

## EXTENDED REPORT

# First-line analysis of the effects of treatment on progression of structural changes in knee osteoarthritis over 24 months: data from the osteoarthritis initiative progression cohort

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## ABSTRACT

**Objective** To determine, using data from participants enrolled in the progression cohort of the OAI, the effects of conventional osteoarthritis (OA) pharmacological treatment and those of the combination of glucosamine and chondroitin sulfate (Glu/CS) on knee structural changes.

**Methods** Six hundred patients with knee OA were stratified based on whether or not they received for 24 consecutive months the OA conventional pharmacological treatment and/or Glu/CS. The main outcomes were knee structural changes, including the loss of joint space width (JSW) and of cartilage volume measured by quantitative MRI.

**Results** Participants reported taking (+) (n=300) or not taking (-) (n=300) OA treatment (analgesic/NSAIDs). The +analgesic/NSAIDs participants had higher Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores (p<0.001) and smaller JSW (p=0.01), reflecting more severe disease at baseline. In the -analgesic/NSAIDs group, participants taking Glu/CS had significantly reduced loss of cartilage volume at 24 months in the medial central plateau (p=0.007). Further subdivision revealed that this effect of Glu/CS occurred in participants with a higher severity of the disease (JSW≤median). In the +analgesic/NSAIDs group, those taking Glu/CS had significantly reduced loss of cartilage volume in the global plateau at 12 months (p=0.05), and in the central plateau at 24 months (p=0.05). These effects occurred in participants with less disease severity (JSW>median). By contrast, no significant reduction in JSW was found between all groups.

**Conclusions** In +analgesic/NSAIDs groups and -analgesic/NSAIDs groups, participants who took Glu/CS had reduced loss of cartilage volume over 24 months in subregions when assessed with qMRI, arguing for a disease-modifying effect of Glu/CS which could not be identified by X-rays.

## INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis, and the knee the most common joint affected by symptomatic radiographic OA (sROA).<sup>1</sup> Although several clinical trials have examined the structure-modifying effects of drugs and biological agents,<sup>2-3</sup> the effects of treatment with conventional pharmacological agents and/or a combination

of glucosamine and chondroitin sulfate (Glu/CS) on knee OA progression are still under debate. Glu/CS are the most commonly used slow acting drugs for OA, and some studies have reported structure-modifying effects in knee OA.<sup>4-9</sup>

The National Institutes of Health Osteoarthritis Initiative (OAI) is a longitudinal observational cohort study designed to identify biomarkers for the development and progression of sROA. The extensive imaging data collected as part of the OAI allowed for a comprehensive cross-sectional and longitudinal evaluation of knee structural changes.<sup>10</sup> A number of publications, particularly those reporting analyses of the OAI 'progression' subcohort, have provided very useful information on the structural changes that occur over time in established sROA, as well as important clues about the risk factors associated with those changes.<sup>11-14</sup> A recent study has also reported a potential beneficial effect of bisphosphonates on disease symptoms and radiographic progression.<sup>15</sup>

The aim of this present study was to examine, for the first time, the effects of commonly used pharmacological treatments on the structural knee changes in participants from the OAI progression subcohort with sROA who had complete data available over a period of 24 consecutive months, assessing cartilage volumes with a fully automated MRI technology.<sup>16</sup>

## PATIENTS AND METHODS

### Study population

We used the original OAI progression cohort (V00COHORT=1; n=1390) from the OAI database (<http://www.oai.ucsf.edu/>). The participants, who were recruited by four clinical centres, had sROA in at least one knee at the time of enrolment between February 2004 and July 2006. To be included in the present study, participants had to have undergone 24 consecutive months of follow-up with complete radiographic and MRI data for the most symptomatic knee, based on the highest WOMAC pain score at the onset of the study (Time [T] 0). Of the eligible participants, 600 were included in the analysis (figure 1).

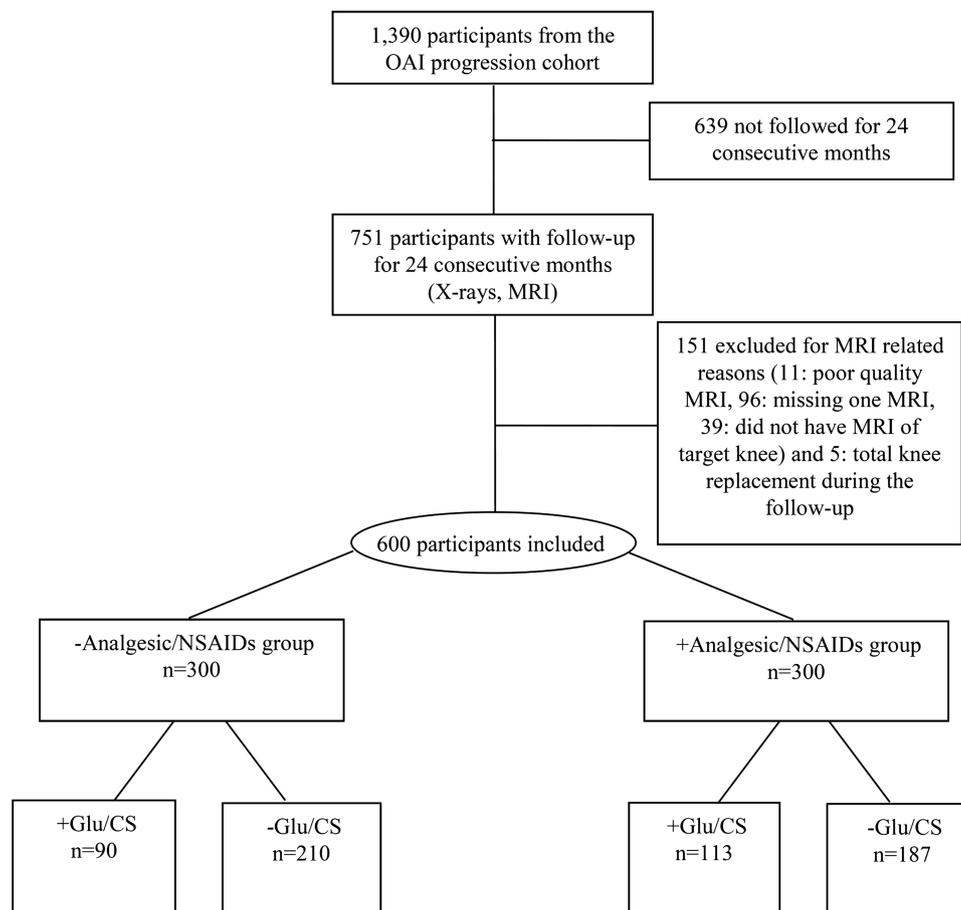
### Study design

The participants were stratified into two main groups based on whether or not standard OA



