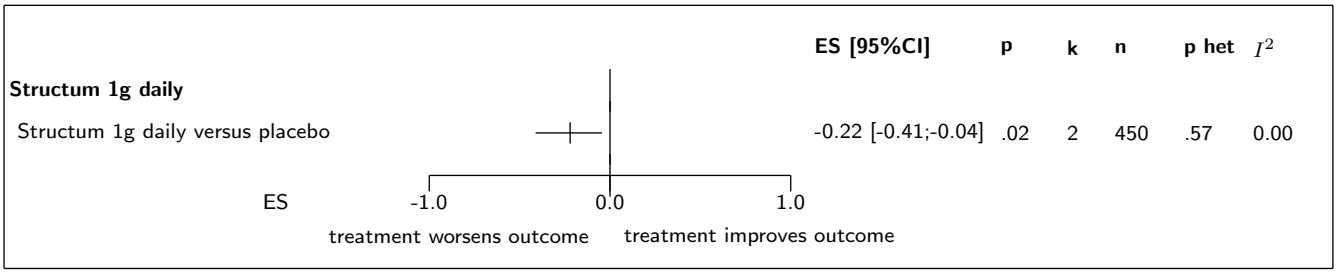
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 6.7: *Forest's plot for pain during activity at 3 months*



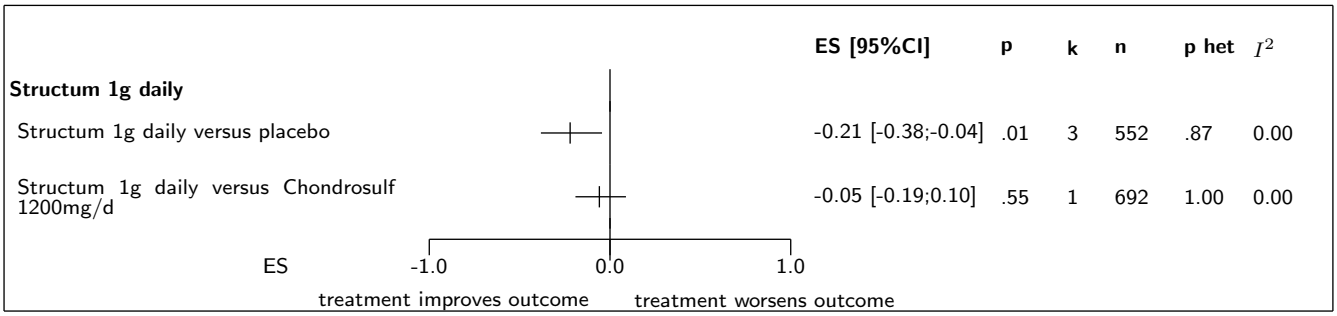
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 6.8: *Forest's plot for pain during activity at 6 months*



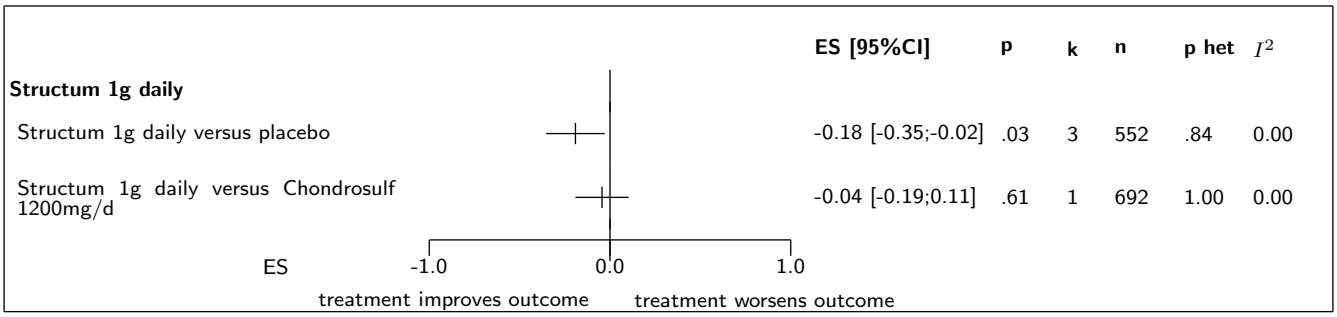
Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 6.9: *Forest's plot for EVA*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

Figure 6.10: *Forest's plot for AFI*



Results obtained with a fixed effect model except in case of heterogenity where a random model was used
ES: effect size; 95% CI: 95% confidence interval; p: p-value of the association test; k: number of trials; n: total number of patients involving in the pooled trials; p het: p-value of the hetereogenity test; I^2: inconsistance degree; ^{r}: random effect model used

7 Details

7.1 Available trials

A total of 4 RCTs which randomized 1425 patients were identified: 3 trials compared Structum 1g daily with placebo and it compared Structum 1g daily with Chondrosulf 1200mg/d.
The average study size was 356 patients (range 132 to 837). The first study was published in 2001, and the last study was published in 2007.
All trials were double blind in design. All included studies were reported in English language. We found 2 unpublished trials.
EVA data was reported in 4 trials; 4 trials reported data on pain during activity (VAS); 4 trials reported data on algo-functional Index (AFI); 4 trials reported data on AFI; 4 trials reported data on pain at rest (VAS); 3 trials reported data on OMERACT-OARSI responders; 3 trials reported data on pain during activity at 3 months; 2 trials reported data on pain during activity at 6 months; 2 trials reported data on paracetamol consumption; 1 trials reported data on NSAID consumption; and 1 trials reported data on WOMAC index.
Following tables **??** (page **??**), **??** (page **??**), **??** (page **??**), and **??** (page **??**) summarized the main characteristics of the trials including in this systematic review of randomized trials of Structum 1g daily.

