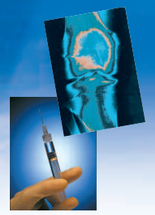

A MULTICENTRE, RANDOMISED, LONG-TERM (6-MONTH) PHASE IV COMPARATIVE CLINICAL STUDY ARTHRUM H 2% ADMINISTERED BY INTRA-ARTICULAR INJECTION INTO THE KNEE IN PATIENTS WITH OSTEOARTHRITIS

GUIDANCE FOR READING THE RESULTS

All the tables below will be presented as follows :

	TOTAL base %	CRITERION 1 base % (A)	CRITERION 2 base % (B)	CRITERION 3 base % (C)	CRITERION 4 base % (D)
• Item 1	x_1 %	α_1%	β_1%	γ_1%	δ_1%
• Item 2	x_2 %	α_2% B (1)	β_2% c(2)	γ_2% **d**(3)	δ_2%
•	…	…	…	..	..
• Item i.....	x_i %	α_i%	β_i%	γ_i%	δ_i%

The test used in this report is an intercolumn Z_test to 1% and 5% between independent columns A, B, C, D, etc.
The test is performed when the base of a column is ≥ 30.
The test is read as follows :

(1) : the proportion α_2% (column A) is significantly (to 1%) higher than β_2% (column B)

(2) : the proportion β_2% (column B) is significantly (to 5%) higher than γ_2% (column C)

(3) : the proportion γ_2% (column C) is significantly (to 10%) higher than δ_2% (column D)

The tables where the letters A, B, C, etc. do not appear in a column are tables where there is no significant difference, or where bases are insufficient for the test.
Capitals : significant difference to 1%; lowercase : significant difference to 5%; bold lowercase : significant difference to 10%.

The complete document of the statistical analysis of the "long-term (6 months) phase IV, multicentered, randomized, comparative clinical study on ARTHRUM H 2% injection into the knee joint of patients suffering from arthrosis" is available upon request.

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LCA PHARMACEUTICAL

9, Allée Prométhée, F-28000 Chartres, France
Phone : +33 (0)2 37 33 39 30 - Fax : +33 (0)2 37 33 39 39 - E-mail : arthrum@lca-pharma.com

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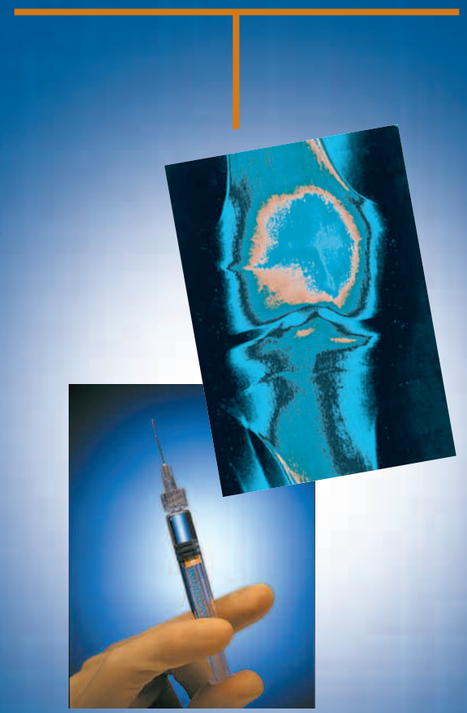
A MULTICENTRE, RANDOMISED, LONG-TERM (6-MONTH) PHASE IV COMPARATIVE CLINICAL STUDY

ARTHRUM H 2%

ADMINISTERED BY INTRA-ARTICULAR INJECTION INTO THE KNEE IN PATIENTS WITH OSTEOARTHRITIS

A STATISTICAL STUDY INVOLVING 496 PATIENTS

TNS SOFRES Département Santé - Geneviève BONNELYE
Pascal KIEFFER, Françoise VINCENT-AUBRY, Patrice VINCENT



LCA PHARMACEUTICAL

A MULTICENTRE, RANDOMISED, LONG-TERM (6-MONTH) PHASE IV COMPARATIVE CLINICAL STUDY ARTHRUM H 2% ADMINISTERED BY INTRA-ARTICULAR INJECTION INTO THE KNEE IN PATIENTS WITH OSTEOARTHRITIS

INTRODUCTION

Osteoarthritis of the knee is increasingly being treated by viscosupplementation, because the advantages of this method and its efficacy are so evident, in terms of recovery of mobility and pain relief.