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**Figure 1** Study design. CS, chondroitin sulfate; Glu, glucosamine sulfate; –analgesic/NSAIDs group, did not take analgesics or NSAIDs; +analgesic/NSAIDs, took analgesics or NSAIDs; +Glu/CS, took glucosamine and chondroitin sulfate; –Glu/CS, did not take glucosamine and chondroitin sulfate; MRI, magnetic resonance imaging; n, number of participants; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis, OAI, Osteoarthritis Initiative.

pharmacological treatment (including analgesics and NSAIDs) was taken for disease symptoms over a continuous period of 24 months (+analgesic/NSAIDs and –analgesic/NSAIDs groups, table 1); this stratification was based on regrouping patients with similar clinical characteristics at baseline. These two groups were further stratified into subgroups based on whether or not participants reported taking a combination of Glu and CS (figure 1). Definition of OA pharmacological treatment and questions from the OAI workbook related to medications the participants took are reported in the online supplementary Material, Methods.

The –analgesic/NSAIDs group comprised 300 participants. This group was divided into two subgroups based on whether they reported taking Glu and CS (+Glu/CS group, n=90) or not (–Glu/CS group, n=210) during 24 consecutive months. The +analgesic/NSAIDs group comprised 300 participants who reported taking an OA pharmacological treatment combined with Glu and CS (+Glu/CS group, n=113) or not (–Glu/CS group, n=187) during this period.

### Clinical and X-ray outcomes

Clinical and X-ray outcomes are detailed in online supplementary Material, Methods.

### Knee MRI acquisition

All knee MRI acquisitions were performed at T0, T12 and T24 as described per the OAI protocol<sup>17</sup> using 3.0 T apparatus

(Magnetom Trio, Siemens, Erlangen, Germany) at the four OAI clinical centres. MR images were acquired using a DESS imaging protocol with sagittal slices.

### MRI cartilage and meniscal assessments

Cartilage volume was measured using the automatic human knee cartilage segmentation (ArthroLab, Montreal, Quebec, Canada) as previously described and validated.<sup>16</sup> The meniscal evaluation (presence or absence of extrusion) was performed at T0 as previously described.<sup>18</sup>

### Definition of outcomes

The main outcomes were knee structural changes, including the decline in joint space width (JSW) and cartilage volume measured by quantitative MRI.

### Statistical analyses

All the data (clinical, radiological, MRI) were systematically entered into a computerised database after which descriptive statistics for participant characteristics were tabulated. T0 characteristics are presented as mean±SD or percentage (%) where appropriate. We compared the demographic, clinical and imaging characteristics of +analgesic/NSAIDs and –analgesic/NSAIDs groups at T0, and then of each subgroup (+Glu/CS and –Glu/CS), using the Pearson's  $\chi^2$  test for categorical data and the Mann–Whitney test for continuous variables. Comparison of structural changes (JSW and cartilage volume)

**Table 1** Time 0 demographic, clinical, and imaging characteristics of participants\*

	−Analgesic/NSAIDs (n=300)	+Analgesic/NSAIDs (n=300)	p Value†
Demographic and clinical			
Age (years)	61 (9)	62 (9)	0.32
Male, n (%)	164 (55)	119 (40)	<0.001‡
BMI (kg/m <sup>2</sup> )	29 (4)§	31 (5)¶	<0.001
Consumption of bone anti-remodelling medication, n (%)**	24 (8)	50 (17)	0.001‡
WOMAC			
Pain (0–20)	3.4 (3.1)	6.0 (4.4)	<0.001
Function (0–68)	11.0 (10.2)††	19.3 (13.0)§	<0.001
Stiffness (0–8)	2.0 (1.6)	3.1 (1.7)	<0.001
Total (0–96)	16.4 (14.0)††	28.4 (18.1)§	<0.001
KOOS			
Pain (0–100)	77.1 (16.4)	64.3 (20.8)§	<0.001
Quality of life (0–100)	61.7 (18.2)	47.3 (19.2)	<0.001
Symptoms (0–100)	80.1 (15.9)	68.0 (18.9)	<0.001
Imaging			
Kellgren-Lawrence, n (%)	(n=298)	(n=299)	0.006‡
Grade 0,1	57 (19)	33 (11)	
Grade 2	108 (36)	96 (32)	
Grade 3	94 (32)	111 (37)	
Grade 4	39 (13)	59 (20)	
JSW (mm)	3.80 (1.70)††	3.43 (1.89)‡‡	0.01
Meniscal extrusion, n (%)	145 (48)	168 (56)	0.06‡
MRI (mm <sup>3</sup> )			
Global knee			
Condyle	10 451 (2775)	10 219 (2874)	0.25
Plateau	6758 (1771)	6640 (1882)	0.27
Central plateau	3693 (1180)	3580 (1176)	0.17
Peripheral plateau	1715 (552)	1644 (544)	0.08
Medial compartment	1978 (643)	1935 (654)	0.31
Condyle	5020 (1553)	4728 (1682)	0.01
Plateau	3376 (1035)	3201 (1115)	0.02
Central plateau	1644 (635)	1528 (672)	0.01
Peripheral plateau	743 (279)	680 (287)	0.005
Lateral compartment	901 (368)	847 (401)	0.02
Lateral compartment			
Condyle	5431 (1579)	5491 (1615)	0.97
Plateau	3382 (986)	3439 (1037)	0.69
Central plateau	2049 (737)	2052 (727)	0.68
Peripheral plateau	972 (362)	964 (353)	0.58
Peripheral plateau	1077 (389)	1088 (390)	0.86

\*Results are shown as mean (±SD), unless otherwise mentioned.

†p Values were assessed using the Mann–Whitney test.

‡Pearson's  $\chi^2$  test.

§n=299.

¶n=298.

\*\*The bone anti-remodelling medication included bisphosphonates, teriparatide and parathyroid hormone, raloxifene, combination of oestrogen and testosterone, testosterone, GnRH antagonist injections and calcitonin.

