

# Symptom-modifying effects of oral avocado/soybean unsaponifiables in routine treatment of knee osteoarthritis in Poland. An open, prospective observational study of patients adherent to a 6-month treatment

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## Abstract

**Objectives:** Observational studies provide insights into real-life situations. Therefore, we assessed the effects of oral avocado/soybean unsaponifiable (ASU) capsules on pain relief and functional ability in patients, while they were receiving a routine treatment for knee osteoarthritis (OA).

**Material and methods:** An open, prospective, observational 6-month study was conducted in 99 centers in Poland in a group of 4822 patients with symptomatic knee OA receiving one 300 mg ASU capsule/day as a routine medication. The patients had no diagnoses of other rheumatic diseases and were not treated with other symptomatic slow-acting drugs for osteoarthritis (SYSADOAs). Data on OA symptoms and therapy were collected from the initiation of ASU treatment (visit 0) and during 3 consecutive control visits performed every 2 months (visits 1–3). Functional Lequesne index, severity of joint pain of one symptomatic knee (Laitinen index and VAS), use of analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), adherence to treatment and adverse events were evaluated and recorded using electronic Case Report Forms.

**Results:** Four thousand one hundred and eighty-six patients (86.8%) attended all 4 visits. In 94.2% of patients (mean age 60.7 ±11.6 years SD, 73.4% female) at least one OA risk factor was identified. There was a significant improvement in functional ability between the last and baseline visits as evidenced by the median Lequesne index decreasing from 8 to 4 points ( $p < 0.001$ ). Measures of pain intensity also fell significantly ( $p < 0.001$ ) throughout the study: median Laitinen score decreased from 6 to 3 points, median pain at rest VAS – from 1.8 to 0 cm and median pain during walking VAS – from 5.6 to 1.9 cm. The significant differences were also noted between consecutive visits. The proportion of patients using analgesics and NSAIDs declined from 58.8% at the baseline visit to 24.9% at the last visit 3 ( $p < 0.001$ ). Defined daily dose of NSAIDs decreased significantly from 1 at the baseline visit to 0.67 at the visit 3. Severe adverse events associated with ASU treatment were not observed.

**Conclusions:** It was the first observational study in Poland evaluating the effects of routine knee OA treatment with oral ASU. Only a small group of patients (13.2%) treated with ASU discontinued the study. The majority of patients adherent to the ASU treatment for 6 months showed gradual alleviation of joint pain, improvement in functional ability and a significant reduction in NSAIDs intake.

**Key words:** osteoarthritis treatment, avocado/soybean unsaponifiables, NSAIDs-sparing effect.

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## Introduction

Osteoarthritis (OA) is one of the most common conditions affecting middle-aged to elderly people and decreasing patient's ability to perform activities of daily living. The disease is more often observed in women and overweight subjects. The most prevalent localisations of osteoarthritis are knee and hip joints [1, 2]. Despite the fact, that OA is common and causes pain, stiffness and progressive disability, there are only a few pharmacological treatment options for OA patients [2–6]. Most current, international and local guidelines strongly recommend both oral and topical NSAIDs, which are very frequently used worldwide [2–4, 7]. It is known, however, that the widespread treatment with oral NSAIDs is associated with a high number of adverse events [8]. Intra-articular treatment with glucocorticoids and hyaluronic acid is recommended as well by some expert groups [2, 4]. Short-term weak opioids and opioids are used to treat severe pain as an alternative option to NSAIDs [2].

Avocado/soybean unsaponifiables (ASU), glucosamine and chondroitin sulfate belong to a class of the *Symptomatic Slow-Acting Drugs for Osteoarthritis* (SYSADOA) which are recommended by European experts [2, 4]. There are studies suggesting, that some agents including ASU may have structure-modifying properties [5, 9], but the development of clinically meaningful *Structure-Modifying Drugs for Osteoarthritis* remains a challenge.

