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KNEE OSTEOARTHRITIS: BIOLOGICAL RESPONSE TO PHARMACEUTICALS FROM SYSADOA GROUP

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SUMMARY

The purpose of the trial was to determine the effect of pharmaceuticals from the SYSADOA group on the rheological properties of the knee joint with osteoarthritis and the subjective perception of these effects by patients. The trial participants were 15 probands (45–77 years) with diagnosed osteoarthritis of the knee joint. They took a preparation containing substances from the SYSADOA group for a period of 13 weeks. The evaluation of the effect of pharmaceuticals was performed by means of the WOMAC index and changes in rheological properties of the knee joint measured on a special apparatus – the knee biorheometer. The effects were compared after 13 weeks of taking the preparation and subsequently after another 6 weeks without any therapy. According to the WOMAC index there was an improvement in 13 probands out of 15 after 13 weeks (the average value of the index fell from 25.5 to 17.8). The discontinuation of the preparation did not manifest any significant change the WOMAC index. Using the Wilcoxon test for paired sets a statistically significant difference (i.e. improvement) of the WOMAC index was discovered between the 1st and the 2nd, but also the 1st and the 3rd measurements. Results of rheological measurement: comparing the 1st and the 3rd measurement, which shows the long-term trend of SYSADOA effects, the rheological properties improved in 10 osteoarthritic knee joints out of 22, there was no change in 8, and it was only in 4 osteoarthritic knee joints out of 22 that the rheological properties worsened.

Key words: knee osteoarthritis, knee joint rheology, SYSADOA, biorheometer, WOMAC index

INTRODUCTION

Osteoarthritis (OA) is the most common knee disorder characterized by the imbalance between the processes of synthesis and degradation of knee cartilage and the subchondral bone. This imbalance is accompanied by the fibrosis of the joint capsule, development of osteophytes and different degrees of the inflammation of the synovial membrane in the

joint. It is not a disease, but a process which not always results in clinical manifestations of pain, stiffness and joint instability (Gremion et al., 2009; Moskowitz et al., 2001). According to WHO, 40% of people over 70 years of age suffer from gonarthrosis (knee joint OA) (Pavelka, 2002).

The EULAR (European League against Rheumatism) research group published recommendations for the treatment of gonarthritis in 2003 (Jordan et al., 2003) where the usage of combinations of non-pharmaceutical and pharmaceutical procedures is recommended. One of the possibilities of pharmacological treatment is represented by SYSADOA ("symptomatic slow acting drugs of osteoarthritis"). These drugs act with a certain time lag where the effect is gradually manifested during 4–6 weeks and persists even after the drug is discontinued. They do not produce typical undesirable side effects of non-steroidal antirheumatics (NSA) and allow reducing their consumption. SYSADOA inhibit the action of interleukins, which allows a gradual set-up of a steady state in osteoarthritic cartilage and regeneration of the intracellular tissue structures (Marek, 2006). Glucosamine sulfate (hereinafter GS) and chondroitin sulfate (hereinafter CHS) belong to the most known representatives of the SYSADOA group being also part of publicly available preparations offered in large quantities under the name of "joint nutrition".

In 2005, the Cohrane Collaboration group published the update of the meta-analysis of Randomized Controlled Trials dealing with the GS efficiency in the OA treatment. 20 randomized trials stated that GS had better effects than a placebo, both in the parameters of pain (by 28%) and the parameter of the joint function using the Lequesne index (by 21%). Another five trials did not prove a higher efficiency of GS than a placebo (Towheed, Anastassiades, 2007).

GS is also studied from the perspective of its potential structure-modifying effect in OA. These problems were investigated in 2 similar trials (Reginster et al., 2001; Pavelka et al., 2002), which independently confirmed the GS efficiency for the OA symptomatology and structure. The former trial involved 212 patients with gonarthrosis, the latter 2002 patients with gonarthrosis. The patients were randomly divided into two groups –the group with a placebo and the group taking GS daily for a period of three years. The changes occurring during these three years were compared according to the width of the joint aperture on X-ray images and the WOMAC index. In the former trial, the joint aperture in the patients with a placebo narrowed on average by 0.31 mm, while in the latter it was on average by 0.19 mm. No narrowing was reported in the patients taking GS – this applied to both trials. According to the WOMAC index, the symptoms got worse in the group with a placebo during three years, while in the group with GS, on the contrary, there was an improvement; again, this improvement was reported in both trials.