A multicentre, randomised, phase IV comparative clinical study was conducted between 2002 and 2004, in order to evaluate the various viscosupplementation products used in the treatment of osteoarthritis of the knee and administered by intra-articular injection.

THE OBJECTIVE OF THE STUDY

The main purpose of this study was to evaluate changes in the functional capacity and pain scores of the WOMAC index over a 6-month period, in patients with osteoarthritis of the knee treated with **ARTHRUM H** and to compare these results with those obtained using other viscosupplementation products.

MATÉRIALS AND MÉTHODS

Patients

496 patients that met the ACR criteria for osteoarthritis of the knee (R. ALTMAN et al., Arthritis Rheumatology 1986; 29 : 1039-49) were enrolled by 11 French rheumatologists.

The final sample comprised 490 patients, as 6 cases were excluded (missing evaluation) :

- 271 patients treated with ARTHRUM H®	- 35 patients treated with OSTENIL®
- 85 patients treated with SYNVISC®	- 30 patients treated with ADANT®
	- 69 patients treated with SUPLASYN®

The procedure

The viscosupplementation products currently available all contain sodium hyaluronate (NaHA), but differ greatly in their molecular weight and concentration.

The treatment regimen for each different product comprised three intra-articular injections administered at intervals of one week.

Patients follow-up

Product name	Manufacturer	Sodium hyaluronate			Dynamic viscosity (Pa.s)
		Concentration	Source	Molecular weight (kDa)	At 1 s^{-1}
ARTHRUM H (CE0120)	LCA (France)	2,00%	biofermentation	2400	60
SYNVISC (CE0483)	Biomatrix (USA)	0,80% (Hylane A + B)	Chicken comb	6000 Cross-linked bi-composant	45 (Determinations made by LCA)
ADANT (CE0318)	Tedec-Meji (Espagne)	1,00%	Biofermentation	-	2,2 (Determinations made by LCA)
SUPLASYN (CE0473)	Bioniche Teo (Irlande)	1,00%	Biofermentation	> 40	0,5 (Determinations made by LCA)
OSTENIL (CE0123)	Chemedica (Allemagne)	1,00%	Biofermentation	1000 at 2000	0,5 (Determinations made by LCA)

The patient follow-up lasted 180 days.
Three visits were scheduled, on days 0, 90 and 180.
The efficacy of the treatment was assessed at each follow-up visit by evaluating the WOMAC functional capacity and pain scores.
Pain was also assessed according to the ANAES criteria, using a 10-point visual analogue scale.

The consumption of analgesics, steroids and NSAIDs was noted at each visit, and the name and dose of the drug taken was specified.
The results of these two measurements (pain and concomitant treatments) will be released later.

Statistical methods

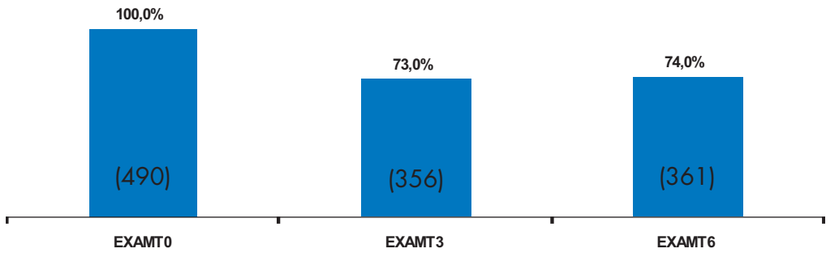
The data were analysed and used by TNS SOFRES Santé.
Frequency tables were generated, through computer processing, to :

- Calculate the WOMAC index ;
- Measure pain using the ANAES criteria ;
- Establish the quantity and type of concomitant treatments prescribed.