Avocado/soybean unsaponifiables are made up of unsaponifiable fractions of avocado and soybean extracts. The results of *in vitro* studies showed that ASU inhibits interleukin 1, increases the expression of TGF- $\beta$  in chondrocyte cultures and stimulates collagen synthesis in articular chondrocytes [10, 11]. Avocado/soybean unsaponifiables also reduces production of stromelysin, IL-6, IL-8 and PGE-2 [12], which implies that it might have anticatabolic and “chondroprotective” properties. A “chondroprotective” potential of ASU tablets in OA patients was observed in a double-blind 3-year trial by Maheu et al. [9]. In that study, ASU treatment slowed down radiographic progression of symptomatic hip osteoarthritis. It is clear however, that the clinical relevance of these findings requires further investigation, whereas symptomatic efficacy of ASU tablets in the treatment of osteoarthritis of the knee and hip was confirmed in several, randomized, double blind clinical studies [6, 13–15]. Interestingly, not only a persistent reduction of pain and improvements in Lequesne functional index (LFI) were observed in ASU arm, but also a valuable NSAIDs-sparing effect favored ASU treatment over placebo [6, 15]. All studies reported an excellent safety profile of ASU treatment.

While randomized, controlled clinical trials are performed in the strictly controlled circumstances and defined populations, real-life research can use observational designs to provide information on treatment effectiveness in actual clinical practice. Patients are simply “observed” while they are receiving a routine intervention. In real-world many factors (comorbidities, concomitant medication, etc.) may interfere with the efficacy and safety of the therapy. Therefore, we designed an open, prospective, observational study to determine the effects of ASU capsules on pain relief and functional ability in patients with symptomatic knee osteoarthritis adherent to a 6-month routine treatment.

## Material and methods

In 4822 recruited outpatients with mean age of 60.64 years, women constituted 74%. The study included patients with symptomatic knee OA. Each participant had only one selected knee joint evaluated. Patients were diagnosed, invited to participate and treated by one of 99 rheumatologists participating in this survey. Knee OA diagnosis was conducted by a specialist and based on clinical and radiographic judgement (with preference for ACR criteria) [16].

Invited patients were selected independently on values of Lequesne Functional index (LI) [17] at baseline, had no indications for surgery or have not been qualified for surgical treatment of knee OA. Clinical records of patients were collected anonymously by our research team.

The exclusion criteria for participation in the study were as follows:

- hypersensitivity to the active substances of piascledine or to any of the excipients,
- pregnancy or lactation,
- the scheduled surgery on the evaluated knee,
- intake of glucocorticoids (oral, i.v., i.m., i.a.) within a month prior to the enrolment,
- intake of any SYSADOA within 4 months before the enrolment,
- patients who do not agree on medication or participation in the survey,
- recent trauma or other affliction of the joints.

The 6-month observation was completed by 4186 patients (87%). Each patient was observed for four consecutive visits (the average duration of observation was 6 months). Data on OA symptoms and therapy effects was collected from the initiation of ASU treatment (visit 0) and during the next 3 consecutive control visits scheduled every 2 months (visits 1–3). The patients with symptomatic knee OA were treated with 300 mg ASU capsule (Piascledine)/day, as a routine medication in 99 centers (outpatient clinics) in Poland. The use of analgesics and NSAIDs for OA was allowed before and after the

entry to the study and the amount taken was carefully recorded during control visits. Data were recorded using an electronic case report form (eCRF) available to physicians via online application along with the methodology described in the study protocol. The study was approved by the local Bioethics Committee of the Regional Chamber of Physicians in Krakow (Nr 39/KBL/OIL/2013).

The data collected included information on:

- basic characteristics of patients,
- pharmacologic management of knee OA,
- analgesics and NSAIDs used for OA-related conditions within 7 days prior to initial visit,
- comorbidities and treatments,
- adverse reactions to ASU capsules (Piascledine),
- results from the assessment of the impact of symptomatic knee OA on selected aspects of patients' life,
- patient compliance and possible reasons for termination of ASU treatment,
- VAS and modified Laitinen pain intensity scores [18],
- functional impairment measured with the Lequesne Functional Index [17].

