ARTHRUM 75 VISC
SODIUM HYALURONATE
75mg/3ml
MONO INJECTION

Assessment of the real-life efficacy of one joint injection of Sodium Hyaluronate 75mg/3ml on patients suffering from osteoarthritis of the knee

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TABULATED SUMMARY OF THE ART-ONE 75 CLINICAL STUDY	
Reference	**Assessment of the real-life efficacy of the ARTHRUM VISC 75 healthcare product administered in one joint injection in patients suffering from osteoarthritis of the knee.**
Type of study	Multicentre, open-label, prospective study on the real-life efficacy of ARTHRUM VISC 75 for a period of 6 months, in the symptomatic treatment of osteoarthritis of the knee.
Date and duration of the study	Enrolment dates between April 2014 and January 2015. Overall duration of the study is about 2 years.
Objectives of the study	**Main objective** To demonstrate the efficacy of a single joint injection of ARTHRUM VISC 75 on pain in patients, from the beginning of the 2nd month (to D60) in the symptomatic treatment of osteoarthritis of the knee. **Secondary objectives – considered for the entire duration of the trial (6 months)** • Analyse the progress of the pain and physical function scores (including stiffness scores as well). • Analyse the tolerance under actual conditions of prescription and use. • Evaluate its ability to reduce the consumption of analgesics and NSAIDs. • Analyse the impact on the patient's activity and quality of life.
METHOD	
Inclusion/ non-inclusion criteria	**Inclusion criteria:** • Male or female patient aged 40 or over. • With unilateral osteoarthritis of the knee: - confirmed by radiology in the past 6 months (Kellgren-Lawrence stage I to III). - with minimal pain when walking (2 points on the Likert scale for the WOMAC A1 index) and functional impairment for at least three months. • Able to understand the trial process and give their written consent. • Geographically stable throughout the duration of the study. • Patient affiliated to a social security system or benefiting from a similar scheme. **Exclusion criteria:** • Inflammatory arthritis. • Infection of the studied knee. • Previous treatment with viscosupplementation within the past year. • Injection of corticosteroids into the knee under observation within the past three months. • Known hypersensitivity to hyaluronic acid or substances with a similar effect. • Ongoing anticoagulant therapy. • Insulin-dependent/type I diabetes. • Pregnant or breast-feeding women. • Patient under guardianship or tutorship or under judicial protection. • Patient currently taking part in another clinical research study.
Organisation of the trial	**Multicentre study.** Consultancy practices with specialist doctors (rheumatologists, physical medicine and rehabilitation specialists and orthopaedic surgeons) in France.
Product studied	ARTHRUM VISC 75: A single joint injection of 3 ml containing 75 mg of high molecular weight Sodium Hyaluronate.
Ethical aspects	**Non-interventional study** that does not change the patient's usual treatment protocol, does not need to be registered with the health authorities* and does not require the opinion of a French prevention and precaution committee ("CPP"): • ARTHRUM VISC 75 treatment prescribed and agreed to by the patient before any offer is made to participate freely in the trial, hence prior to the person's enrolment. • Patient rights observed (written consent). • ARTHRUM VISC 75 treatment provided free of charge as part of the trial (as not reimbursed). • Patient's personal data processed anonymously (encrypted data). (*) French public health code § R.1121-2 and § L.5311-1
Primary criterion	**Mean variation of the "Western Ontario & McMaster Universities"**, (WOMAC A) pain index sub-score (composed of 5 items) between D0 (baseline) when ARTHRUM VISC 75 was injected and D60. Each item is rated on the Likert scale (5-level verbal scale where 0 = no pain, 1 = mild pain, 2 = moderate, 3 = severe, 4 = very severe). ITT (intention to treat) and PP (per protocol) analyses.