††n=297.

‡‡n=296.

BMI, Body Mass Index; JSW, joint space width; KOOS, Knee injury and Osteoarthritis Outcome Score (0=worst, 100=best score); n, number of participants; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index (0=best, 96=worst score).

was performed using the Mann–Whitney test. The change in cartilage volume between the above groups was also analysed using multivariate regression models adjusting for potential confounding factors at the onset of the study. Other multivariate regressions were performed to assess whether the variables ‘bone anti-remodelling medications’ or ‘clinical centres’ had an impact on the effects of Glu/CS on cartilage volume loss at T24. All tests were two-sided, and a p value  $\leq 0.05$  was considered statistically significant. All statistical analyses were performed using SAS software, V.9.2 (SAS Institute, Cary, North Carolina, USA).

## RESULTS

### Baseline characteristics

The demographic and clinical characteristics of the + and −analgesic/NSAIDs groups (table 1) were different at T0, except for age. Compared with the +analgesic/NSAIDs group, participants who did not take analgesic/NSAIDs were predominantly male and had lower body mass index (BMI) and WOMAC scores, and higher KOOS scores. The imaging characteristics showed that the −analgesic/NSAIDs participants had lower KL grades and greater JSW and cartilage volume in the medial compartment compared to those in the +analgesic/NSAIDs group,

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suggesting that the latter group had more severe disease symptoms and joint structural damage at T0.

When each group was further stratified into two subgroups based on whether or not they reported taking Glu/CS, differences emerged within the +analgesic/NSAIDs group (+Glu/CS vs -Glu/CS) but not in the -analgesic/NSAIDs group (table 2). Participants taking analgesic/NSAIDs and Glu/CS had significantly lower BMI, lower WOMAC total and subscale scores for pain and function, and higher KOOS scores, compared to those

taking analgesic/NSAIDs without Glu/CS, consistent with milder symptoms at T0 among those taking Glu/CS (table 2). Of note, participants taking analgesic/NSAIDs and Glu/CS consumed more bone anti-remodelling medication than those taking analgesic/NSAIDs only; however, a multivariate regression demonstrated that they did not interfere with the effect of Glu/CS on cartilage volume loss at T24 (data not shown). There were no differences between the subgroups, +Glu/CS or -Glu/CS, in regard to the distribution of KL grades, JSW, the presence of

**Table 2** Time 0 demographic, clinical, and imaging characteristics of participants in treatment groups\*

	-Analgesic/NSAIDs			+Analgesic/NSAIDs		
	+Glu/CS (n=90)	-Glu/CS (n=210)	p Value†	+Glu/CS (n=113)	-Glu/CS (n=187)	p Value†
<b>Demographic and clinical</b>						
Age (years)	62 (9)	61 (10)	0.38	63 (8)	61 (9)	0.14
Male, n (%)	45 (50)	119 (57)	0.29‡	48 (42)	71 (38)	0.44‡
BMI (kg/m <sup>2</sup> )	28 (4)	29 (4)§	0.13	30 (5)¶	32 (5)	<b>0.03</b>
Consumption of bone anti-remodelling medication, n (%)**	8 (9)	16 (8)	0.71‡	27 (24)	23 (12)	<b>0.009‡</b>
<b>WOMAC</b>						
Pain (0–20)	3.2 (2.9)	3.5 (3.1)	0.44	4.7 (3.5)	6.8 (4.6)	< <b>0.001</b>
Function (0–68)	10.2 (10.1)	11.3 (10.3)††	0.29	16.1 (10.4)	21.3 (14.0)‡‡	<b>0.003</b>
Stiffness (0–8)	2.0 (1.6)	2.0 (1.6)	0.84	2.8 (1.5)	3.2 (1.9)	0.06
Total (0–96)	15.4 (13.9)	16.9 (14.0)††	0.33	23.7 (14.2)	31.3 (19.6)‡‡	<b>0.001</b>
<b>KOOS</b>						
Pain (0–100)	79.0 (16.5)	76.3 (16.4)	0.15	69.6 (17.0)	61.1 (22.2)‡‡	<b>0.001</b>
Quality of life (0–100)	62.9 (17.0)	61.1 (18.6)	0.53	51.1 (18.3)	45.1 (19.5)	<b>0.008</b>
Symptoms (0–100)	80.3 (15.7)	80.1 (16.0)	0.96	70.9 (17.0)	66.2 (19.7)	<b>0.04</b>
<b>Imaging</b>						
Kellgren-Lawrence, n (%)		(n=208)	0.46‡	(n=112)		0.18‡
Grade 0,1	17 (19)	40 (19)		11 (10)	22 (12)	
Grade 2	30 (33)	78 (38)		36 (32)	60 (32)	
Grade 3	27 (30)	67 (32)		36 (32)	75 (40)	
Grade 4	16 (18)	23 (11)		29 (26)	16 (30)	
JSW (mm)	3.75 (1.86)§§	3.82 (1.64)§	0.74	3.37 (2.02)¶¶	3.47 (1.82)¶¶¶	0.61
Meniscal extrusion, n (%)	47 (52)	98 (47)	0.38‡	58 (51)	110 (59)	0.21‡
MRI (mm <sup>3</sup> )						
<b>Global knee</b>	10 522 (2614)	10 420 (2846)	0.87	10 595 (2951)	9992 (2811)	0.11
Condyle	6835 (1643)	6725 (1826)	0.66	6921 (1877)	6470 (1870)	0.06
Plateau	3688 (1131)	3695 (1203)	0.99	3675 (1252)	3523 (1128)	0.41
Central plateau	1707 (520)	1719 (567)	0.95	1687 (575)	1619 (524)	0.41
Peripheral plateau	1981 (627)	1976 (651)	0.95	1988 (698)	1904 (626)	0.46
<b>Medial compartment</b>	5048 (1535)	5008 (1564)	0.98	4941 (1752)	4600 (1629)	0.16
Condyle	3381 (1004)	3374 (1050)	0.92	3338 (1130)	3118 (1101)	0.14
Plateau	1667 (640)	1634 (634)	0.72	1603 (715)	1482 (643)	0.37
Central plateau	756 (283)	737 (278)	0.67	708 (297)	663 (280)	0.31
Peripheral plateau	911 (369)	896 (369)	0.78	895 (431)	818 (380)	0.35
<b>Lateral compartment</b>	5475 (1618)	5412 (1566)	0.72	5655 (1718)	5392 (1546)	0.19
Condyle	3453 (1016)	3351 (973)	0.46	3583 (1068)	3351 (1010)	0.09
Plateau	2021 (737)	2061 (739)	>0.99	2072 (800)	2041 (682)	0.68
Central plateau	951 (355)	981 (366)	0.70	978 (389)	955 (330)	0.53
Peripheral plateau	1071 (396)	1080 (387)	0.80	1093 (426)	1085 (367)	0.92

\*Results are shown as mean (±SD), unless otherwise mentioned.