Pain assessment using the Laitinen scale and VAS was carried out during each of four visits. The Laitinen questionnaire assessing intensity of pain within last seven days comprises four questions concerning the severity and frequency of pain, analgesics intake, and reduced mobility. The final scores range from 0 to 16 points. Patients evaluated their pain at rest and while walking separately on the standard 10 cm horizontal line VAS (one end of the line represents *no pain at all* and the other represents *the worst pain imaginable*).

The Lequesne functional index [17] was employed to determine the level of functional impairment of patients. Based on the scores, patients were assigned to one of the following categories:

- 0 points: no functional impairment of joints,
- 1–4 points: mild functional impairment of joints,
- 5–7 points: moderate functional impairment of joints,
- 8–10 points: severe functional impairment of joints,
- 11–13 points: very severe functional impairment of joints,
- $\geq 14$  points: extremely severe functional impairment of joints.

The efficacy of ASU treatment was evaluated at each visit using pain measures (Laitinen scale and VAS), LFI, dose of NSAIDs and by summing up patients on analgesics and NSAIDs. Monitoring of patients compliance was based on patients reports and physician's judgment. Safety and tolerability of treatment were assessed according to the protocol for a routine procedure.

Statistical analysis was performed by independent statisticians in the Quality Audit House in Łódź and in HTA Consulting in Krakow. Differences in characteristics

between subjects were tested using the Mann-Whitney test (in case of continuous variables) or  $\chi^2$  test (in the case of proportions), or Fisher's exact test (in the case of proportions with a small number of observations). Since none of the continuous outcome parameters had a normal distribution (which was checked using the Shapiro-Wilk test) their values at consecutive visits (sequential) and between visit 0 and at each subsequent visit were compared using Wilcoxon test (for dependent samples) with Bonferroni correction. The intergroup comparisons between continuous variables were tested using the Kruskal-Wallis test with *post-hoc* nonparametric Mann-Whitney test. For the percentage of patients who used analgesics the McNemar test with Bonferroni correction was used. The difference in proportion of patients discontinuing analgesics and NSAIDs at given visit between subgroups was tested using  $\chi^2$  test. Changes in the LFI score categories between visits were analyzed using Stuart-Maxwell test with Bonferroni correction. The level of significance was set at  $p = 0.05$ . The calculations were performed using R statistical software.

## Results

Basic characteristics of patients recruited to the study are presented in the Table I. The study involved patients with various severity levels of symptomatic knee OA as measured with Lequesne functional index, including 54.9% of patients with more than moderate impairment of function (Table I). Of all patients, 96.1% indicated knee pain as a main symptom of osteoarthritis. According to physicians diagnosis, 75.5% of patients suffered from the primary form of the disease and 94.4% had at least one OA risk factor, and most often (71.9%) high BMI  $> 25$ . Prior to the study and at baseline, 58.8% of participants used analgesics or NSAIDs. Most often diclofenac (11.68%) or meloxicam (9.6%) were reported, and paracetamol in 5.9% of patients (data not shown).

4186 patients attended all four visits as outlined in the study protocol and were included for the final efficacy analysis of ASU treatment. A small percentage of patients ( $n = 636$ , 13.19% of all included patients) discontinued their participation in the study (did not show up) at a given visit (visit 1 – 6.37%, visit 2 – 3.66%, visit 3 – 2.94%). In the vast majority of cases (above 90%) there were no available data on reasons for withdrawal from the survey. Only 56 patients provided reasons for ASU treatment discontinuation. Almost 50% simply did not want to continue prescribed medication, 34% reported treatment failure, 4 discontinued treatment because of adverse events (diarrhea, nausea, flatulence), in two cases kidney cancer surgery was performed, in two further cases the price of