Secondary efficacy criteria	**Pain and functional capacity: WOMAC index** • Mean variation in the WOMAC A (pain) index between D0 and D30, D120 and the end of the study (D180), according to the Likert scale. • Mean variation of the WOMAC C (physical function) index (composed of 17 items) between D0 and D30, D60, D120 and the end of the study (D180), according to the Likert scale. **Assessment of the quality of life and disability** • Variation between D0 and D30, D60, D120 and the end of the study (D180) in the following criteria assessed using the Likert scale (6 levels). - impact on the ability to walk. - impact on the ability to perform routine tasks. - impact on sleep. • Variation between D0 and D30, D60, D120 and the end of the study (D180) of disability using the Likert scale (5 levels) – while making a distinction between functional and occupational disabilities. - according to the patient. - according to the investigating physician. • Efficacy of the treatment on D30, D60, D120 and at the end of the study (D180) according to the patient and according to the investigating physician, using the Likert scale (5 levels). - pain reduction. - improved mobility. - ability to reduce analgesic consumption. - ability to reduce NSAID consumption. ITT analysis.
Other efficacy criteria	• Assessment of stiffness: WOMAC B index (composed of 2 items) on D0, D30, D60, D120 and at the end of the study (D180), according to the Likert scale (5 levels). • Variation in the score of the WOMAC global (equal to the sum of the 3 sub-scores A, B and C) index between D0 and D30, D60, D120 and the end of the study (D180). • Treatment tolerance and safety (according to investigating physician). • Patient's overall impression of the disease, according to a relative binary scale: "better"; "worse". • Assessment of the tolerance. - local or general clinical tolerance. - frequency, type and severity of adverse events (AEs).
Sample size	Number of subjects necessary (NSN), estimated at 116, based on the following bilateral test formula: $N = 2*(\sigma^2/\Delta^2)*(Z_{1-\alpha/2} + Z_{1-\beta})^2$ where α=0.025, β=0.05 (95% power), Δ=9.7/100 (MPCI[1]) for the WOMAC index variation from 0 to 6 months, σ=19/100 (ET[2]). In order to anticipate for patients lost to follow-up and the inclusion deviations, which are unacceptable in the PP analysis, as well as the reluctance of certain patients due to the product being non-reimbursable, albeit free of charge within the context of the trial, the recruitment objective was finally doubled. (1) **Ehrich EW, Davies GM, Watson DJ, Bolognese JA, Seidenberg BC, Bellamy N**: Minimal Perceptible Clinical Improvement with the Western Ontario and McMaster Universities osteoarthritis index questionnaire and global assessment in patients with osteoarthritis. J Rheumatol.2000 Nov;27(11):2635-41 (2) **Mazières B, Bard H, Ligier M et al.** Medicoeconomic evaluation of hyaluronic acid for knee osteoarthritis in everyday practice: the MESSAGE study. Joint Bone Spine. 2007, 74(5):453-60.
Deviations from the protocol	• Minor deviations (accepted). - injection of the ARTHRUM VISC 75 product from 30 to < 90 days after the enrolment visit. - extended visiting time slots to limit data loss: D30 (15-44), D60 (45-89), D120 (90-149), D180 (150-209). - visits adjusted according to the dates on which they actually occurred: dates after D210 taken into consideration. - radiology only exceeding 6-month limit by a few days. • Missing data. - recorded as such after the investigator's attempts to contact them (telephone, letter).
Statistical analysis method	• Data from the CRFs (paper), entered into the Clinsight 7.0 software by 2 data entry clerks. • Comparison of both entries by the data manager. • Quality control for √(n + 1) records: error rate required < 1%.

RESULTS

Number of subjects analysed

- Population enrolled from 48 centres (45 private centres and 3 hospitals).
  - 38 rheumatologists, 6 physical medicine and rehabilitation specialists and 4 orthopaedic surgeons.

Population	N	Visits conducted (adjusted)	Patients excluded for the following stage
Enrolled	218		Not treated: 2 (removed by the investigator)
Safety population	216	D0: 216	Not seen again: 2
ITT	214	D30: 210 D60: 200 D120: 185 D180: 183 D240: 23* (*) after exclusion of 2 patients seen again at D330 and D427	Major deviations/inclusion: 32 • Age < 40: 1 • Radiology > 6 months: 10 • Key data missing: 19 • Bilateral knee osteoarthritis: 1 • Inclusion time/D0 > 90 days: 1 Not seen again on D180: 31 Lost-to-follow-up: 8
PP	165	Patients seen right up to the end of the study	

Duration of follow-up

6 months (and up to 8 months for 23 patients).