Table 7.1: *Treatment description - Structum - Structum 1g daily*

Trial	Studied treatment	Control treatment
Structum 1g daily versus placebo		
GE 301 (Uebelhart) (0) [**?**]	structum 500mg twice daily for 6 months	placebo
	Concomittant treatment: if intolerable pain persisted beyond 3 days, paracetamol up to 2000 mg/day and/or a NSAID (diclofenac, ibuprofen) was prescribed and could be continued for the duration of the study, although moderation in usage was recommended; other treatments for OA, all corticosteroids, all analgesics except paracetamol, and aspirin >375 mg/day were not allowed	
GE 301 1 (Mazires) (2001) [**?**]	structum 500mg twice daily for 3 months	placebo
	Concomittant treatment: if intolerable pain persisted beyond 3 days, paracetamol up to 2000 mg/day and/or a NSAID (diclofenac, ibuprofen) was prescribed and could be continued for the duration of the study, although moderation in usage was recommended; other treatments for OA, all corticosteroids, all analgesics except paracetamol, and aspirin >375 mg/day were not allowed	
GE 402 (Mazires) (2007) [**?**]	structum 500mg twice daily for 6 months	placebo
	Concomittant treatment: rescue drugs: paracetamol (up to 4 g/day); in cases where paracetamol treatment proved to be insufficient, NSAIDs allowed (rescue drugs were forbidden before each evaluation visit: NSAIDs in the 2 days and paracetamol in the 12 h before the visit). SYSADOA, opioids or steroids by any route of administration, topical drugs or any physical therapy applied to the painful knee were forbidden during the trial	
Structum 1g daily versus Chondrosulf 1200mg/d		
GE 409 (Fardellone) () [**?**]	Structum 500mg twice daily	Chondrosulf 1200 mg/d (400mg tid)

Table 7.2: *Descriptions of participants - Structum - Structum 1g daily*

Trial	Patients	
Structum 1g daily versus placebo		
GE 301 (Uebelhart) (0) [**?**]	Patients with symptomatic knee osteoarthrosis **Inclusion criteria:** male or female outpatient suffering from painful femorotibial osteoarthritis; age between 50 and 80 years; algo-functional Index (AFI) =4 and =13; pain during activity =30 mm on Visual Analogue Scale (VAS); regular consumption of NSAID for a minimum of 3 weeks during the last 3 months; Kellgren-Lawrence Scale: grade II or III	**Exclusion criteria:** isolated patellofemoral OA;disabling OA or OA scheduled for surgery within the next 6 months;OA treated with surgical intervention or arthroscopy within the preceding 6 months;OA with an effusion needing aspiration or being aspirated within the last 30 days;OA with a genu varum >8 degrees;chondrocalcinosis;OA due to Pagets disease, rheumatoid arthritis, inflammation, infection, metabolic disease;treatment with: Structum, Chondrosulf or Art 50 during the last 6 months, hyaluronic acid during the last 9 months or osmic acid during the last 6 months;patients not able to reduce their NSAID consumption during the run-in period;OA treated within the last 6 months with topic corticosteroids;disturbance of hepatic function (ASAT/ALAT >2x upper normal limit);disturbance of renal function (plasma creatinine >150 micromol/l);haematopoetic disease (platelets <100,000/mm3), haemoglobin <10.0 g/dl (women) or 12.0 g/dl (men), WBC <3000/mm3);severe cardiovascular disease (cardiac failure NYHA IV or myocardial infarction within the last 3 months);history or current illness of duodenal ulcer or other conditions which contraindicate treatment with NSAID;hypersensitivity to NSAID;concomitant illness that may interfere with the study course;participation in a concomitant trial or included previously in this or another clinical trial within the last 3 months;treatment with non-registered drugs within the last 4 weeks;lack of signed informed consent;patients unable to comply with requirements of the study, including non-co-operation, psychiatric illness, and those with linguistic difficulties, as well as drug or alcohol addiction;pregnant or nursing mothers

continued...

Trial	Patients	
GE 301 1 (Mazires) (2001) [?]	Patients with symptomatic femorotibial osteoarthritis	
	Inclusion criteria: outpatients with femorotibial osteoarthritis; >50 years old; algo-functional Index (AFI) >=4 and <=11; pain with activity >=30 mm on the Visual Analog Scale (VAS); regular consumption of NSAID for 3 months; radiographic grade II or III on Kellgren-Lawrence Scale	**Exclusion criteria:** isolated patellofemoral OA;OA with a AFI <4 or >11;OA pain on VAS <30 mm;radiographic grade I or IV on the Kellgren-Lawrence Scale need for surgery in the coming months;OA treated with surgical intervention or arthroscopy within the preceding 6 months;OA with an effusion needing aspiration;OA with a genu varum >8 degrees;chondrocalcinosis;OA secondary to Pagets disease, inflammation, infection, metabolic diseas;eOA treated by anti-arthritic drugs, such as Structum, Chondrosulf, Art 50 (for a complete list, see amendment 1, 16.1.1) <2 months preceding selection;OA treated with NSAID other than Diclofenac, Ketrofen, Naproxen ;liver insufficiency (ASAT/ALAT >2x upper normal limit);cardiovascular disease;haematopoetic disease (platelets <100,000/mm3), haemoglobin <10.5 g/l, WBC <3000/mm3);renal insufficiency (plasma creatinine >150 micromol/l);history or current illness of duodenal ulcer;history or allergy to NSAID or other treatments for OA;insulin-dependent diabetes;concomitant illness that may interfere with the study course;participation in a concomitant trial or included previously in this or another clinical trial in the previous 3 months;patients unable to comply with requirements of the study, including non-cooperation, psychiatric illness, and those with linguistic difficulties;drug or alcohol addiction;
GE 402 (Mazires) (2007) [?]	Patients with symptomatic knee osteoarthritis	
	Inclusion criteria: outpatients of both sexes, aged 5080 years, with medial knee OA, defined according to American College of Rheumatology criteria; lasted for >6 months, with pain during daily activity >=40 mm on a 0100 mm visual analogue scale (VAS), a Lequesnes Index Score of between 6 and 12; stages 2/3 of the Kellgren and Lawrence (K/L) classification on an anteriorposterior view in an extended standing position taken within the previous 6 months	**Exclusion criteria:** secondary knee OA; isolated patello-femoral OA; knee surgery needs in the coming year; known hypersensitivity or allergy to chondroitin sulphate or paracetamol; use of nonsteroidal anti-inflammatory drugs (NSAIDs) for >50% of the time during the 2 months before inclusion; use of NSAIDs within 48 hours before inclusion or SYSADOA, steroid by any route, intra-articular hyaluronic acid or arthroscopic debridement within 6 months before inclusion; other active or severe diseases
Structum 1g daily versus Chondrosulf 1200mg/d		
GE 409 (Fardellone) () [?]	Patients with symptomatic knee osteoarthrosis	