†p Values were assessed using the Mann-Whitney test.

‡Pearson's  $\chi^2$  test.

§n=209.

¶n=111.

\*\*The bone anti-remodelling medication includes bisphosphonates, teriparatide and parathyroid hormone, raloxifene, combination of oestrogen and testosterone, testosterone, GnRH antagonist injections and calcitonin.

††n=207.

‡‡n=186.

§§n=88.

¶¶n=185.

BMI, Body Mass Index; JSW, joint space width; KOOS, Knee injury and Osteoarthritis Outcome Score (0=worst, 100=best score); MRI, magnetic resonance imaging; n, number of participants; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index (0=best, 96=worst score).

meniscal extrusion, or the cartilage volume at T0 (table 2). The only difference was a generally higher cartilage volume in subgroup +Glu/CS with a numerical trend reached for the global condyle ( $p=0.06$ ) in the +analgesic/NSAIDs group.

### Structural changes

Participants in the +analgesic/NSAIDs group had significantly more cartilage volume loss at T24 in the global knee, and in the medial and the lateral compartments, than the –analgesic/NSAIDs participants (see online supplementary material, table), further confirming that the +analgesic/NSAIDs participants had more severe disease.

Within the –analgesic/NSAIDs group, the –Glu/CS subgroup had more cartilage volume loss at T24 in the medial central plateau ( $p=0.007$ ) than the +Glu/CS subgroup (table 3).

In the +analgesic/NSAIDs group, the –Glu/CS subgroup had more cartilage volume loss at T12 in the global ( $p=0.05$ ) and lateral ( $p=0.005$ ) plateau compared to the +Glu/CS subgroup (table 3). At T24, significance was reached for the global central plateau ( $p=0.05$ ), and a numerical trend found ( $p=0.08$ ) for the lateral plateau (table 3). Additionally, a multivariate analysis adjusted for BMI and WOMAC pain at baseline (which were different between the + and –Glu/CS subgroups at T0 [table

**Table 3** Changes in imaging characteristics in treatment groups at 12 and 24 months: Univariate analyses\*

	–Analgesic/NSAIDs			+Analgesic/NSAIDs		
	+Glu/CS (n=90)	–Glu/CS (n=210)	p Value†	+Glu/CS (n=113)	–Glu/CS (n=187)	p Value‡
<b>12 Months</b>						
<b>Loss of JSW (mm)</b>	0.02 (0.61)‡	–0.12 (0.47)§	0.25	–0.16 (0.64)¶	–0.14 (0.57)**	0.30
<b>MRI change (%)</b>	(n=85)	(n=195)		(n=108)	(n=175)	
Global knee	–1.2 (3.4)	–1.6 (3.1)	0.44	–1.8 (3.6)	–2.2 (3.7)	0.60
Condyle	–1.2 (3.4)	–1.3 (3.2)	0.86	–1.9 (4.3)	–1.9 (3.9)	0.57
Plateau	–1.2 (4.8)	–2.1 (4.6)	0.28	–1.5 (4.6)	–2.8 (5.1)	<b>0.05</b>
Central plateau	–1.2 (4.9)	–2.2 (5.1)	0.14	–1.5 (5.0)	–2.9 (5.2)	0.09
Peripheral plateau	–1.3 (5.3)	–1.9 (4.8)	0.47	–1.5 (4.9)	–2.8 (5.5)	0.07
Medial compartment	–1.3 (4.2)	–1.9 (3.6)	0.43	–2.1 (5.9)	–2.4 (4.7)	0.66
Condyle	–1.1 (4.8)	–1.5 (4.0)	0.61	–2.1 (7.3)	–2.2 (5.1)	0.93
Plateau	–1.5 (6.2)	–2.5 (6.8)	0.32	–2.2 (7.1)	–2.7 (7.3)	0.48
Central plateau	–1.2 (6.3)	–2.5 (7.2)	0.19	–2.5 (7.5)	–2.6 (7.9)	0.72
Peripheral plateau	–1.7 (6.6)	–2.4 (7.5)	0.58	–2.0 (7.6)	–2.6 (7.5)	0.52
Lateral compartment	–1.2 (3.9)	–1.5 (3.8)	0.65	–1.6 (4.0)	–2.3 (4.1)	0.17
Condyle	–1.2 (3.7)	–1.2 (3.9)	0.83	–1.8 (4.6)	–1.7 (4.1)	0.67
Plateau	–1.3 (6.6)	–1.8 (6.0)	0.12	–0.9 (5.4)	–3.2 (6.1)	<b>0.005</b>
Central plateau	–1.4 (7.2)	–2.0 (6.0)	0.13	–0.8 (6.1)	–3.2 (6.5)	<b>0.009</b>
Peripheral plateau	–1.3 (6.8)	–1.6 (7.6)	0.33	–0.9 (6.0)	–3.1 (6.8)	<b>0.007</b>
<b>24 Months</b>						
<b>Loss of JSW (mm)</b>	–0.05 (0.85)††	–0.16 (0.65)‡‡	0.65	–0.16 (0.72)§§	–0.20 (0.66)¶¶	0.99
<b>MRI change (%)</b>						
Global knee	–2.4 (4.0)	–2.7 (3.8)	0.52	–3.3 (3.8)	–3.8 (4.5)	0.57
Condyle	–1.9 (4.4)	–2.1 (3.7)	0.52	–3.2 (3.7)	–3.0 (4.5)	0.62
Plateau	–3.2 (5.1)	–3.8 (5.5)	0.47	–3.7 (5.6)	–5.3 (6.5)	0.10
Central plateau	–3.4 (5.7)	–3.9 (6.1)	0.36	–3.7 (5.6)	–5.4 (6.8)	<b>0.05</b>
Peripheral plateau	–3.1 (5.3)	–3.6 (5.8)	0.48	–3.7 (6.1)	–5.2 (7.0)	0.17
Medial compartment	–2.3 (4.7)	–3.0 (4.6)	0.23	–3.8 (5.4)	–4.0 (6.1)	0.92
Condyle	–2.0 (5.8)	–2.4 (4.7)	0.46	–3.5 (5.0)	–3.3 (6.1)	0.48
Plateau	–2.3 (6.7)	–4.2 (8.5)	0.08	–4.4 (9.0)	–5.9 (9.4)	0.39
Central plateau	–2.0 (7.5)	–4.4 (8.6)	<b>0.007</b>	–3.9 (8.9)	–5.8 (10.4)	0.30
Peripheral plateau	–2.6 (6.9)	–4.0 (9.6)	0.37	–4.8 (10.1)	–6.0 (9.8)	0.46
Lateral compartment	–2.8 (4.8)	–2.5 (4.5)	0.76	–3.2 (4.3)	–3.9 (5.0)	0.25
Condyle	–2.1 (5.0)	–1.9 (4.3)	0.96	–3.0 (4.6)	–3.1 (4.8)	0.92
Plateau	–4.1 (6.8)	–3.2 (6.4)	0.61	–3.9 (7.0)	–5.3 (7.6)	0.08
Central plateau	–4.5 (8.0)	–3.5 (7.0)	0.59	–4.0 (7.8)	–5.4 (8.4)	0.11
Peripheral plateau	–3.7 (6.9)	–2.8 (7.5)	0.73	–3.8 (7.4)	–5.1 (8.1)	0.14