Patient characteristics

Baseline patient characteristics	N = 218	Percentages
Age, in years Average (SD) Mini–Maxi	 62.9 (12.6) 24–88	
Gender, n (%) Men Women	 95 123	 43.6 % 56.4 %
Radiological stage, n (%) Stage I Stage II Stage III	 33 85 99	 15.2 % 39.2 % 45.6 %
Weight, in kg (SD)	76.5 (14.7)	
Height, in m (SD)	1.675 (0.092)	
Body Mass Index (BMI), in Kg/m²	27.20 (4.32)	
Knee osteoarthritis period, in months (SD) Less than or equal to 1 year (N = 83) More than 1 year (N =130)	 6.75 (3.45) 77.1 (70.2)	 39.0 % 61.0 %

Results inherent to the primary criterion

Primary criterion	Baseline	D60	Difference* (SD)	[95% CI]*	Effect size* [95% CI]	p-value
ITT analysis	n=213	n=199	n=199	Base=20		
WOMAC A (SD) ***Standard error x 2***	**10.05 (3.12)**	**4.28 (3.49)**	**5.68 (3.52)** ***0.50***	**[5.18; 6.18]**	**1.61 [1.47; 1.75]**	**< 0.0001**
PP analysis	n=165	n=165	n=165	Base=20		
WOMAC A (SD) ***Standard error x 2***	**9.88 (2.93)**	**4.33 (3.42)**	**5.55 (3.51)** ***0.55***	**[5.01; 6.10]**	**1.58 [1.43; 1.74]**	**< 0.0001**

The observed effect size (ES) is significant, which is normal compared to baseline: Mean reference values, comparing to the baseline, are provided by Miller[3], i.e 1.37 [1.12; 1.61] for pain (p < 0.01) after 4-13 weeks and the results for ARTHRUM VISC 75 are noticeably better.

(*) Positive values with a favourable progression from D0 – calculated in relation to the baseline.

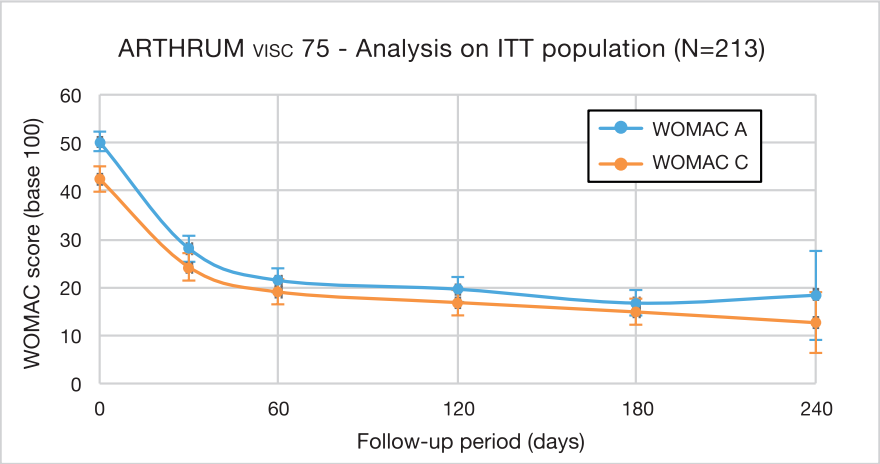
(3) **Miller LE, Block JE**: US-Approved Intra-Articular Hyaluronic Acid injections are Safe and Effective in Patients with Knee Osteoarthritis: Systematic Review and Meta-Analysis of Randomized, Saline-Controlled Trials – Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders 2013;6:57-63.