Table 7.3: *Main patients characteristics - Structum - Structum 1g daily*

Trial	Characteristics
Structum 1g daily versus placebo	
GE 301 (Uebelhart), 0 [?]	age (years): 61.29 women (%): 70.3% joint affected: knee symptom duration (years): NA pain intensity at rest: 31.9 pain intensity during activity: 54.05
GE 301 1 (Mazires), 2001 [?]	age (years): 67 y women (%): 74.2% joint affected: knee symptom duration (years): NA pain intensity at rest: 28.77 pain intensity during activity: 53.68
GE 402 (Mazires), 2007 [?]	age (years): 66 y women (%): 70% joint affected: knee symptom duration (years): 6.4 pain intensity at rest: 40 pain intensity during activity: 61.5
Structum 1g daily versus Chondrosulf 1200mg/d	
GE 409 (Fardellone), [?]	

Table 7.4: *Design and methodological quality of trials - Structum - Structum 1g daily*

Trial	Design	Duration	Centre	Primary endpoint
Structum 1g daily versus placebo				
GE 301 (Uebelhart), 0 [?] n=145	Parallel groups double-blind confirmatory trial at low risk of bias	6 months inclusion period: jan 1997 - oct 1998	Switzerland 25 centres	algo-functional Index (AFI)
GE 301 1 (Mazires), 2001 [?] n=132	Parallel groups double-blind confirmatory trial at low risk of bias	3 months inclusion period: jan 1995 - apr 1996	France 47 centres	algo-functional Index (AFI)
GE 402 (Mazires), 2007 [?] n=311	Parallel groups double-blind confirmatory trial at low risk of bias	6 months inclusion period: oct 2003 - mar 2005	France, Switzerland 99 centres	pain on activity and Lequesnes Index Score
Structum 1g daily versus Chondrosulf 1200mg/d				
GE 409 (Fardellone), [?] n=837	Parallel groups double-blind	9 months	126 centres	

7.2 Meta-analysis results

The results are detailed in table **??** (page **??**). This table is followed by the Forest's plot corresponding to each endpoint.

Structum 1g daily versus placebo

All the 3 studies had extractable data about the number of participants with **algo-functional Index (AFI)**. The analysis detected a statistically significant difference in favor of Structum 1g daily in algo-functional Index (AFI), with a ES of -0.21 (95% CI -0.38 to -0.05, p=0.0102). No heterogeneity was detected (p = 0.9621, I^2 = 0.00%).
Only one of the 3 studies eligible for this comparison provided data on **NSAID consumption**. The analysis detected a statistically significant difference in favor of Structum 1g daily in NSAID consumption, with a ES of -0.42 (95% CI -0.76 to -0.09, p=0.0122).
All the 3 studies had extractable data about the number of participants with **pain at rest (VAS)**. When pooled together, there was no statistically significant difference between the groups in pain at rest (VAS), with a ES of -0.09 (95% CI -0.30 to 0.11, p=0.3752). No heterogeneity was detected (p = 0.2165, I^2 = 0.35%).
All the 3 studies had extractable data about the number of participants with **pain during activity (VAS)**. The analysis detected a statistically significant difference in favor of Structum 1g daily in pain during activity (VAS), with a ES of -0.23 (95% CI -0.40 to -0.07, p=0.0051). No heterogeneity was detected (p = 0.8264, I^2 = 0.00%).
All the 3 studies had extractable data about the number of participants with **OMERACT-OARSI responders**. The analysis detected a statistically significant difference in favor of Structum 1g daily in OMERACT-OARSI responders, with a RR of 1.20 (95% CI 1.06 to 1.36, p=0.0030). No heterogeneity was detected (p = 0.5117, I^2 = 0.00%).
Only one of the 3 studies eligible for this comparison provided data on **WOMAC index**. No statistically significant difference between the groups was found in WOMAC index, with a ES of -0.14 (95% CI -0.48 to 0.19, p=0.4031).
All the 3 studies had extractable data about the number of participants with **pain during activity at 3 months**. When pooled together, there was no statistically significant difference between the groups in pain during activity at 3 months, with a ES of -0.14 (95% CI -0.30 to 0.03, p=0.1101). No heterogeneity was detected (p = 0.6084, I^2 = 0.00%).
A total of 2 of the 3 studies eligible for this comparison provided data on **pain during activity at 6 months**. The analysis detected a statistically significant difference in favor of Structum 1g daily in pain during activity at 6 months, with a ES of -0.22 (95% CI -0.41 to -0.04, p=0.0189). No heterogeneity was detected (p = 0.5718, I^2 = 0.00%).
All the 3 studies had extractable data about the number of participants with **EVA**. The analysis detected a statistically significant difference in favor of Structum 1g daily in EVA, with a ES of -0.21 (95% CI -0.38 to -0.04, p=0.0146). No heterogeneity was detected (p = 0.8702, I^2 = 0.00%).
All the 3 studies had extractable data about the number of participants with **AFI**. The analysis detected a statistically significant difference in favor of Structum 1g daily in AFI, with a ES of -0.18 (95% CI -0.35 to -0.02, p=0.0316). No heterogeneity was detected (p = 0.8404, I^2 = 0.00%).