\*Results are shown as mean ( $\pm$ SD), unless otherwise mentioned.

†p Values were assessed using the Mann–Whitney test.

‡n=86.

§n=201.

¶n=107.

\*\*n=172.

††n=88.

‡‡n=209.

§§n=106.

¶¶n=179.

BMI, Body Mass Index; JSW, joint space width; KOOS, Knee injury and Osteoarthritis Outcome Score (0=worst, 100=best score); n, number of participants; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index (0=best, 96=worst score).

2)], showed a numerical trend ( $p=0.07$ ) at T24 regarding the reduction in cartilage volume loss in the global plateau in favour of the +Glu/CS subgroup (data not shown). Furthermore, as the study was conducted in four centres, we also performed multivariate regressions for +analgesic/NSAIDs and -analgesic/NSAIDs groups including this variable, and data showed no effect on the structural changes (data not shown).

Additional multivariate analysis revealed that JSW at T0 was the strongest predictor of cartilage volume change. Participants in +analgesic/NSAIDs and -analgesic/NSAIDs groups were then further subdivided using the respective median value of JSW at T0 (table 4).

In the -analgesic/NSAIDs group, among those with a JSW at T0 greater than the median (less severe disease), the -Glu/CS participants had significantly more cartilage volume loss in the global ( $p=0.04$ ) and medial ( $p=0.02$ ) condyle at T24 compared with the +Glu/CS (table 4). For those with a JSW at T0 lower than the median (more severe disease), the -Glu/CS participants had more cartilage volume loss in the lateral central plateau ( $p=0.03$ ) at T12 and in the medial central plateau at T24 ( $p=0.004$ ) compared to the +Glu/CS.

In the +analgesic/NSAIDs group, among participants who had a JSW at T0 greater than the median, the -Glu/CS participants had significantly more cartilage volume loss than the +Glu/CS participants in the lateral plateau at T12 ( $p=0.02$ ) and T24 ( $p=0.03$ ) (table 4). Moreover, at T24 there was significantly more cartilage volume loss in the global plateau ( $p=0.02$ ) in the -Glu/CS compared to the +Glu/CS subgroup (table 4).

## DISCUSSION

The aim of this study was to examine the effects of the most common OA pharmacological treatments and the combination of Glu/CS on structural progression of knee OA, by analysing data from the OAI progression cohort. We considered the concomitant usage of Glu/CS since very few patients (<5%) reported taking these agents separately. This is likely linked to the fact that these are among the most commonly available over-the-counter treatments in the USA, and most individuals with knee OA who use nutritional supplements in the USA take both together.

The results from this observational study of participants with sROA provide support for the structure-modifying effects of the Glu/CS combination using cartilage volume assessment. Data first showed that participants who reported taking pharmacological OA treatment were found to have a more advanced disease as they had, at T0, more severe knee symptoms and structural damage than those who did not take such treatment; this is consistent with a bias by indication. Hence, these characteristics are consistent with those previously reported by Lapane *et al.*<sup>19</sup> Of the participants who reported not taking pharmacological OA treatment (-analgesic/NSAIDs group) over a 24-month period, those taking Glu/CS had reduced cartilage volume loss in the medial central plateau. Of the participants who reported taking pharmacological OA treatment (+analgesic/NSAIDs group) over a 24 month period, those taking Glu/CS had reduced cartilage volume loss in the central plateau and a trend in the lateral plateau.

Unlike the MRI outcomes, no significant reduction in JSW was found between groups. These findings may argue for using MRI as an alternative to radiography for the evaluation of disease-modifying osteoarthritis drugs (DMOADs), especially in individuals with early knee OA and/or less advanced disease. Indeed, all participants in the present study, regardless of their

treatment, had a milder OA disease than those usually recruited in clinical trials; at T0, WOMAC pain ranged from 3.4 to 6.0 on a scale of 20, and the majority had a KL grade of 2 in the -analgesic/NSAIDs group, and 3 in the +analgesic/NSAIDs group. Therefore, the MRI data demonstrating a significant reduction in cartilage volume loss in specific subregions in individuals with early/mild/moderate OA taking Glu/CS, which would not have been detected by radiograph, may encourage going one step further and having MRI as a relevant tool for DMOAD effect evaluation instead of the radiographic current gold standard.

In the -analgesic/NSAIDs participants, the Glu/CS effect was found to prevent cartilage loss in some subregions at T12 and T24 regardless of the radiographic changes. However, in the +analgesic/NSAIDs participants, the Glu/CS effect was also found in subregions at T12 and T24, but only in those with less severe radiographic changes (JSW >median). Hence, in the -analgesic/NSAIDs group, participants with less radiographic changes (greater JSW) experienced a protective effect of Glu/CS in the medial condyle at T24, whereas, for those with greater radiographic changes (smaller JSW), the protective effect of Glu/CS was in the lateral central plateau at T12 and in the medial central plateau at T24 (table 4). These data may be explained by the fact that the protective effect of such treatment was easier to detect on plateaus using MRI in patients with more rapidly progressive disease (smaller JSW). Additionally, this suggests that the protective effect of Glu/CS may mostly target the medial subregions in subjects with less severe damage (-analgesic/NSAIDs group), thus, in the more early stages of knee OA.