Results inherent to the secondary and other efficacy criteria

ITT population analysis

Secondary & other criteria	Date	Score variation (SD)*	N	[95% CI]*	Effect size* [95% CI]	p-value
WOMAC A (pain) *(base 20)*	D30	4.44 (3.65)	207	[3.94; 4.95]	1.22 [1.08; 1.36]	**< 0.0001**
	D120	5.99 (3.68)	180	[5.44; 6.54]	1.63 [1.48; 1.78]	**< 0.0001**
	D180	6.62 (3.76)	183	[6.06; 7.17]	1.76 [1.61; 1.91]	**< 0.0001**
	D240	7.05 (4.63)	21	[5.03; 9.07]	1.52 [1.09; 1.96]	**< 0.0001**
WOMAC B (stiffness) *(base 8)*	D30	1.70 (1.67)	208	[1.47; 1.93]	1.02 [0.88; 1.16]	**< 0.0001**
	D60	2.15 (1.70)	200	[1.91; 2.39]	1.27 [1.12; 1.41]	**< 0.0001**
	D120	2.41 (1.94)	181	[2.13; 2.70]	1.24 [1.10; 1.39]	**< 0.0001**
	D180	2.55 (1.97)	182	[2.26; 2.84]	1.29 [1.15; 1.44]	**< 0.0001**
	D240	2.71 (2.05)	21	[1.82; 3.61]	1.32 [0.89; 1.76]	**< 0.0001**
WOMAC C (physical function) *(base 68)*	D30	12.42 (10.27)	185	[10.91; 13.93]	1.21 [1.06; 1.36]	**< 0.0001**
	D60	15.44 (10.88)	181	[13.83; 17.06]	1.42 [1.27; 1.57]	**< 0.0001**
	D120	16.96 (10.93)	160	[15.23; 18.69]	1.55 [1.39; 1.71]	**< 0.0001**
	D180	18.07 (11.88)	165	[16.22; 19.92]	1.52 [1.37; 1.68]	**< 0.0001**
	D240	21.00 (13.50)	17	[14.45; 27.55]	1.55 [1.07; 2.04]	**< 0.0001**
Global WOMAC *(base 96)*	D30	18.76 (14.59)	185	[16.61; 20.90]	1.29 [1.14; 1.43]	**< 0.0001**
	D60	23.31 (14.96)	180	[21.08; 25.54]	1.56 [1.41; 1.71]	**< 0.0001**
	D120	25.34 (15.27)	160	[22.93; 27.76]	1.66 [1.50; 1.82]	**< 0.0001**
	D180	27.24 (16.24)	164	[24.71; 29.78]	1.68 [1.52; 1.83]	**< 0.0001**
	D240	31.82 (18.83)	17	[22.69; 40.96]	1.69 [1.20; 2.17]	**< 0.0001**

(*) Positive values with a favourable progression from D0 – calculated in relation to the baseline.



Patients *(N)* Patients % answers**	Minimal pain or disability-						Significant disability+ or severe pain+					
	D0	D30	D60	D120	D180	D240	D0	D30	D60	D120	D180	D240
quality of life	*(214)*	*(208)*	*(198)*	*(181)*	*(184)*	*(20)*	*(214)*	*(208)*	*(198)*	*(181)*	*(184)*	*(20)*
• ability to walk	14.0	53.4	71.7	77.9	83.2	75.0	38.3	12.5	7.1	6.1	5.4	0.0
• ability to work	16.9	58.4	72.1	66.8	79.4	80.0	39.4	14.5	7.6	5.0	3.3	5.0
• sleep	64.5	85.1	91.9	92.8	92.9	80.0	13.6	3.4	2.0	1.7	2.2	5.0
Functional disability	*(214)*	*(208)*	*(200)*	*(181)*	*(184)*	*(21)*	*(214)*	*(208)*	*(200)*	*(181)*	*(184)*	*(21)*
• patient	9.3	50.5	65.0	68.0	58.2	85.7	40.2	14.4	9.0	7.2	7.1	0.0
• doctor	9.3	58.1	72.0	74.6	58.2	85.7	27.6	7.7	5.0	6.6	5.4	0.0
Occupational disability	*(145)*	*(138)*	*(130)*	*(118)*	*(119)*	*(14)*	*(145)*	*(138)*	*(130)*	*(118)*	*(119)*	*(14)*
• patient	32.4	64.5	76.2	80.5	85.7	78.6	36.6	13.8	9.2	7.6	3.4	7.1
• doctor	33.1	70.3	80.0	82.2	89.1	92.9	31.0	8.7	6.9	5.9	3.4	7.1