The complex meta-analysis of 2002, made by the University of Liëgein Belgium, dealt with the results of randomized controlled trials studying the GS and CHS effects on gonarthrosis. These trials had been published between 1980 and 2002. The results manifested a very significant efficiency rate of GS as well as CHS in all monitored parameters – the visual analogue scale, joint mobility, the Lequesne and WOMAC index, tolerance by the patients, patients' subjective feelings and a medical examination. The changes in the joint aperture on X-ray images confirmed its structure-modifying effect (Richy et al., 2003).

The CHS efficiency for knee OA was studied byMazzieres et al. (2001) in a double-blind, randomized, placebo-controlled trial. 130 patients took either a placebo or 1g of

CHS for a period of 3 months. The primary evaluation criterion was the Lequesne Algofunctional Index, while the secondary criterion was subjective assessment of pain progression in a quiescent state and during common daily activities and the consumption of analgesics. The results manifested an insignificant improvement in all parameters in the group with the CHS therapy.

There are preparations available on the market containing a combination of glucosamine sulfate and chondroitin sulfate. The question is whether a combination is more efficient than separately used substances. This problem was investigated in the GAIT trial (Glucosamine/Chondroitin Arthritis Intervention Trial) where the efficiency of GS and CHS and their mutual combinations with a placebo and celecoxib (NSA) for knee joint OA were compared. The efficiency was compared according to the results of the WOMAC index after 24 weeks of taking the drugs. The resulting efficiency of GS, CHS and combinations of both was roughly the same as in the placebo group (Clegg et. al., 2006).

All these trials assessed the effects on the basis of a predominantly subjective pain evaluation, or X-ray images. This led to considering the possibility of an objective evaluation of the effects of these substances on the joint properties, specifically on the rheological properties in gonarthrosis. Rheology (from a Greek word *rheos* – flow) deals with the study of mass deformations and finding relationships between stress, deformation and deformation velocity for individual types of substances. Biorheology is a field of rheology dealing with specific rheological properties of biomaterials. A typical characteristic modifying the yielding capacity of biological structures is viscoelasticity. Joint rheology depends on the rheological properties of all its components –both intraarticular and extraarticular (Otáhal, Tlapáková, 1999).

PURPOSE, HYPOTHESES

The objective of our trial was to determine the effects of pharmaceuticals from the SYSADOA group on the rheological properties of the knee joint with osteoarthritis. The probands participating in the trial took a preparation containing a combination of substances from the SYSADOA group (500 mg of GS and 400 mg of CHS in one tablet) for a period of 13 weeks. A change in rheological properties was observed after 13 weeks of taking the drugs and after another 6 weeks without medications. The assessment of the changes in rheological properties was complemented by a subjective probands' evaluation using the WOMAC index. Our assumption was that there would be an improvement in both rheological properties and a subjectively perceived improvement and this improvement would persist even after the discontinuation of the medication.

METHODS

Subjects

15 probands participated in the trial – 13 women aged from 45 to 77 years with an average BMI (Body Mass Index) value of 26.9, and 2 men aged 62 and 64 with an

average BMI value of 30.0. The probands were not allowed to undertake any other treatment than by SYSADOA during the trial time. 2 probands suffered from diagnosed gonarthrosis stage III on the Kellgrena and Lawrence grading scale (Kellgren, Lawrence, 1957), the others from gonarthrosis stage II. One proband (man) withdrew from the trial after the second measurement for health reasons. Not all the probands had a diagnosis of both-sided gonarthrosis, therefore the results relate to the number of gonarthrosis cases, i.e. 24 units after the second measurement, and 22 units after the third measurement. The trial was performed with the approval of the Ethics Committee of the Faculty of Physical Education and Sport, CU.