These findings are most relevant and have clinical significance as they could, for example, be predictive of total knee replacement (TKR). In a recent report by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) consensus meeting, it is concluded that the MRI parameter of medial compartment cartilage volume/thickness loss seems to be able to predict progression to TKR.<sup>20</sup> Moreover, this is also consistent with a recent report on a case control study from the same OAI patient cohort showing that loss of cartilage thickness in the central medial tibiofemoral compartment, and more precisely in the central tibia, was the most predictive of TKR,<sup>13</sup> and with others,<sup>21-23</sup> including a recent report,<sup>23</sup> showing that a treatment that can reduce cartilage loss in these specific anatomical regions could possibly reduce the need for TKR.

In the group taking pharmacological agents for the management of OA, the Glu/CS effect was found to prevent cartilage loss mostly in the lateral plateau (table 3), and more particularly in participants with less severe radiographic changes (greater JSW; table 4). A possible explanation could be that the preferential protective effect on the lateral compartment in more severe knee OA (+analgesic/NSAIDs) may result from a reduced potential of Glu/CS to impact the already severely damaged medial compartment. This agrees with data from a previous CS double-blind clinical trial in knee OA patients, in which, using qMRI, the cartilage volume loss was found to have decreased predominantly in the lateral compartment.<sup>24</sup> Hence, the suggestion that Glu/CS may not be able to protect the cartilage in very severe knee OA is supported by the data showing no effect in participants with the most severe disease (+analgesic/NSAIDs group) and the most narrowed JSW (table 4), which likely reflects irreversible damage.

All together, these results may argue for a targeted structural impact of Glu/CS on the medial plateau in early OA and on the

**Table 4** Joint space width and MRI changes in patients who took or did not take glucosamine/chondroitin sulfate\*

	-Analgesic/NSAIDs					
	JSW >median (4.09 mm)			JSW ≤median (4.09 mm)		
	+Glu/CS (n=38)	-Glu/CS (n=110)	p Value†	+Glu/CS (n=50)	-Glu/CS (n=99)	p Value†
<b>12 Months</b>						
<b>Loss of JSW (mm)</b>	0.09 (0.53)‡	-0.13 (0.47)§	0.12	-0.02 (0.66)¶	-0.10 (0.47)**	0.80
<b>MRI change (%)</b>	(n=36)	(n=102)		(n=47)	(n=93)	
Global knee	-0.82 (2.99)	-1.32 (2.82)	0.37	-1.34 (3.68)	-1.97 (3.34)	0.49
Condyle	-0.65 (2.97)	-1.00 (3.11)	0.52	-1.47 (3.75)	-1.66 (3.32)	0.96
Plateau	-1.29 (4.29)	-1.74 (3.84)	0.58	-0.95 (5.16)	-2.44 (5.35)	0.18
Central plateau	-1.40 (3.98)	-1.77 (4.35)	0.51	-0.79 (5.49)	-2.71 (5.85)	0.10
Peripheral plateau	-1.19 (5.00)	-1.69 (4.17)	0.76	-1.13 (5.38)	-2.15 (5.49)	0.30
Medial compartment	-0.49 (3.29)	-1.25 (3.02)	0.29	-1.80 (4.76)	-2.57 (4.11)	0.52
Condyle	-0.17 (3.50)	-0.72 (3.54)	0.40	-1.78 (5.57)	-2.32 (4.34)	0.79
Plateau	-1.14 (4.66)	-2.05 (4.92)	0.43	-1.45 (7.03)	-2.94 (8.32)	0.42
Central plateau	-1.25 (4.62)	-2.18 (5.57)	0.31	-0.91 (7.40)	-2.92 (8.67)	0.28
Peripheral plateau	-1.04 (5.25)	-1.90 (5.79)	0.56	-1.87 (7.35)	-2.92 (9.06)	0.57
Lateral compartment	-1.29 (3.70)	-1.41 (3.64)	0.50	-0.98 (4.10)	-1.56 (4.01)	0.74
Condyle	-1.11 (3.43)	-1.34 (3.93)	0.70	-1.09 (3.97)	-1.08 (3.88)	0.69
Plateau	-2.16 (7.01)	-1.30 (5.61)	0.53	-0.39 (6.32)	-2.35 (6.40)	0.07
Central plateau	-2.37 (7.10)	-1.33 (5.70)	0.81	-0.40 (7.36)	-2.68 (6.37)	<b>0.03</b>
Peripheral plateau	-1.98 (7.56)	-1.09 (7.46)	0.64	-0.49 (6.16)	-2.07 (7.85)	0.21
<b>24 Months</b>						
<b>Loss of JSW (mm)</b>	0.02 (0.50)††	-0.17 (0.59)‡‡	0.12	-0.10 (1.03)¶¶	-0.14 (0.72)§§	0.55
<b>MRI change (%)</b>						
Global knee	-1.52 (3.51)	-2.39 (3.33)	0.14	-3.11 (4.35)	-3.04 (4.25)	0.84
Condyle	-0.60 (3.20)	-1.83 (3.36)	<b>0.04</b>	-2.96 (4.92)	-2.43 (4.01)	0.50
Plateau	-2.99 (5.50)	-3.35 (4.79)	0.71	-3.33 (4.93)	-4.21 (6.30)	0.44
Central plateau	-3.14 (6.24)	-3.46 (5.11)	0.59	-3.53 (5.35)	-4.51 (7.09)	0.39
Peripheral plateau	-2.82 (5.29)	-3.22 (5.35)	0.71	-3.19 (5.43)	-3.91 (6.29)	0.44
Medial compartment	-0.59 (3.93)	-2.27 (3.92)	0.06	-3.59 (4.94)	-3.81 (5.26)	0.77
Condyle	0.39 (3.80)	-1.60 (4.07)	<b>0.02</b>	-3.95 (6.38)	-3.23 (5.16)	0.51
Plateau	-2.34 (5.60)	-3.72 (6.74)	0.34	-2.28 (7.51)	-4.78 (10.22)	0.09
Central plateau	-2.89 (7.01)	-3.80 (6.92)	0.40	-1.36 (8.01)	-5.15 (10.07)	<b>0.004</b>
Peripheral plateau	-1.87 (5.18)	-3.60 (7.94)	0.37	-3.01 (8.10)	-4.42 (11.24)	0.47
Lateral compartment	-2.57 (4.48)	-2.58 (4.31)	0.68	-2.85 (5.11)	-2.31 (4.74)	0.45
Condyle	-1.66 (4.42)	-2.12 (4.40)	0.37	-2.21 (5.35)	-1.64 (4.31)	0.42
Plateau	-4.21 (7.50)	-3.05 (6.07)	0.82	-4.00 (6.39)	-3.43 (6.79)	0.57
Central plateau	-3.91 (8.42)	-3.37 (6.16)	0.88	-4.97 (7.82)	-3.69 (7.80)	0.40
Peripheral plateau	-4.40 (7.80)	-2.56 (8.15)	0.60	-3.21 (6.30)	-3.16 (6.83)	0.90
	+Analgesic/NSAIDs					
	JSW >median (3.59 mm)			JSW ≤median (3.59 mm)		
	+Glu/CS (n=53)	-Glu/CS (n=95)	p Value†	+Glu/CS (n=58)	-Glu/CS (n=90)	p Value†
<b>12 Months</b>						
<b>Loss of JSW (mm)</b>	-0.15 (0.60)¶¶¶	-0.13 (0.57)***	0.11	-0.16 (0.69)†††	-0.16 (0.58)‡‡‡	0.96
<b>MRI change (%)</b>	(n=51)	(n=87)		(n=55)	(n=86)	
Global knee	-1.12 (3.15)	-1.28 (3.13)	0.89	-2.35 (3.92)	-3.21 (4.04)	0.47
Condyle	-1.14 (3.61)	-0.85 (3.26)	0.76	-2.38 (4.78)	-2.95 (4.15)	0.93
Plateau	-0.87 (4.44)	-1.96 (4.43)	0.27	-2.27 (4.64)	-3.70 (5.61)	0.15
Central plateau	-1.15 (4.70)	-1.93 (4.43)	0.55	-2.12 (5.29)	-3.76 (5.76)	0.13
Peripheral plateau	-0.57 (4.78)	-1.94 (4.97)	0.13	-2.33 (4.95)	-3.60 (6.04)	0.24
Medial compartment	-0.73 (3.69)	-0.57 (3.75)	0.80	-2.95 (6.71)	-4.18 (4.97)	0.41
Condyle	-0.25 (3.94)	-0.44 (3.95)	0.96	-3.23 (8.08)	-4.09 (5.40)	0.88
Plateau	-1.56 (6.28)	-0.61 (6.31)	0.62	-2.83 (7.74)	-4.60 (7.64)	0.19
Central plateau	-1.96 (6.66)	-0.51 (6.89)	0.37	-2.99 (8.33)	-4.55 (8.38)	0.21
Peripheral plateau	-1.20 (6.45)	-0.62 (6.39)	0.64	-2.67 (8.45)	-4.57 (8.07)	0.20