(**) Patients taken into consideration are those who provided answers (base = numbers in brackets):
- The percentages on the left of the table are for the least disabled patients.
- The percentages on the right of the table are for the most disabled patients.
- The remainder (making up 100%) is the proportion of patients with an intermediate disability.
- The study demonstrates a favourable outcome: the percentages increase on the left and decrease on the right.
- Theoretically, there is a reduction in the population affected by an occupational disability: pensioners, etc.

Results inherent to the secondary and other efficacy criteria

Treatment efficacy Patients % answers***	Satisfied and very satisfied					Insufficient results				
	D30	D60	D120	D180	D240	D30	D60	D120	D180	D240
pain reduction	*(208)*	*(199)*	*(182)*	*(183)*	*(21)*	*(208)*	*(199)*	*(182)*	*(183)*	*(21)*
• patient	61.1	68.8	72.0	75.4	76.2	16.3	10.6	9.3	7.1	9.5
• doctor	63.2	72.4	74.2	80.3	81.0	14.8	9.0	8.2	6.6	9.5
Improved mobility	*(208)*	*(198)*	*(181)*	*(182)*	*(21)*	*(208)*	*(198)*	*(181)*	*(182)*	*(21)*
• patient	61.1	66.7	72.9	76.4	81.0	14.9	10.6	7.2	7.1	4.8
• doctor	64.4	68.7	73.5	80.8	85.7	13.5	8.1	6.1	5.5	4.8
Decrease in analgesics	*(191)*	*(182)*	*(170)*	*(167)*	*(19)*	*(191)*	*(182)*	*(170)*	*(167)*	*(19)*
• patient	66.0	69.8	74.7	76.6	73.7	17.8	13.2	10.6	9.0	10.5
• doctor	67.5	72.0	75.9	79.6	84.2	17.3	11.0	8.2	10.2	10.5
Decrease in NSAIDs	*(177)*	*(166)*	*(157)*	*(155)*	*(16)*	*(177)*	*(166)*	*(157)*	*(155)*	*(16)*
• patient	66.7	71.7	76.4	78.1	81.3	16.9	12.7	8.3	7.7	6.3
• doctor	70.1	75.9	77.7	80.6	87.5	16.4	7.8	8.9	7.7	6.3

(***) The table is designed in the same way as the previous one, with the 1st observation on D30:
- The percentages on the left of the table are patients who are satisfied and very satisfied.
- The percentages on the right of the table are dissatisfied patients.
- The remainder (making up 100%) is the proportion of patients who are moderately satisfied.
- The study demonstrates a favourable outcome: the percentages increase on the left and decrease on the right.
- According to these figures, approximately 91% and 84% of the patients initially used analgesics and NSAIDs respectively: this was followed by a sharp decrease in use.
- If we estimate that 50% of the satisfied patients stopped using them, the population continuing to take them is 57% for analgesics and 52% for NSAIDs.

Discussion on clinical results

The effect sizes for pain and physical function are compared to those of Miller[3] vs baseline:

1.14 [0.89; 1.39] pain after 14-26 weeks ($p < 0.001$)
1.16 [0.99; 1.34] function after 4-13 weeks ($p < 0.001$)
1.07 [0.84; 1.39] function after 14-26 weeks ($p < 0.001$)

The results of ARTHRUM VISC 75 for pain and physical function are noticeably better than those of Miller, which uses the same method found in the primary criterion.
In the long term there is a progressive improvement in results with ARTHRUM VISC 75:

- The results show that ARTHRUM VISC 75 significantly improves the patient's disability (activity) and quality of life.
- A decrease in concomitant medications is observed.
- The results are similar to those of ARTHRUM H 2% (3 injections), illustrating the benefits of ARTHRUM VISC 75 in the symptomatic treatment of knee osteoarthritis by a single injection.