Investigations and measurements performed

All investigations were performed 3× – during the entrance measurement, after 13 weeks of taking the preparation and then after 6 weeks from the preparation discontinuation. After taking the case a clinical examination of the knee joint followed, including the examination by inspection, palpation, checking the extent of motion and muscular power. The probands filled in the WOMAC (West Ontario and McMaster Osteoarthritis Index) questionnaire, which serves for the evaluation of functional affection with gonarthrosis. Its results were used as the subjective component within the assessment of the effects of substances from the SYSADOA group on gonarthrosis. The WOMAC questionnaire has

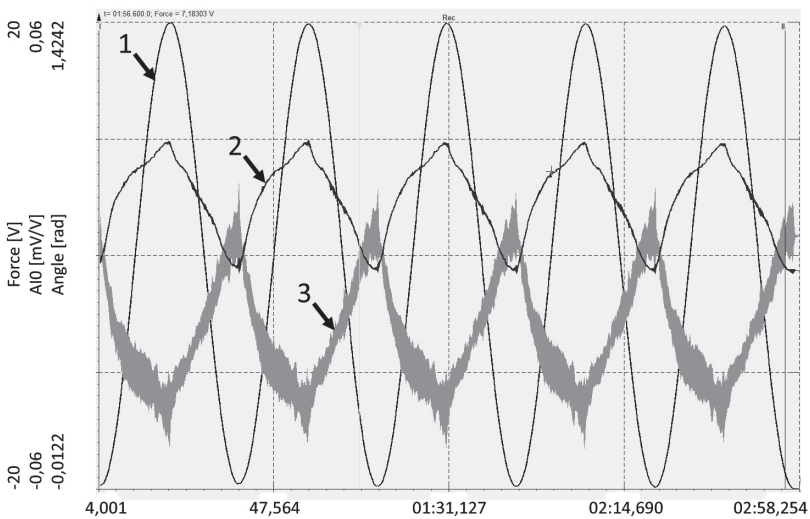

Figure 1. Detected parameters for the calculation of knee joint rheological identifiers on the biorheometer.
axis x –time axis [s]
axis y
1 – angle of motion [rad];
2 – resistance force [N];
3 – output stress on the sensor detecting resistance force [V]

three categories – pain, stiffness and common daily activities. Answers to the questions are quantitatively assessed in categories on the Likert scale: no trouble, slight, medium, severe and very severe trouble. These items correspond to the ordinary scale of 0–4. The points for single items are added up and the higher the score, the greater the patient's trouble with knee joint OA.

The investigation of the rheological properties of the knee joint (objective component of the evaluation) was performed by a special apparatus- the knee biorheometer. The biorheometer allows non-invasive and painless recording of the magnitude of passive resistance of the knee joint during passive motion into flexion and extension (Fig. 1). The proband's investigation is performed in the side-lying position lying on the side of the non-investigated leg where the gravity effect on the knee is minimized. The bending moment is screened by tensometric sensors, the joint rotation angle being screened by the optical incremental sensor. The detected pattern of the dependence of the knee joint bending moment on the angle or on time makes it possible to analyze the physiological condition of the knee, including the corresponding positions of its segments.

Analysis of results on the biorheometer

The basic and complex variable is the moment of force pattern. It, in turn, serves for plotting the hysteresis curve (Fig. 2) whose analysis allows assessing selected properties of the knee joint. The hysteresis loop denotes the relationship of the resistance moment [Nm] on the knee flexion angle from 10° to 90° and back.

Individual measurements consisted of 3 + 5 cycles. 3 cycles served as a warm-up and for the proband's getting used to the executed motion, 5 cycles served for the assessment. Out of these five cycles, one loop with the best quality was selected and 5 specific parameters were selected and calculated from it.

1) Knee joint rigidity, which provides information on the passive resistance of the knee joint to motion and depends on the condition of the connective tissue apparatus, the

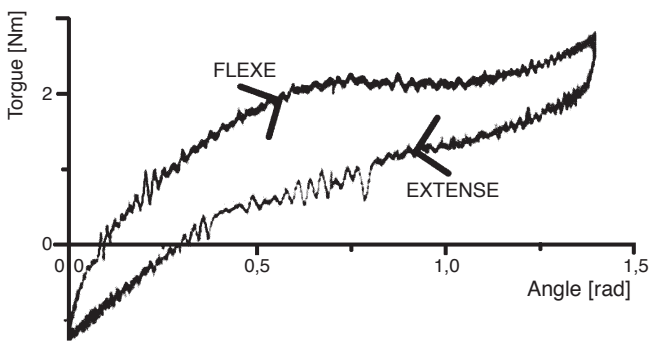

Figure 2. Illustrative graph – the hysteresis loop showing the dependence of the resistance moment of force [Nm] on the knee flexion angle [rad] – direct output from the apparatus without modifications (RAW data), only with an activated hardware filter of frequencies above 1 kHz, calculated by calibration constants and converted from angular degrees into arc radians.