**Table I.** Basic characteristics of patients selected into the study;  $N = 4822$ 

Feature		N or mean (SD)	% or median (min-max)
Age [years]		60.64 (11.59)	61 (18–95)
Sex	Female	3565	73.93%
	Male	1257	26.07%
BMI	Underweight	29	0.60%
	Normal weight	1322	27.42%
	Overweight	2276	47.20%
	Obesity	1194	24.76%
Symptoms of osteoarthritis	Joint pain reported at the selected knee	4634	96.10%
	Reduced mobility of the knee with the secondary atrophy of surrounding muscles	901	18.69%
	Thickening and deformation of bone contours in the region of the knee	1482	30.73%
	Tenderness on palpation of the knee	1857	38.51%
	Fine crepitus during knee movement	2723	56.47%
	Exudation in the joint	329	6.82%
Risk factors for osteoarthritis of the knee	Age > 65 years old	1649	34.2%
	Excessive weight (BMI > 25)	3470	71.96%
	Mechanical factors	2019	41.87%
	Proprioceptive disturbances in the evaluated limb	85	1.76%
	Other	150	3.11%
	No risk factors	270	5.60%
	At least one risk factor	4552	94.40%
Form of the disorder	Primary	3641	75.51%
	Secondary	1181	24.49%
SYSADOA over 4 months prior to visit 0	Glucosamine sulfate	328	6.80%
	Chondroitin sulfate	131	2.72%
	Avocado and soybean unsaponifiables	31	0.64%
	Diacerein	0	0.00%
	Hyaluronic acid joint injections 6 months prior to the study	101	2.09%
Physiotherapy over 2 weeks prior to visit 0		1296	26.88%
mean $\pm$ SD and median values of Lequesne scores at visit 0		8.43 (4.69)	8 (0–24)
Lequesne score at visit 0 (categories)	No impairment	160	3.32%
	Mild impairment	964	19.99%
	Moderate impairment	1041	21.59%
	Severe impairment	1038	21.53%
	Very severe impairment	904	18.75%
	Extremely severe impairment	715	14.83%

the medicine was deemed unacceptable and in one case complete resolution of pain occurred.

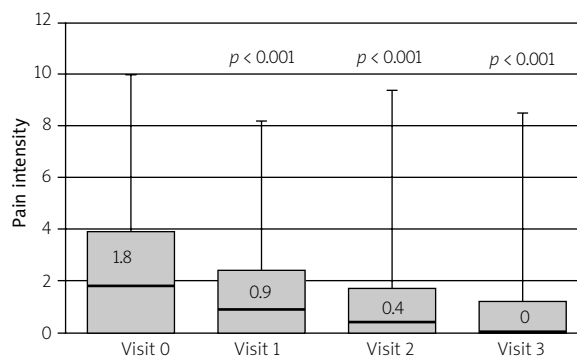
It was an open study and physician's assessment of patient compliance was based on the question: *Do relevant premises exist on the basis of which it may be concluded that*

*the patient is non-compliant?* The physician could choose one of the following answers: *Yes, It is difficult to say*, or *No*. On the basis of the answers to the aforementioned question, patients were divided into compliant ( $N = 2973$ ; 71.02%) and not fully compliant ( $N = 1213$ ; 28.98%) groups.