Safety population

The population studied is made up of the 216 patients treated with ARTHRUM VISC 75
27 cases of adverse events (AE) were reported for 26 patients:

- 18 local and transient AE cases (8.3%) disappeared spontaneously within 3 days:
  pain in the injection site, pain when walking, stiffness and moderate swelling of the knee.
  These 18 cases of transient AEs were due to the way the product was injected.
  These AEs are known, expected, non-serious and not related to the product injected.
- 6 cases of pain or discomfort in the knee, attributable to the osteoarthritis and its progression:
  - 5 cases persisting between 1 - 2 weeks after the injection.
  - 1 case occurring during the study.
- 2 cases of benign AEs reported by patients, which disappeared spontaneously, without being medically confirmed, with no confirmed causal relationship with ARTHRUM VISC 75:
  - 1 case of redness in the face for 12 hours after the injection.
  - 1 case of diffuse moderate intermittent pruritus for 50 days after the injection.
- 1 case of chondrocalcinosis – confirmed to be unrelated to ARTHRUM VISC 75: this case of chondrocalcinosis was removed from the study once the doctor made the diagnosis.

Safety population

To summarise, according to the doctors, none of the AEs described had a causal relationship with ARTHRUM VISC 75.

Note: Excluding the case of chondrocalcinosis, no patients were seen again by the doctor before D30. Therefore, the observations are only based on patients' statements. Of the 25 remaining patients, 2 were lost-to-follow-up and 19 said they were satisfied with ARTHRUM VISC 75, which puts the impact of the AEs into perspective.

No cases of pseudoseptic arthritis were observed.
No serious adverse events (SAE) were reported during the study.

ADDITIONAL RESULTS (post-study results)

OMERACT-OARSI responders

Method

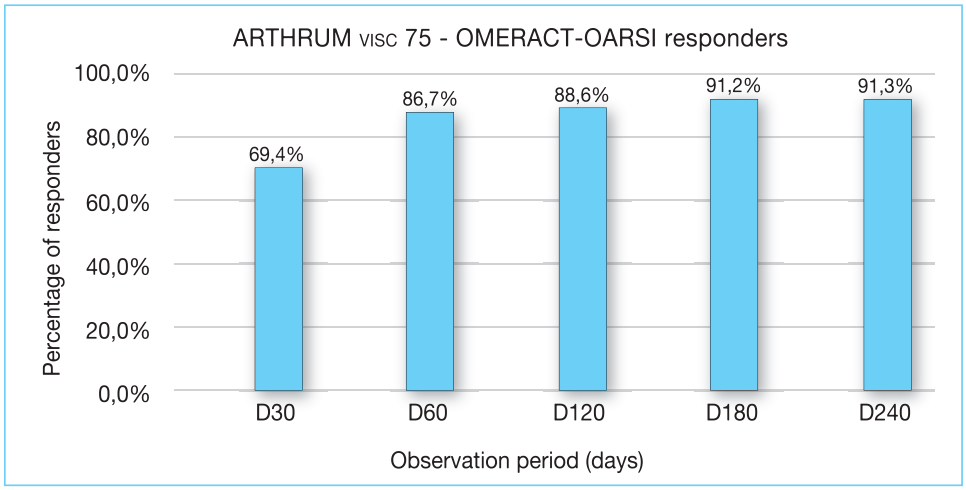
- The percentages of OMERACT-OARSI[4] responder patients were calculated in an additional analysis, that was part of an addendum.
- The available data that was studied was the WOMAC A for pain, the WOMAC C for physical function and the disability assessment made by the patient as the 3rd criteria.
- These 3 criteria were based on a scale from 0 to 100 for each duration since the inclusion.

(4) **Pham T, Van der Heidje D, Altman RD, Anderson JJ, Bellamy N, Hochberg M**, et al. OMERACT-OARSI Initiative: Osteoarthritis Research Society International set of responder criteria for clinical trials revisited – Osteoarthritis Cartilage 2004;12:389-99.