Structum 1g daily versus Chondrosulf 1200mg/d

The single study eligible for this comparison provided data on **algo-functional Index (AFI)**. There was no statistically significant difference in algo-functional Index (AFI) between Structum 1g daily and Chondrosulf 1200mg/d, with a ES of 0.06 (95%CI -0.09 to 0.21, p=0.4482) in favour of Structum 1g daily. In other words, algo-functional Index (AFI) was slightly lower in the Structum 1g daily group , but this was not statistically significant.

The single study eligible for this comparison provided data on **pain at rest (VAS)**. No statistically significant difference between the groups was found in pain at rest (VAS), with a ES of 0.00 (95% CI -0.15 to 0.15, p=0.9940).
The single study eligible for this comparison provided data on **pain during activity (VAS)**. No statistically significant difference between the groups was found in pain during activity (VAS), with a ES of 0.00 (95% CI -0.15 to 0.15, p=0.9940).
The single study eligible for this comparison provided data on **EVA**. No statistically significant difference between the groups was found in EVA, with a ES of -0.05 (95% CI -0.19 to 0.10, p=0.5533).
The single study eligible for this comparison provided data on **AFI**. No statistically significant difference between the groups was found in AFI, with a ES of -0.04 (95% CI -0.19 to 0.11, p=0.6099).

Table 7.5: *Results details - Structum - Structum 1g daily*

Comparison Endpoint	Effect	95% CI	p ass	p het	k	n
Structum 1g daily versus placebo						
algo-functional Index (AFI)	ES=-0.21	[-0.38;-0.05]	0.0102	0.9621 (I^2=0.00)	3	580
NSAID consumption	ES=-0.42	[-0.76;-0.09]	0.0122	1.0000 (I^2=0.00)	1	143
pain at rest (VAS)	ES=-0.09	[-0.30;0.11]	0.3752	0.2165 (I^2=0.35)	3	580
pain during activity (VAS)	ES=-0.23	[-0.40;-0.07]	0.0051	0.8264 (I^2=0.00)	3	580
OMERACT-OARSI responders	RR=1.20	[1.06;1.36]	0.0030	0.5117 (I^2=0.00)	3	580
WOMAC index	ES=-0.14	[-0.48;0.19]	0.4031	1.0000 (I^2=0.00)	1	134
pain during activity at 3 months	ES=-0.14	[-0.30;0.03]	0.1101	0.6084 (I^2=0.00)	3	557
pain during activity at 6 months	ES=-0.22	[-0.41;-0.04]	0.0189	0.5718 (I^2=0.00)	2	450
EVA	ES=-0.21	[-0.38;-0.04]	0.0146	0.8702 (I^2=0.00)	3	552
AFI	ES=-0.18	[-0.35;-0.02]	0.0316	0.8404 (I^2=0.00)	3	552
Structum 1g daily versus Chondrosulf 1200mg/d						
algo-functional Index (AFI)	ES=0.06	[-0.09;0.21]	0.4482	1.0000 (I^2=0.00)	1	692
pain at rest (VAS)	ES=0.00	[-0.15;0.15]	0.9940	1.0000 (I^2=0.00)	1	692
pain during activity (VAS)	ES=0.00	[-0.15;0.15]	0.9940	1.0000 (I^2=0.00)	1	692
EVA	ES=-0.05	[-0.19;0.10]	0.5533	1.0000 (I^2=0.00)	1	692
AFI	ES=-0.04	[-0.19;0.11]	0.6099	1.0000 (I^2=0.00)	1	692

CI: confidence interval; p ass: p-value of association test; p het: p-value of the heterogeneity test; k: number of trials; n: total number of patients; ES: effect size; I^2: inconsistance degree