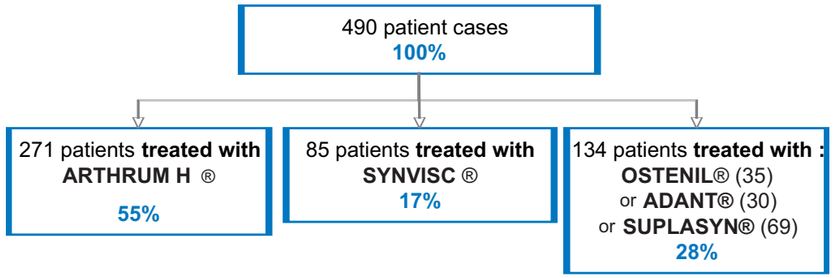
The composition (1% sodium hyaluronate, produced by fermentation biotechnology) and the rheological properties of the 3 products OSTENIL®, ADANT® and SUPLASYN® are similar. They were therefore grouped together as the category "other products" for the statistical analysis.

Number of evaluable patients at each visit

Based on the patients present at the evaluation



Products injected

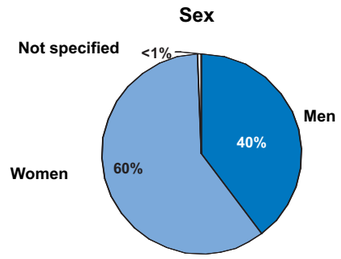


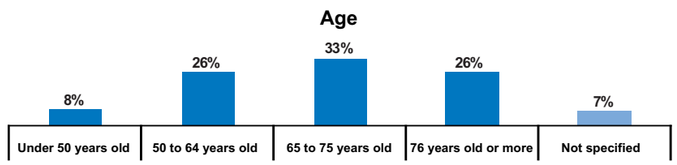
A MULTICENTRE, RANDOMISED, LONG-TERM (6-MONTH) PHASE IV COMPARATIVE CLINICAL STUDY ARTHRUM H 2% ADMINISTERED BY INTRA-ARTICULAR INJECTION INTO THE KNEE IN PATIENTS WITH OSTEOARTHRITIS

RESULTS

Sociodemographic profile of the patients

Mean age of the patients : 67.2 years
SD : (12.6)
Median : 68.8
min / max : 16 years / 95 years





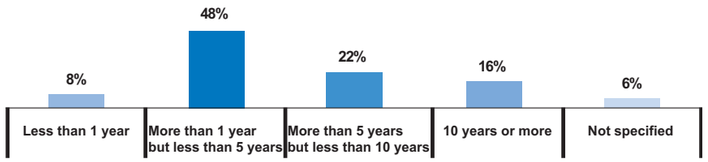
The sex and age profiles of the patients were similar for all the treatment groups, whatever product had been injected.

The patients' rheumatological history

Mean time since the start of the patients' osteoarthritis : 6.2 years
SD : 6.5
Median : *3.6*
min / max : 1 / 43

	ARTHRUM H N= 271 (A) %	SYNVISC N= 85 (B) %	OTHERS N= 134 (C) %
1-Less than 1 year	9	5	8
2-1 to 5 years	47	43	54
3-6 to 10 years	23	24	20
4-More than 10 years	16	22	11
5-Not specified	5	6	7
Mean (ET)	6.2 C(6.4)	7.9 aC(8.3)	4.9 (4.8)

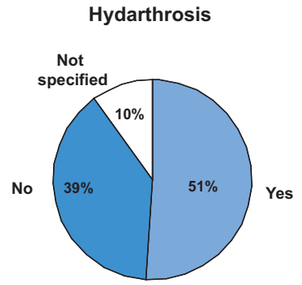
How long since the start of the patients' osteoarthritis



RESULTS

Clinical history

Base total : 490 patients
Hydarthrosis : 51%

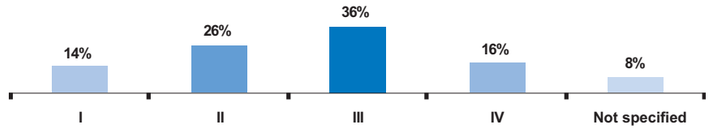


	ARTHRUM H N= 271 (A) %	SYNVISC N= 85 (B) %	OTHERS N= 134 (C) %
1 Yes	53	48	49
2 No	38	38	41
3 Not specified	9	14	10