- Each percentage corresponds to the following definition: **no.**of responders **/ no.**of responders + non-responders.
  - When the 3 criteria were not available at the same time, those responders were treated the same as non-responders.
  - Uncertain cases were considered missing data and excluded from the calculation.

Results

- The results for the OMERACT-OARSI responders are provided in the following chart:



The base population analysed is the ITT population observed for each duration (§ patient number table):
- Given that a conclusion cannot be made due to the missing data cases, the latter were all excluded.
- The progression shows a gradual increase in the percentage of responders.
- The results after D240, based on only 23 patients are provided as an indication but are in line with the trend.

OMERACT-OARSI responders

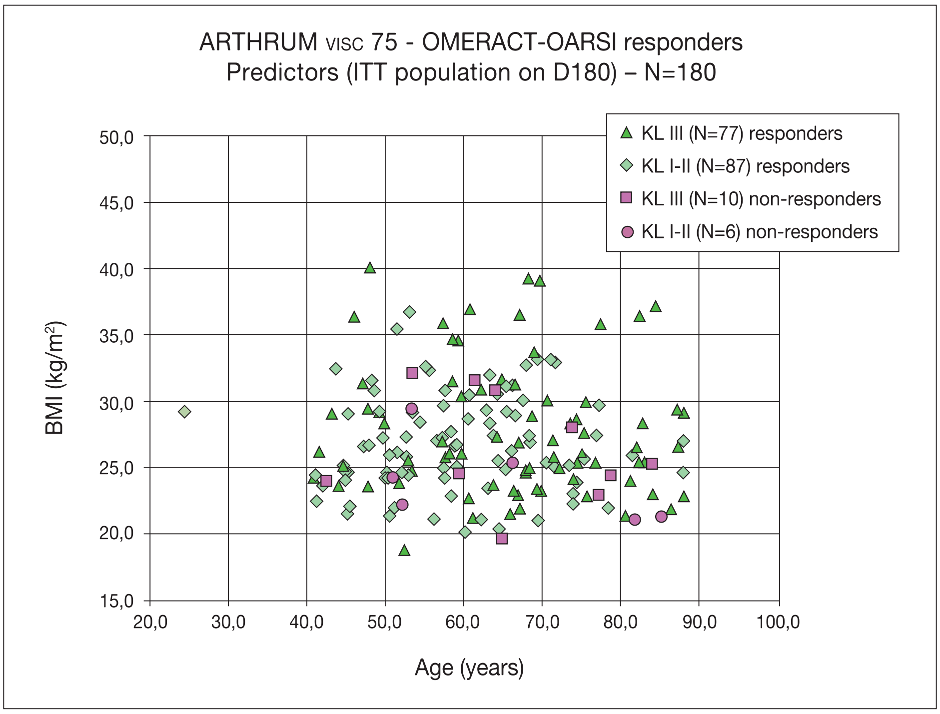
Predictors

- The table below shows the results for OMERACT-OARSI responders, broken down according to the predictors of progression of osteoarthritis: BMI (kg/m (kg/m^2) and radiological stage (KL):

Responders % (N)	D30	D60	D120	D180	D240
BMI < 30	66.9% (148)	85.8% (151)	87.4% (135)	90.6% (138)	88.9% (18)
BMI ≥ 30 (obesity)	66.0% (47)	84.4% (45)	84.1% (44)	86.7% (45)	*100.0% (5) NS*
KL I-II	71.4% (105)	84.6% (104)	91.8% (97)	93.5% (92)	86.7% (15)
KL III (advanced)	66.7% (87)	88.9% (90)	84.4% (77)	88.5% (87)	*100.0% (8) NS*
BMI ≥ 30 + KL III	69.6% (23)	87.5% (24)	90.5% (21)	87.5% (24)	*100.0% (3) NS*

These results conclude that the predictors have no significant impact.

- The following scatter plot chart confirms this interpretation.



According to the chart, the responder and non-responder patients are evenly distributed: All the patients can therefore benefit from the ARTHRUM VISC 75 treatment, regardless of their predictors of progression for osteoarthritis of the knee: Body mass index and radiological stage (KL).

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