joint capsule and the knee joint soft tissues. It is determined as the average gradient of the approximation function under flexion and calculated from the derivation of the corresponding approximation function.

$$k = \text{tg}\ \varphi \qquad [\text{Nm} \times \text{rad}^{-1}]$$

2) Dissipated (lost) energy in motion in the knee joint – E_D
   The loss of energy occurs due to the friction of the joint surfaces and adjoining structures, synovial fluid viscosity etc. The dissipated energy corresponds to the size of the area delimited by curves. It is given in joules [J].
3) Knee joint efficiency is calculated from the ratios of integral surfaces in the graphic plotting of the loop using the formula:

$$\eta = 1 - \frac{E_D}{E_{celk}}$$

E_D – dissipated energy
E_{celk} – total energy

It is presented in an interval of 0–1 [–].

4) Effective variation amplitude. It is the area of the amplitudes of deflections in relation to smooth approximation related to the length of this curve. It is given in the same units as the bending moment [Nm] and the lower the evaluation parameter, the better the knee condition.
5) Expert assessment is based on long-term experience in the evaluation of hysteresis curves. It is a subjective evaluation of changes in the total shape of the curve.

Only medium parts of the curves in the motion there and back in the knee flexion interval of 20°–80° were used for the determination of all parameters (Fig. 3). Motion within this range is smooth, while in extreme positions the parameters may be distorted by changes in the motion direction.

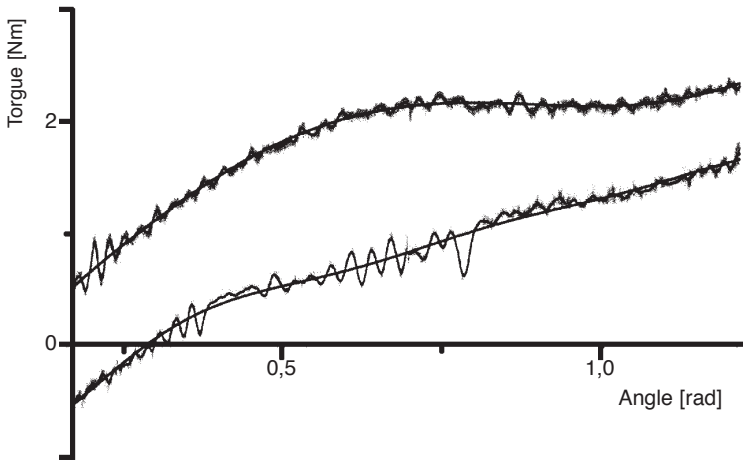

Figure 3. Selected section of the hysteresis curve used for calculations of evaluation parameters.

The calculated rheological parameters were used for the determination of their percentage change between individual measurements, and the results were classified on a three-point scale –improvement in condition, the same condition and worsened condition.

RESULTS

No prominent changes occurred in the clinical examination and BMI, therefore, clinical examinations were not included in the total results.

The WOMAC index fell from the average value of 25.5 to 17.8 after 13 weeks of taking the preparation. After the treatment was discontinued, its effect persisted – the index slightly grew from 17.8 to 18.6. The development of the WOMAC index is plotted in Graph 1.

The WOMAC index values for individual probands are presented in Table 1. After 13 weeks of taking the preparation, the WOMAC index improved in 13 probands out of 15, while the condition of the others got worse. After the discontinuation of the preparation, there was a slight worsening in 8 probands, the condition of 5 probands improved and in 1 proband the condition remained unchanged. Comparing the 1st and the 3rd measurement, which shows the long-term trend of SYSADOA effects on the subjective perception of trouble connected with knee joint OA, there was an improvement in 13 probands out of 15.