Radiological history

Base total : 490 patients
Grade III and IV : 52%
Kelgreen index

	ARTHRUM H N= 271 (A) %	SYNVISC N= 85 (B) %	OTHERS N= 134 (C) %
1 Grade I	12 b	5	24 AB
2 Grade II	24	25	31
3 Grade III	42 C	35	27
4 Grade IV	15 c	29 AC	8
5 Not specified	7	6	10



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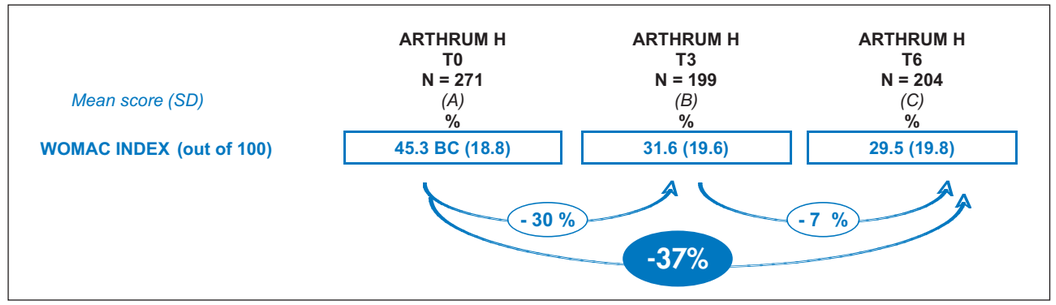
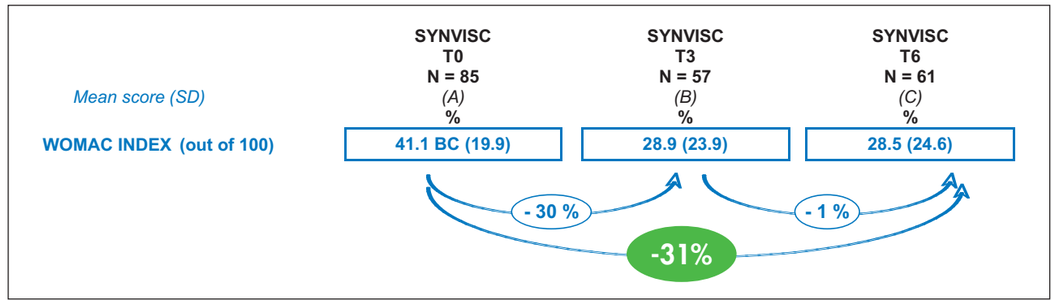
RESULTS