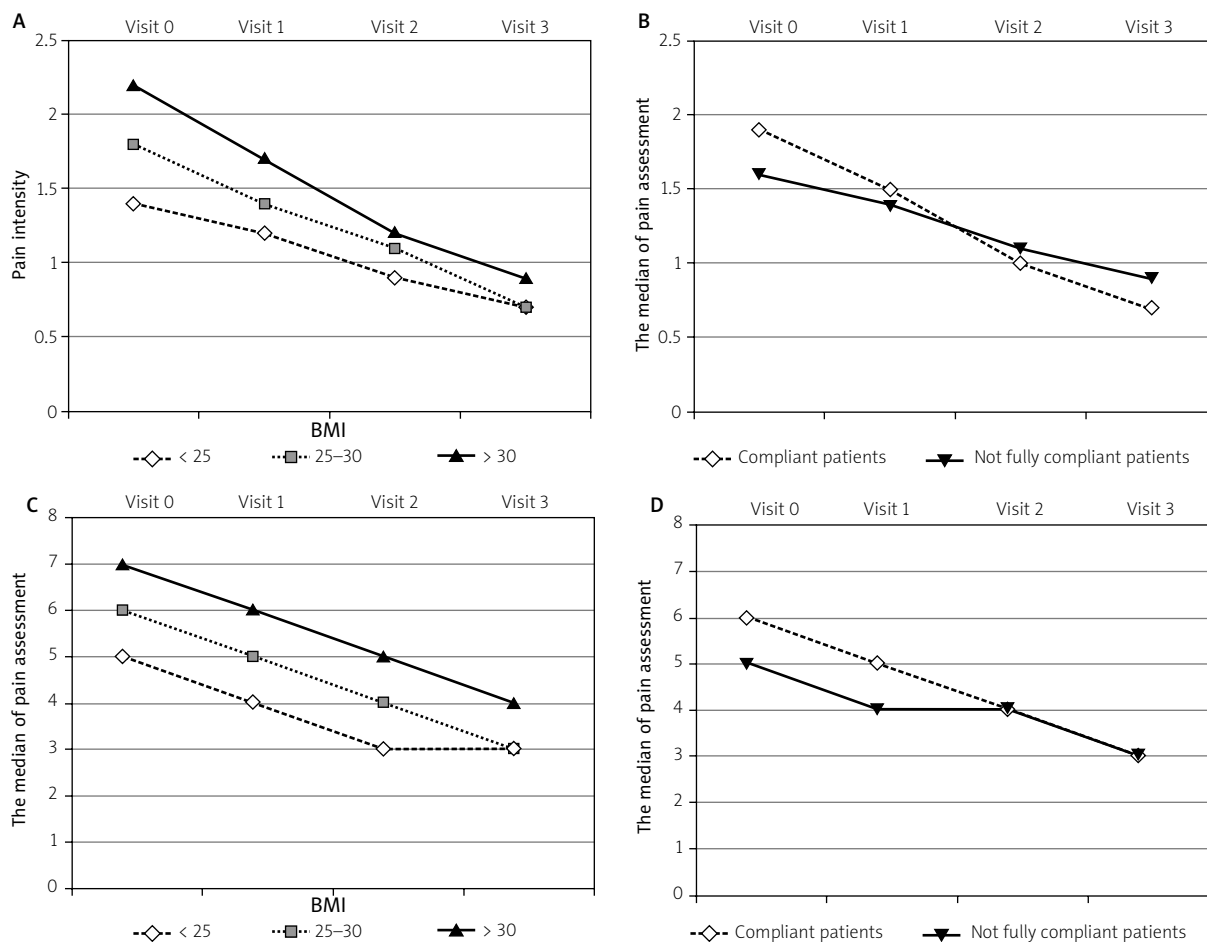
Patient self-assessment of pain at rest measured with the VAS at consecutive visits indicates a significant decrease in pain intensity (Fig. 1). At least 50% of patients reported “no pain” at the last visit.

Treatment with oral ASU was equally effective in women and in men. The greatest pain at baseline was reported by patients aged over 65 years (data not shown) and by obese patients. Interestingly, a reduction in pain intensity was greater ( $p < 0.001$ ) in obese patients compared to normal-weight subjects (Fig. 2A).

In compliant a patients significantly greater decrease in VAS intensity of pain at rest was noted at subsequent visits vs. visit 0 compared to not fully compliant subjects  $p < 0.001$  (Fig. 2B).



**Fig. 1.** Assessment of pain at rest. The figure presents the significance of differences between median VAS values (Q1–Q3, min–max) at a given visit vs. visit 0 tested with Wilcoxon test ( $n = 4186$ ).



**Fig. 2.** Pain at rest during ASU treatment measured with the VAS and with Laitinen scale in the subgroups of patients: A) VAS values in BMI subgroups, B) VAS values in the compliant and not fully compliant patients, C) Laitinen scale values in BMI subgroups, D) Laitinen scale values in the compliant and not fully compliant patients.