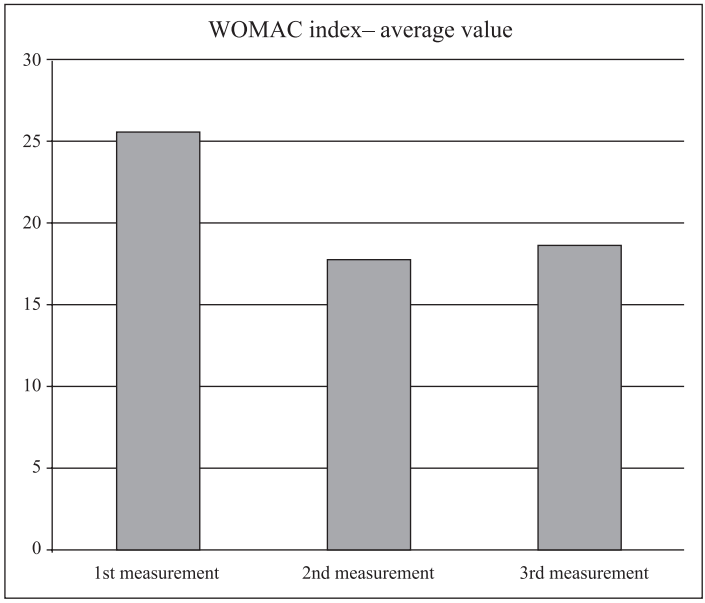

Figure 4. Development of WOMAC index
1st and 2nd measurement – 15 probands
3rd measurement – 14 probands

Table 1. WOMAC index in individual probands
Negative value of the difference = improvement
Positive value of the difference (grey cells) = worsening

WOMAC index in individual probands				
Proband number	**1st measurement**	**2nd measurement**	**3rd measurement**	**Change 1st–3rd measurement**
1	39	15	19	–20
2	54	42	45	–9
3	10	5	9	–1
4	29	21	16	–13
5	9	8	0	–9
6	21	6	7	–14
7	24	21	19	–5
8	50	24	32	–18
9	16	11	7	–9
10	17	10	Neex.	
11	9	20	21	12
12	40	29	34	–6
13	41	24	32	–9
14	12	8	9	–3
15	12	13	13	1

We may say that in the subjective evaluation by means of the WOMAC questionnaire the Wilcoxon rank sum test for paired samples unanimously proved a statistical significance between the 1st and the 2nd as well as the 1st and the 3rd measurements, this being on a significance level of 0.01. Using mathematical statistics we proved that the patients perceived an improvement in their subjective evaluation after taking pharmaceuticals even after another 6 weeks from their discontinuation.

Results of rheological measurement

As was already said, the results are assessed for the number of arthritic knee joints – which means 24 units for the difference between the first two measurements, and 22 units for the difference between the second and the last measurement. The overview of the results is presented in Table 2.

After 13 weeks of taking the preparation there was an improvement in 37.5% of knee joints, the same condition was measured in 41.6% of knee joints, and the condition of 20.8% of knee joints got worse. The discontinuation of the preparations caused the worsening in the rheological properties in 36.4% of knee joints, the same number – i.e. 36.4% of knee joints got better, and the same condition was manifested in 27.3% of knee joints. If we compare the entrance and the final investigation, which shows the long-term trend in SYSADOA effects, there was an improvement in 45.5% of knee joints, in 36.4% the condition remained the same, and the condition of 18.2% of knee joints got worse.

Table 2. Overview of results of rheological investigation
1st–2nd measurement – 24 knee joints with OA
2nd–3rd measurement, 1st–3rd measurement – 22 knee joints with OA

	1st–2nd measurement		2nd–3rd measurement		1st–3rd measurement	
	Count of the knee joints with OA	%	Count of the knee joints with OA	%	Count of the knee joints with OA	%
Improvement	9	37.5	8	36.4	10	45.5
Constant condition	10	41.6	6	27.3	8	36.4
Deterioration	5	20.8	8	36.4	4	18.2

As the amount of total and dissipated energy, stiffness and efficiency are variables that may be expressed on an interval scale, using the t-test for paired values we tried to find out whether there was a statistically significant difference between the 1st and the 2nd and the 1st and the 3rd measurement for the values measured. In this case, however, no statistical significance could be proved by means of mathematical statistics.