Figure 7.1: *Forest's plot for Algo-functional Index (AFI)*

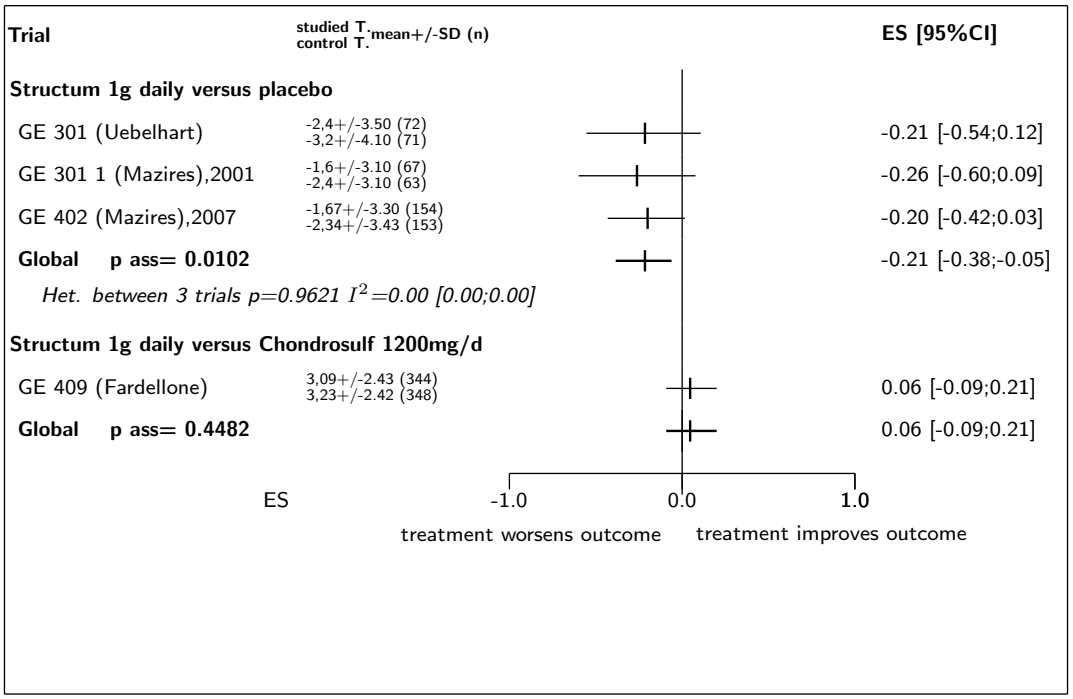


Figure 7.2: *Forest's plot for NSAID consumption*

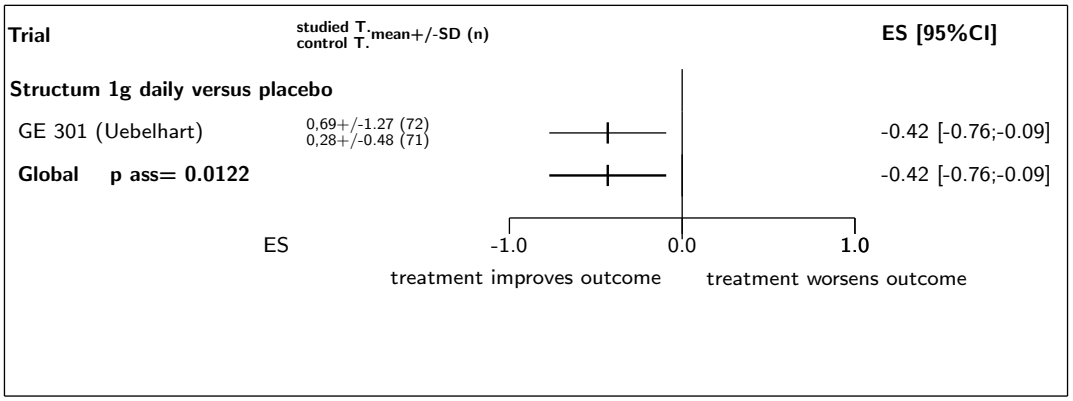


Figure 7.3: *Forest's plot for Pain at rest (VAS)*

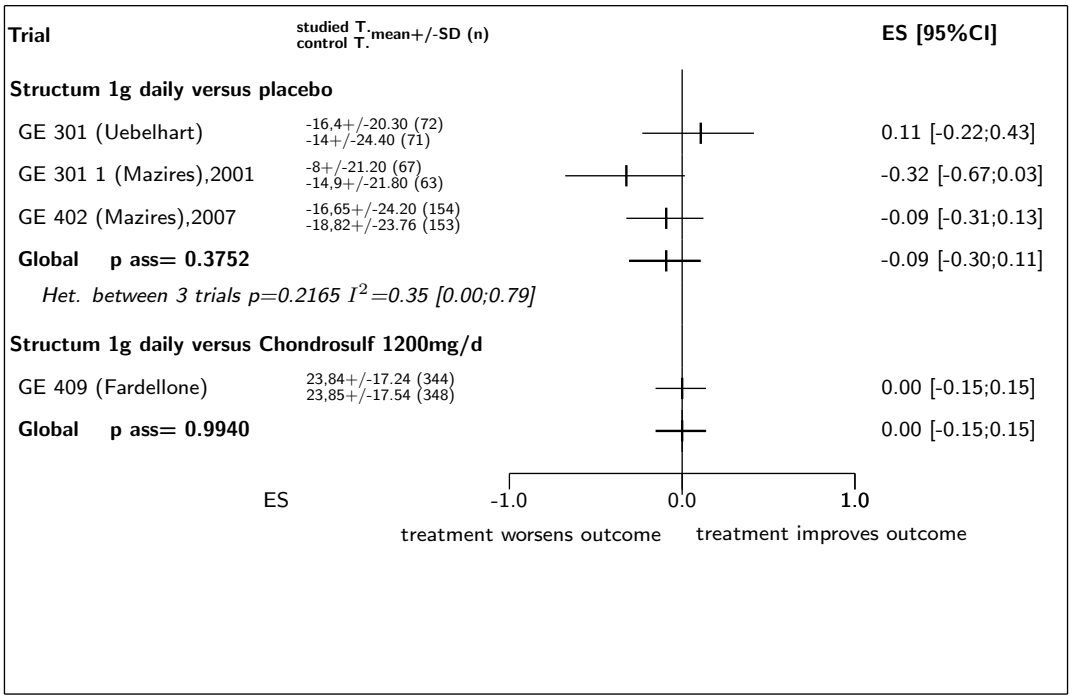


Figure 7.4: *Forest's plot for Pain during activity (VAS)*

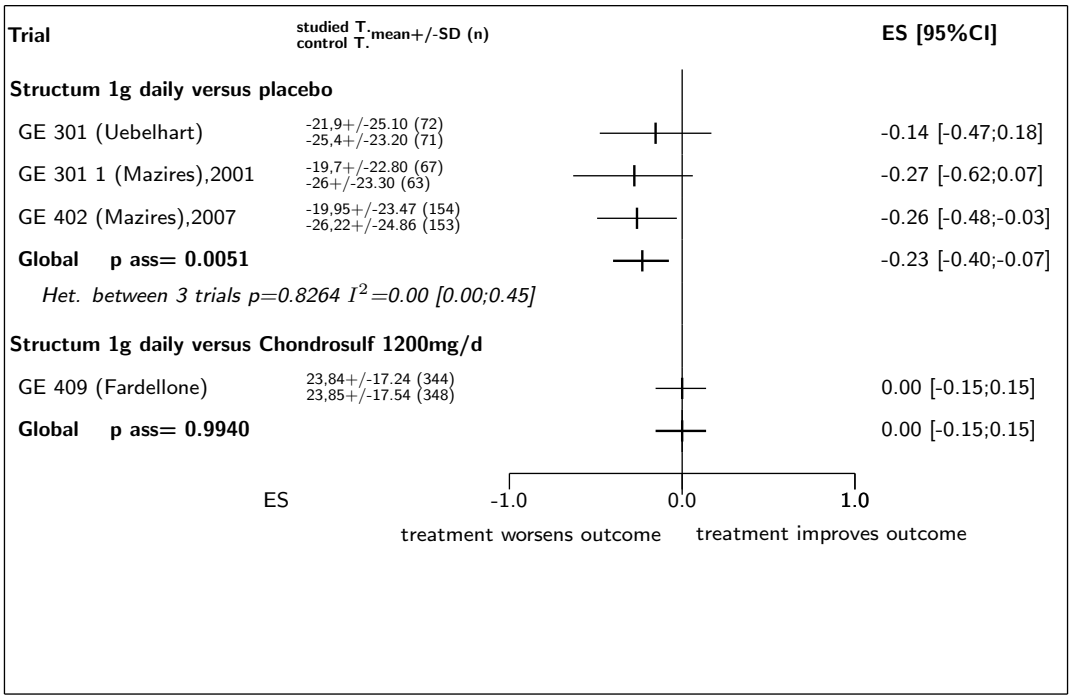


Figure 7.5: *Forest's plot for OMERACT-OARSI responders*

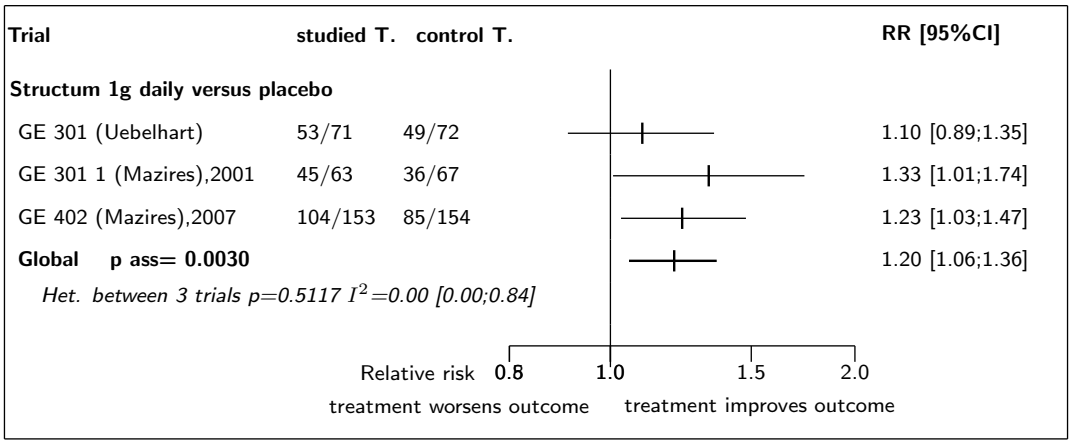


Figure 7.6: *Forest's plot for WOMAC index*

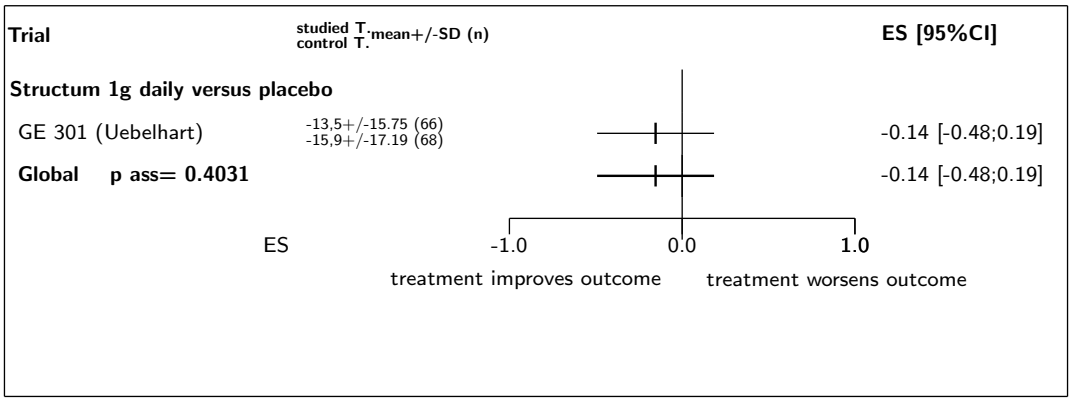


Figure 7.7: *Forest's plot for Pain during activity at 3 months*

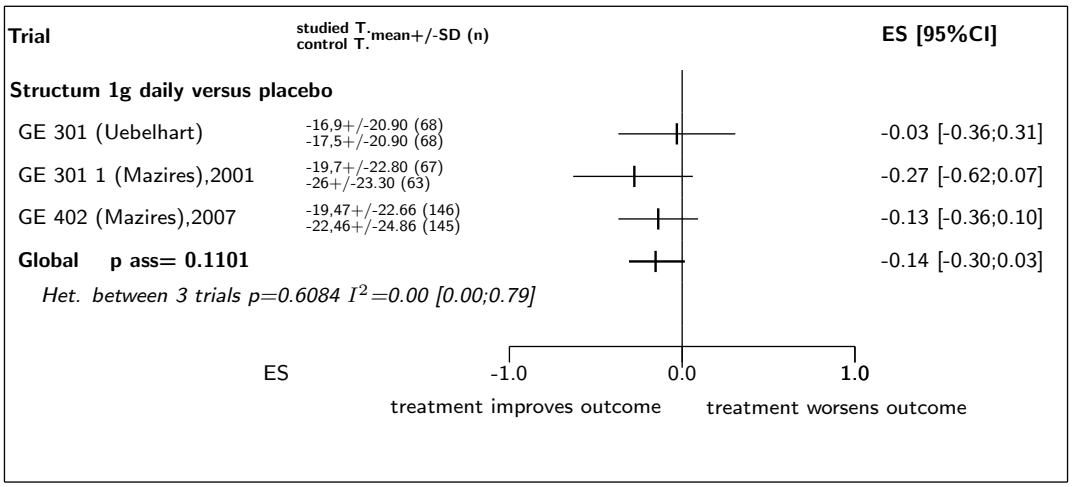


Figure 7.8: *Forest's plot for Pain during activity at 6 months*

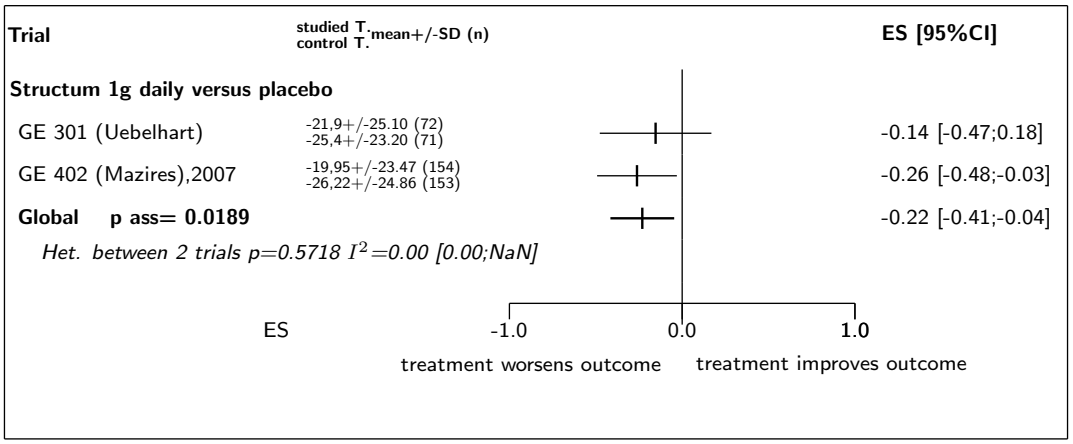


Figure 7.9: *Forest's plot for EVA*