Figures 2A and 2C present medians of pain assessment scores at consecutive visits in patients by BMI subgroups (2A VAS, 2C Laitinen scale). Figures 2B and 2D present medians of pain assessment scores at consecutive visits in the subgroups of compliant and not fully compliant patients (2B VAS, 2D Laitinen scale) ( $n = 4186$ ).

**Table II.** Pain measured with the Laitinen scale – individual items scores ( $N = 4186$ )

Visit	The Laitinen scores					Wilcoxon tests (the Bonferroni-corrected $p$ values)			
	Median	Q1	Q3	Min	Max		Sequentially*		vs. visit 0
<b>Pain intensity</b>									
Visit 0	2	1	2	0	4	$p < 0.001$	–	–	–
Visit 1	1	1	2	0	4		$p < 0.001$	–	$p < 0.001$
Visit 2	1	1	1	0	3	–		$p < 0.001$	$p < 0.001$
Visit 3	1	1	1	0	3	–	–		$p < 0.001$
<b>Frequency of pain</b>									
Visit 0	2	1	2	0	4	$p < 0.001$	–	–	–
Visit 1	1	1	2	0	4		$p < 0.001$	–	$p < 0.001$
Visit 2	1	1	1	0	4	–		$p < 0.001$	$p < 0.001$
Visit 3	1	1	1	0	4	–	–		$p < 0.001$
<b>Use of analgesics and NSAIDs</b>									
Visit 0	1	1	2	0	4	$p < 0.001$	–	–	–
Visit 1	1	0	1	0	4		$p < 0.001$	–	$p < 0.001$
Visit 2	1	0	1	0	4	–		$p < 0.001$	$p < 0.001$
Visit 3	0	0	1	0	3	–	–		$p < 0.001$
<b>Reduced mobility</b>									
Visit 0	1	1	2	0	4	$p < 0.001$	–	–	–
Visit 1	1	0	1	0	4		$p < 0.001$	–	$p < 0.001$
Visit 2	1	0	1	0	4	–		$p < 0.001$	$p < 0.001$
Visit 3	1	0	1	0	4	–	–		$p < 0.001$

\*Comparison of the results obtained at two consecutive

Table II shows the baseline values of individual items included in the Laitinen scale of pain and their changes at consecutive visits. Differences between subsequent visits as well as improvement in each of four items (pain intensity, frequency of pain, use of analgesics and NSAIDs and reduced mobility) were statistically significant compared to visit 0.

At subsequent visits a decrease in scores of knee pain intensity was noted. Differences in scores of Laitinen pain intensity between subsequent visits proved to be statistically significant both, for comparison of each two consecutive visits and in relation to visit 0. This indicates positive impact of ASU treatment on alleviating knee pain in patients with knee OA. The medians of the scores fell by 50% (from 6 at visit 0 to 3 score points at visit 3) during three subsequent visits.

Analysis in subgroups shows, that, similarly to VAS results, the most intense pain was reported by patients aged over 65 years (data not shown) and by obese patients (Fig. 2C).

In the compliant patients significantly greater decrease in intensity of knee pain was observed at subse-

quent visits compared to visit 0 vs. not fully compliant subjects. An improvement in pain intensity in both subgroups at visit 3 vs. the baseline visit was statistically significant with  $p$  value  $< 0.001$  (Fig. 2D).

Significant decrease in knee pain during walking reported by patients and measured with the VAS was noted at each visit as well. At visit 0 the median score was 5.6 points (the median score for “pain at rest” at visit 0 was 1.8 points) and diminished to 1.9 points at last visit. The decrease proved to be statistically significant both, for comparison of each two consecutive visits and in relation to visit 0 (data not shown).