WOMAC INDEX : FUNCTIONAL CAPACITY SUBSCALE

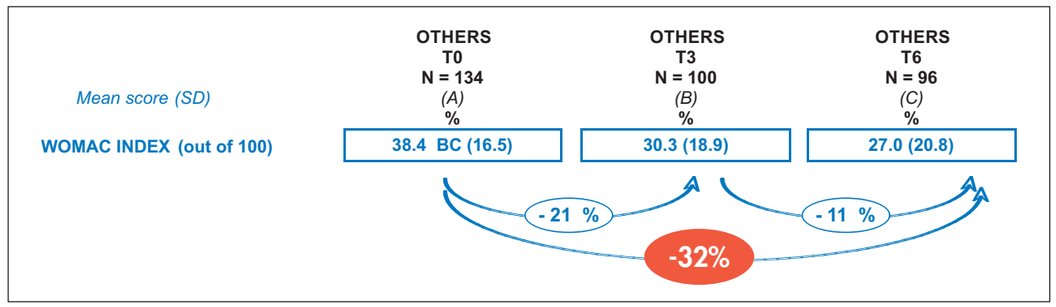
- ARTHRUM H patients



- SYNVISC patients



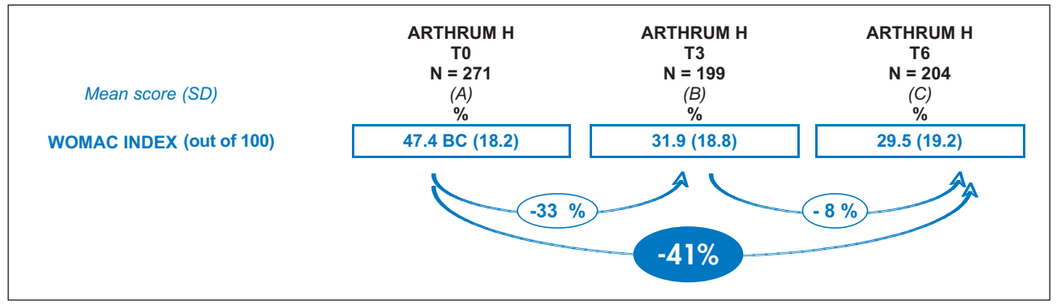
- Patients using other products



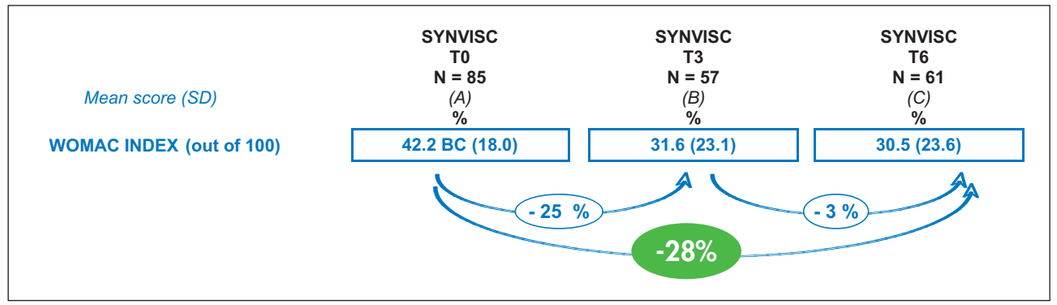
RESULTS

WOMAC INDEX : CHANGE IN THE PAIN SCORE

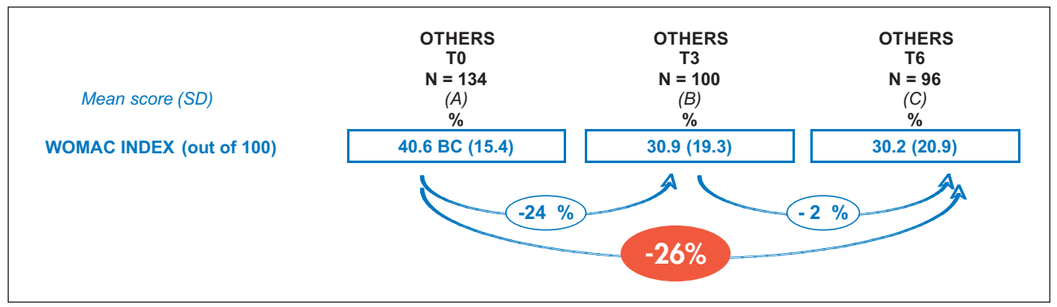
- ARTHRUM H patients

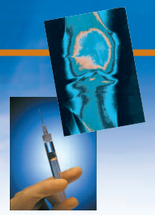


- SYNVISC patients



- Patients using other products



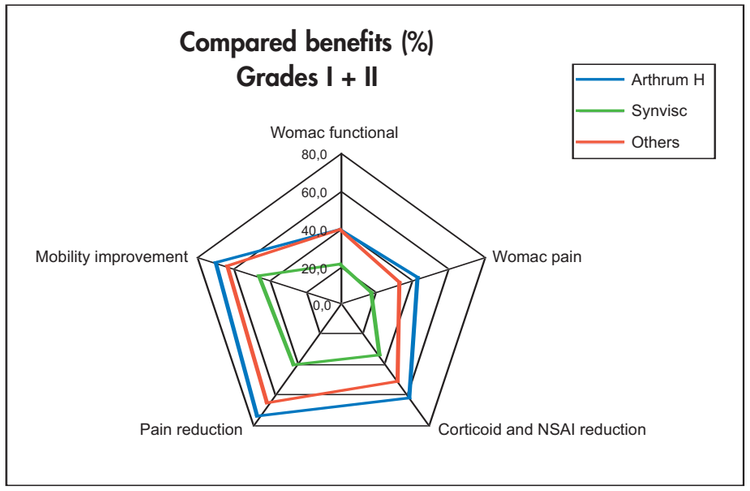


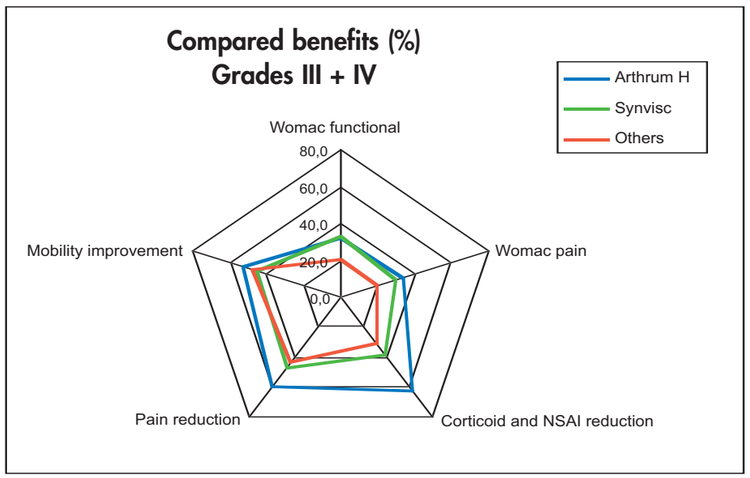
RESULTS

COMPARISON ACCORDING TO RADIOLOGICAL GRADES

A complete clinical comparison has been performed :

- Duration = 6 months
- Comparison with SYNVISC and « Others »
- More complete criteria (WOMAC, ANAES and patients assessment)
- Radiological grades (I ; II ; III and IV)





RESULTS

FUNCTIONAL CAPACITY SUBSCALE

The tables of the change in the WOMAC functional capacity scores show that the ARTHRUM H product was clearly superior : the score improved by 37 points between D0 and D180.

It should be noted that the WOMAC score on D0 in the ARTHRUM H group was higher (45.3) than in the SYNVISC group (41.1), and the score for the other low molecular weight / low concentration products was lower still (38.4).

Between D90 and D180, the WOMAC index for the SYNVISC product only decreased by 1%, whereas with the ARTHRUM H product it decreased by 7%.

These results show that ARTHRUM H is more effective at improving the WOMAC index functional capacity component than the comparators and this was the case throughout the 6 months period.

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RESULTS