Comparison of subjective and objective evaluation

Just for interest's sake, the average value of the WOMAC index was separately calculated for the gonarthrosis cases in which the rheological properties showed a final improvement. After 13 weeks of taking the preparation the average value of the WOMAC index of objectively improved cases of gonarthrosis (37.5% of the total) fell from 21.6 to 15.6. In the knee joints with OA which showed an improvement after another six week without any therapy (36.4%) the WOMAC index remained nearly unchanged. Comparing the first and the last measurement the rheological properties improved in 45.5% of gonarthrosis cases, and their average value of the WOMAC index dropped from 27.6 to 21.7.

DISCUSSION

While presenting the results the low number of probands participating in the trial must be taken into account and also the fact that the results are related to different age categories (45–77 years). OA is a disorder caused by the disruption of the balance between the processes of the joint cartilage and subchondral bone degradation and synthesis, and it is very likely that this balance is more difficult to re-establish in older individuals.

The accuracy of the method of determining the rheological properties of the knee joint by means of the biorheometer may be distorted and affected by many factors. One of these factors is the individual proband's ability to relax during the investigation. Here, it is not only the relaxation of the investigated leg that is important, but the relaxation of the whole body. The biorheometer scans passive resistance during the knee joint motion, and if a proband is unable of relaxation, he/she either aids or impedes passive motion, which subsequently affects the whole evaluation of the rheological properties of the knee joint. The apparatus is highly sensitive and any muscular contraction of the body (talking,

coughing etc.) is displayed in the investigated motion (in the form of greater deflection amplitudes). The rheological properties of the joint are affected by the previous joint loading as according to Olejárová et al. (2003), cartilage changes its volume in relation to previous physical load. Prior to each measurement the probands were ordered a two-day rest without greater loading of their legs, but not everybody respected this rule. Although the rheological results may be affected by numerous factors, we assume that the results of this trial testify to the positive effect of pharmaceuticals from the SYSADOA group on gonarthrosis, both in the sense of improvement, and in the sense of stopping the progression of the disease as it was only in 18% of knee joints that rheological properties got worse.

CONCLUSION

This trial is a sort of pilot study indicating the trend of the effect of substances from the SYSADOA group on the rheological properties in knee joint osteoarthritis. The persistence of the effect even after the medication was discontinued was confirmed. To be able to make a more detailed and more accurate description a trial conducted on a longer-term basis and including more probands with a greater representation of various stages of osteoarthritis is necessary.

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GONARTRÓZA: BIOLOGICKÁ ODEZVA NA FARMAKA SKUPINY SYSADOA

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SOUHRN

Cílem studie bylo určení vlivu farmak ze skupiny SYSADOA na reologické vlastnosti kolenního kloubu s osteoartrózou a jak subjektivně vnímají tyto účinky pacienti. Studie se zúčastnilo 15 probandů (45–77 let) s diagnostikovanou osteoartrózou kolenního kloubu, kteří po dobu 13 týdnů užívali přípravek s obsahem látek ze skupiny SYSADOA. Hodnocení účinku farmak bylo provedeno pomocí indexu WOMAC a pomocí změn reologických vlastností kolenního kloubu, které byly naměřeny na speciálním přístroji – kolenním bioreometru. Účinky se porovnávaly po 13 týdnech užívání přípravku a poté po dalších 6 týdnech bez terapie. Dle indexu WOMAC došlo po 13 týdnech užívání ke zlepšení u 13 probandů z 15 (průměrná hodnota indexu se snížila z 25.5 na 17.8). Vysazení farmak se na indexu WOMAC nijak výrazně neprojevilo. Pomocí Wilcoxonova testu pro závislé soubory jsme zjistili statisticky významný rozdíl (tj. zlepšení) indexu WOMAC mezi 1. a 2, ale i 1. a 3. měřením. Výsledky reologického měření: při porovnání 1. a 3. měření, které ukazuje dlouhodobý trend účinků SYSADOA, se zlepšily reologické vlastnosti u 10 kolenních kloubů s osteoartrózou z 22, u 8 nedošlo ke změně a pouze u 4 gonartróz z 22 došlo ke zhoršení reologických vlastností.

Klíčová slova: gonartróza, reologie kolenního kloubu, SYSADOA, bioreometr, index WOMAC

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