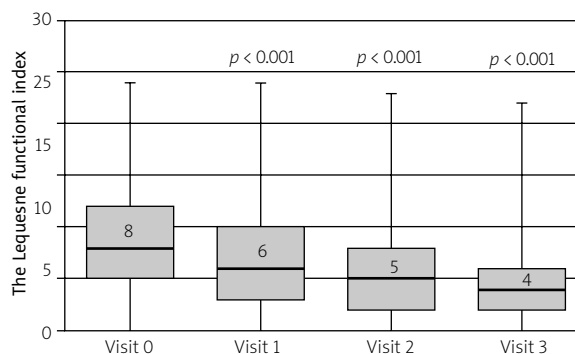
The median value of the LFI decreased significantly at each visit and fell by 50% at the last visit vs. visit 0 (from 8 to 4 points), what indicates functional ability improvement during ASU treatment (Fig. 3).

The percentages of patients with severe, very severe, and extremely severe functional impairment of the knee joint measured with the LFI decreased significantly at each subsequent visit (from 56% at baseline to 18% at visit 3) as shown in Table III. Correspondingly, the per-

centage of patients with mild and “no impairment” increased.

The greatest functional impairment was seen in patients aged over 65 years, obese subjects, and in women. Functional improvement was observed in all subgroups: female, male > 65 years and < 65 years of age with the greatest change in relation to the baseline in population of overweight patients (data not shown). Analogously to outcomes of pain scores analysis, functional improvement measured with the LFI at successive visits was significantly higher in the compliant vs. not fully compliant patients (data not shown).

The careful monitoring of medicine intake related to OA was performed during the entire survey. At baseline 58.8% of patients (N = 2462) used analgesics or NSAIDs (the list of medicines and doses declared are not shown). The percentage of patients using NSAIDs decreased between visits, reaching 25% by visit 3 (Fig. 4A). The reduction in the number of patients taking analgesics or NSAIDs was statistically significant (both for comparison of each two consecutive visits and in relation to visit 0).



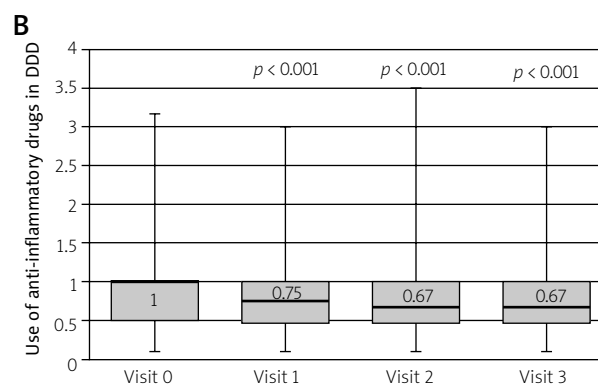
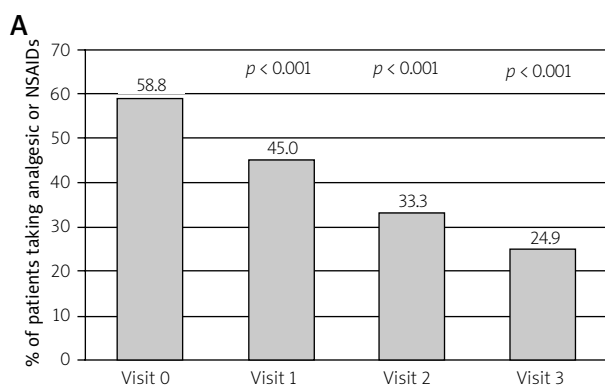
**Fig. 3.** Functional impairment measured with the Lequesne index – overall assessment during ASU treatment (n = 4186)\*.

\*Figure presents the significance of difference between medians of the Lequesne index values at a given visit vs. visit 0 tested with Wilcoxon test.