Continued

Table 4 Continued

	+Analgesic/NSAIDs					
	JSW>median (3.59 mm)			JSW≤median (3.59 mm)		
	+Glu/CS (n=53)	−Glu/CS (n=95)	p Value†	+Glu/CS (n=58)	−Glu/CS (n=90)	p Value‡
Lateral compartment	−1.63 (4.34)	−2.01 (3.83)	0.36	−1.60 (3.75)	−2.65 (4.30)	0.29
Condyle	−2.17 (4.73)	−1.31 (3.85)	0.42	−1.37 (4.54)	−2.22 (4.29)	0.60
Plateau	−0.23 (6.25)	−3.18 (6.04)	<b>0.02</b>	−1.80 (4.32)	−3.33 (6.29)	0.15
Central plateau	−0.39 (6.89)	−3.12 (6.44)	0.06	−1.50 (5.02)	−3.39 (6.73)	0.14
Peripheral plateau	0.06 (6.80)	−3.07 (7.00)	<b>0.008</b>	−2.01 (4.92)	−3.21 (6.57)	0.30
24 Months						
Loss of JSW (mm)	−0.16 (0.73)¶	−0.21(0.71)§§§	0.96	−0.16 (0.71)¶¶¶¶	−0.18 (0.60)****	0.94
MRI change (%)						
Global knee	−2.29 (3.58)	−3.47 (4.42)	0.16	−4.24 (3.77)	−4.11 (4.68)	0.68
Condyle	−2.10 (2.41)	−2.60 (4.52)	0.61	−4.12 (3.71)	−3.48 (4.51)	0.36
Plateau	−2.62 (5.42)	−5.04 (6.14)	<b>0.02</b>	−4.67 (5.63)	−5.49 (7.00)	0.83
Central plateau	−2.94 (5.96)	−4.99 (6.42)	0.10	−4.38 (5.35)	−5.70 (7.20)	0.30
Peripheral plateau	−2.31 (5.41)	−5.05 (6.43)	<b>0.007</b>	−4.88 (6.55)	−5.30 (7.65)	0.68
Medial compartment	−1.58 (4.01)	−2.79 (5.71)	0.29	−5.74 (5.77)	−5.21 (6.20)	0.37
Condyle	−1.07 (3.75)	−1.93 (5.59)	0.40	−5.75 (5.15)	−4.57 (6.39)	0.14
Plateau	−2.46 (6.88)	−4.48 (8.43)	0.36	−6.17 (10.36)	−7.31 (10.17)	0.71
Central plateau	−3.02 (7.62)	−4.26 (9.33)	0.66	−4.70 (9.99)	−7.15 (11.20)	0.26
Peripheral plateau	−1.92 (7.00)	−4.57 (8.80)	0.19	−7.37 (11.80)	−7.38 (10.73)	0.87
Lateral compartment	−3.25 (4.78)	−4.25 (5.22)	0.27	−3.08 (3.94)	−3.54 (4.74)	0.53
Condyle	−3.36 (5.20)	−3.44 (5.23)	0.96	−2.63 (3.98)	−2.87 (4.35)	0.75
Plateau	−3.75 (8.13)	−5.59 (7.45)	<b>0.03</b>	−4.05 (6.01)	−4.97 (7.94)	0.64
Central plateau	−4.10 (8.99)	−5.58 (8.44)	0.16	−4.12 (6.61)	−5.19 (8.47)	0.49
Peripheral plateau	−3.44 (8.25)	−5.51 (7.77)	<b>0.03</b>	−3.91 (6.68)	−4.75 (8.51)	0.95

\*Results are shown as mean (± SD).