CHANGE IN THE PAIN SCORE

The WOMAC pain score for the product ARTHRUM H (over the three periods) improved by 41% between D0 and D180.

For patients who were treated with the low concentration / low molecular weight products, the pain score only improved by 26% and most of this improvement occurred between D0 and D60.

A very important point to bear in mind is that the improvement in the pain score observed with ARTHRUM H between D0 and D90 was excellent (33% improvement) and the score continued to improve between D90 and D180 (improvement of 8%).

These results show that ARTHRUM H provides effective pain relief and its effect is rapid and prolonged, at least over a period of 6 months.

CONCLUSION

Patients treated with ARTHRUM H showed clear improvement in functional capacity (37 % improvement between D0 and D180) and the effect lasted until the end of the follow-up period.

This improvement is even more significant since the WOMAC score at D0 was 45.3 and as the group treated with ARTHRUM H contained more patients with osteoarthritis of radiological grade III or IV.

The WOMAC pain score between D0 and D180 for patients treated with ARTHRUM H improved by 41 %, which was much greater than the SYNVISC group (28%) and the group taking the low concentration / low molecular weight products (26%).

During this long-term phase IV study (180 days), intra-articular injection of ARTHRUM H was an effective treatment for osteoarthritis of the knee. Its effect was rapid and sustained until the end of the study and it was shown to be superior to the other two groups of products.