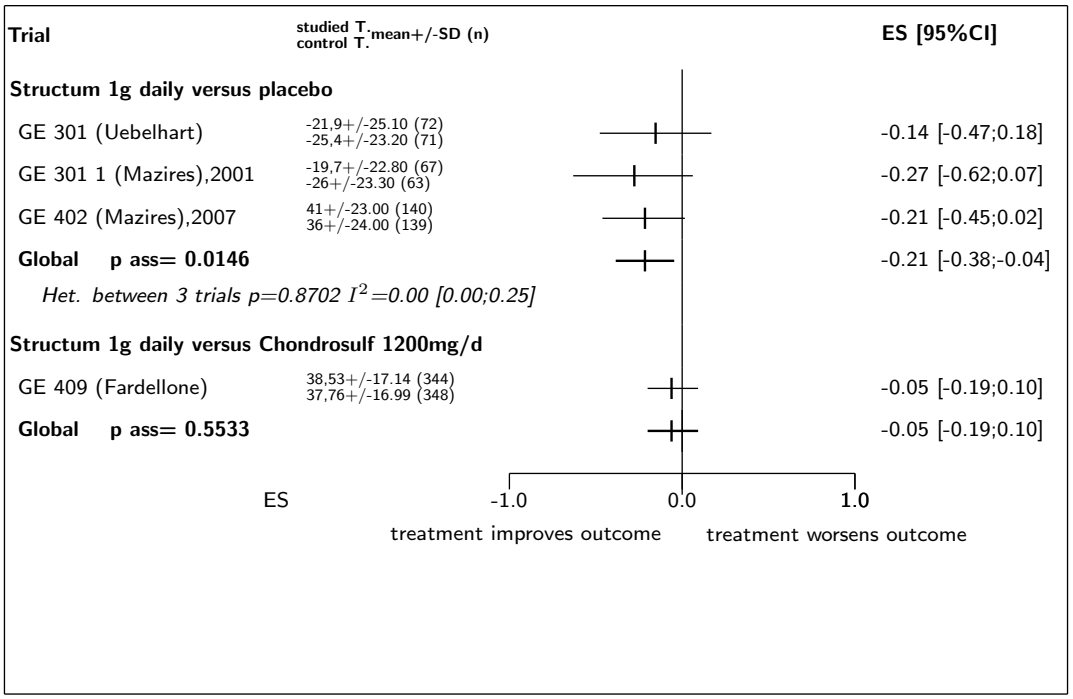
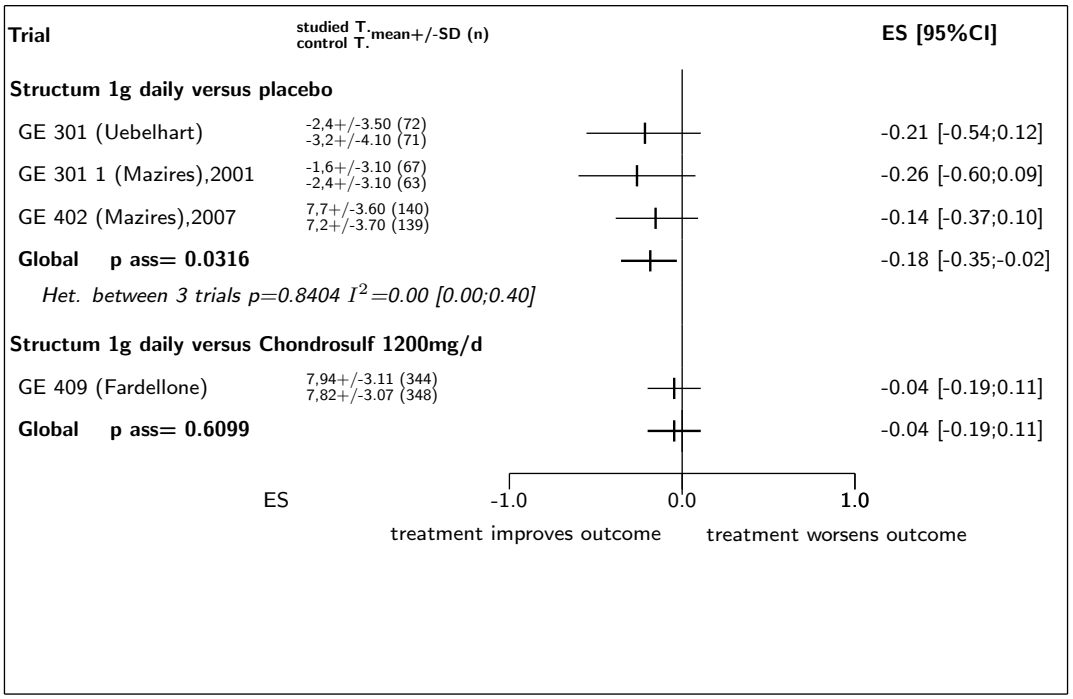


Figure 7.10: *Forest's plot for AFI*



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[1] Uebelhart D. Double blind, randomized, placebo controlled, multicenter trial assessing the efficacy and safety of chrondoitin sulphate 1 gram per day for 6 months in patients with painful femorotibial osteoarthritis. Pierre Fabre Internal report, 2000.

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8 Global meta-analysis: all Structum

8.1 Global meta-analysis: all Structum versus Chondrosulf 1200mg/d

Table 8.1: *All Structumversus Chondrosulf 1200mg/d*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
algo-functional Index (AFI)	ES=0.06	-0.09;0.21	0.4482	1.0000 (0.00)	1	692
pain at rest (VAS)	ES=0.00	-0.15;0.15	0.9940	1.0000 (0.00)	1	692