†p Values were assessed using the Mann–Whitney test.

‡n=37.

§n=106.

¶n=49.

\*\*n=95.

††n=36.

‡‡n=107.

§§n=97.

¶¶n=52.

\*\*\*n=90.

†††n=55.

‡‡‡n=82.

§§§n=92.

¶¶¶n=57.

\*\*\*\*n=87.

JSW, joint space width; n, number of participants.

lateral plateau in moderate OA with enough capacity to slow cartilage damage. These are also in line with the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) study<sup>25</sup> which reported numerical trends toward a structural protective effect of Glu and/or CS among patients with less severe radiographic OA damage (KL grade 2). Furthermore, a meta-analysis<sup>26</sup> showed that the structure-modifying effect of CS remained robust even after inclusion of the results from GAIT, demonstrating a DMOAD effect of the molecule in knee OA. The clinical relevance of the current findings has been highlighted in two recent reports.<sup>24, 27</sup> The first<sup>24</sup> is a randomised controlled trial of patients with moderate knee OA in which CS was found to reduce cartilage loss, particularly in the lateral compartment. The second<sup>27</sup> is a report on a four-year observation period of the patients from the first study showing that the incidence of TKR in these patients was reduced.

The present study has several strengths. First, the OAI cohort offered a unique opportunity to study the disease profile of participants with knee sROA based on their reported

pharmacological treatments, and allowed us to explore the impact of those treatments on the disease evolution in a real-life scenario. Second, the database provided information on clinically relevant imaging outcomes acquired using standard protocols and analysed using reliable validated techniques. Moreover, the use of 3.0 Tesla MRI and the strict imaging protocol in this multicentre cohort study provided high-quality imaging and consistency. Until now, the assessment of knee structural changes, mainly cartilage thickness/volume, by qMRI had been done mostly using manual or semiautomated technologies, which have the intrinsic limitation of variability in results with respect to human intervention. This, in turn, imposed limitations with regard to a complete analysis of the OAI cohort. The recent validation of fully automated technology to assess OA joint structural changes including cartilage thickness/volume<sup>16</sup> greatly improved the capacity and reliability of the analysis of the OAI MRI datasets.

The present study, as with any other, has limitations. First, in order to include the sequence acquisitions from the onset of the

study to the 24-month follow-up for the same patients, a reduced number of participants was used; the 600 participants represent about 40% of the OAI progression cohort. Nevertheless, this longitudinal study argues for a positive structural impact of Glu/CS in some subregions, which, as mentioned above, are clinically relevant. However, although statistical significance was reached in only some subregions, it is noteworthy that the cartilage volume loss was, in general, found to be less in the +Glu/CS compared to the –Glu/CS subgroup in the +analgesic/NSAIDs and the –analgesic/NSAIDs groups as early as 2 years. Of note, recently available, but not yet analysed, are the OAI MRI data from the 6-year follow-up, hence, the assessment of Glu/CS after a longer period of use may result in an additional beneficial structural effect.

Second, patient selection for the OAI study was inherently different from that of randomised controlled trials. Indeed, it has previously been reported<sup>28</sup> that the MRI changes in the OAI progression cohort were far less severe than those seen in clinical trials. Previous work clearly demonstrated that the OAI progression cohort included younger participants with less severe knee symptoms at entry and, more importantly, had less cartilage volume loss, almost half of what is seen in knee OA clinical trials.<sup>28–31</sup> Such a small signal makes it difficult to detect a high level of impact. It was, therefore, logical to assume that the effect size of Glu/CS in the OAI progression cohort would be smaller than those seen in clinical trials.

Third, in assessing the progression of cartilage volume loss over time, we did not consider the impact of other structural tissue damage, such as the presence of bone marrow lesions or synovitis, which could potentially affect the presence of cartilage change over time.<sup>32–34</sup> This should be further explored in follow-up studies.

Fourth, there was no information available about the exact dosage or quality of the medication taken by the patients over time. Likewise, the compliance of participants to treatment was difficult to assess as it was based on information reported by the participants. However, with regard to the frequency of Glu/CS use, the percentage of participants who reported taking them ‘nearly every day or every day’ was  $\geq 85\%$ . This study was done in the USA where Glu and CS are considered to be nutritional supplements, and there is no guarantee of a pharmacological grade of preparation. Furthermore, as previously reported,<sup>19</sup> there are factors unrelated to the disease itself that may have influenced the taking of Glu and CS treatment, such as race and socioeconomic and educational status, to name only a few.

Fifth, some patients also reported taking bone anti-remodelling medications, which were balanced in the –analgesic/NSAIDs but not in the +analgesic/NSAIDs group. However, further analysis revealed that such drugs did not interfere with the effect of Glu/CS on the loss of cartilage volume.

## CONCLUSION

In summary, participants with sROA of the knee who received conventional pharmacological treatment had more severe disease symptoms and structural changes at the onset of the study, and tended to have more rapid structural progression over time. Despite this, there was evidence of a beneficial effect of the Glu/CS at delaying knee OA structural progression (cartilage loss), whether they took OA pharmacological treatment or not. Moreover, these data are consistent with the hypothesis that individuals with milder structural changes would benefit more from structure-modifying agents, such as Glu/CS, than those with a more advanced disease.

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**Contributors** JMP had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. PD and MD performed and are responsible for the statistical analyses for this study. Study concept and design: JMP, J-PR, MD, J-PP. Acquisition of data: JMP, CR, J-PR, FA, PD, J-PP. Analysis and interpretation of data: JMP, CR, J-PR, FA, MCH, MD, PD, J-PP. Drafting of the manuscript: JMP, CR, J-PR, MCH, J-PP. Critical revision of the manuscript for important intellectual content: JMP, CR, J-PR, MCH, J-PP. Statistical analysis: MD, PD. Obtained funding: JMP, J-PP. Administrative, technical, or material support: JMP, FA, J-PP. Study supervision: JMP, J-PP.

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# First-line analysis of the effects of treatment on progression of structural changes in knee osteoarthritis over 24 months: data from the osteoarthritis initiative progression cohort

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