pain during activity (VAS)	ES=0.00	-0.15;0.15	0.9940	1.0000 (0.00)	1	692
EVA	ES=-0.05	-0.19;0.10	0.5533	1.0000 (0.00)	1	692
AFI	ES=-0.04	-0.19;0.11	0.6099	1.0000 (0.00)	1	692

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8.2 Global meta-analysis: all Structum versus placebo

Table 8.2: *All Structumversus placebo*

Endpoint	Effect	95% CI	p ass	p het (I^2)	k	n
algo-functional Index (AFI)	ES=-0.21	-0.38;-0.05	0.0102	0.9621 (0.00)	3	580
NSAID consumption	ES=-0.42	-0.76;-0.09	0.0122	1.0000 (0.00)	1	143
pain at rest (VAS)	ES=-0.09	-0.30;0.11	0.3752	0.2165 (0.35)	3	580
pain during activity (VAS)	ES=-0.23	-0.40;-0.07	0.0051	0.8264 (0.00)	3	580
OMERACT-OARSI responders	RR=1.20	1.06;1.36	0.0030	0.5117 (0.00)	3	580
WOMAC index	ES=-0.14	-0.48;0.19	0.4031	1.0000 (0.00)	1	134
pain during activity at 3 months	ES=-0.14	-0.30;0.03	0.1101	0.6084 (0.00)	3	557
pain during activity at 6 months	ES=-0.22	-0.41;-0.04	0.0189	0.5718 (0.00)	2	450
EVA	ES=-0.21	-0.38;-0.04	0.0146	0.8702 (0.00)	3	552
AFI	ES=-0.18	-0.35;-0.02	0.0316	0.8404 (0.00)	3	552

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9 Ongoing studies of Structum

No ongoing trial was identified.

10 Excluded studies for Structum

A total of studies were not eligible for this systematic review. A list of these excluded studies with the reason of their exclusion is given table **??**.

Table 10.1: *Excluded studies of Structum*

Study	**Exclusion reason**
Alekseeva (1999) [**?**]	not versus placebo
GE C2 (Mazieres) (1992) [**?**]	inadequate dose
Nasonova (2001) [**?**, **?**]	open design, not versus placebo
Soroka and Chyzh (2002) [**?**]	Not randomised controlled trials