The average dosage of NSAIDs in patients included in the final analysis was expressed as the DDD of a given drug. Two thousand two hundred and seventy-two patients reported taking NSAIDs along with a dosage

**Table III.** The distribution of the categories of functional impairment measured with the Lequesne index at the subsequent visits

Visit	Functional impairment						Stuart-Maxwell test with Bonferroni correction		
	No impairment (%)	Mild (%)	Moderate (%)	Severe (%)	Very severe (%)	Extremely severe (%)	Sequentially	vs. visit 0	
0	1.60	20.04	22.65	21.33	19.35	15.03	–	–	
1	3.92	30.41	24.25	22.62	13.16	5.64	p < 0.001	–	
2	7.38	38.68	26.45	16.70	7.41	3.39	–	p < 0.001	
3	11.63	44.19	26.04	11.25	4.73	2.15	–	p < 0.001	



**Fig. 4.** Use of analgesics and NSAIDs – overall assessment.

Figure 4A presents statistical significance of differences between proportions of patients using analgesics and NSAIDs at a given visit and at visit 0. Statistical analysis was performed with McNemar test. Figure 4B shows the use of NSAIDs in defined daily dosage (DDD) median values (only patients taking NSAIDs at a given visit). The significance of differences at a given visit vs. visit 0 were tested with Wilcoxon test.

at visit 0. In this population the median DDD was 1,0 at visit 0. The median DDD of NSAIDs declined to 0.67 at visit 2 and remained at the same level at visit 3. Significant changes are presented in Figure 4B.

In the subgroups, the highest consumption of those drugs was reported in patients aged 65 and older, in obese and in female patients. The percentage of not fully compliant patients who used analgesics and NSAIDs was significantly higher than in compliant patients (data not shown).

In all analyzed subgroups significant decrease in the percentage of patients taking analgesics and NSAIDs at each control visit was observed. Compliance had no impact on the baseline DDD of NSAIDs or its decrease during pharmacotherapy with ASU capsules.

The study demonstrated that treatment with ASU capsules (Piasclidine 300 mg/day) was safe. Adverse reactions to Piasclidine occurred in a very small number of patients: 5 patients had diarrhea, 2 elevated blood pressure and headache, 3 experienced nausea, flatulence or abdominal pain. Serious adverse reactions associated with ASU treatment were not reported.

## Discussion

In our real life 6-month study, physicians reported gradual decrease of pain related to OA in the selected knee in majority of ASU-treated patients. Statistical analysis of data obtained, confirmed significant clinical improvement measured with the VAS and Laitinen scale. The randomized, double blind, placebo-controlled studies [6, 13, 15] show that efficacy parameters including functional LFI improved just after the first 2–4 months of treatment. In our study superior efficacy of ASU treatment was observed after 6 months (visit 3). At least 50% of patients reported “no pain” at the last visit and the median of the Laitinen scores fell by 50% during visits 1–3. Clinical improvement was reported in all subgroups of patients including the compliant and even not fully compliant patients. Analgesics and various NSAIDs were used more or less regularly by 58.8% of patients (real life study) at the visit 0. About 40% of patients with symptomatic OA did not use NSAIDs because of safety concerns, contraindications or ability to tolerate pain without medication. The percentage of patients using NSAIDs decreased during ASU treatment by over 50% and reached 25% by visit 3. Defined daily dosage of NSAIDs among patients using NSAIDs was also significantly reduced. It should be emphasized, that a valuable NSAID-sparing effect is providing convincing evidence of symptomatic efficacy of ASU treatment. This beneficial effect of ASU may contribute to the risk reduction of all adverse events associated with NSAIDs administration

[8]. The very similar NSAID-sparing effect was reported previously in 3-month and 6-month randomized, placebo-controlled trials [6, 13, 15]. Observational studies are characterized by the lack of intervention in treatment decisions [19]. Analgesics, NSAIDs and treatment with Piasclidine were prescribed by rheumatologists based on patients' needs and clinical judgment. At any time patient could discontinue prescribed medication or ask for other form of therapy. Only a small percentage of patients withdrew from the study, reinforcing – like in the previous clinical trial [6] – the robustness of the results.

Our prospective, observational study evaluating the effects of the routine OA treatment with ASU was the first in Poland and one of the largest in the world. Like in other real-life observational studies [19] our goal was not only to complement classical, randomized, placebo-controlled trials, but most of all to assess efficacy of ASU treatment during a usual care of OA provided by Polish rheumatologists. The survey was performed in a large but heterogeneous group of patients including patients with the primary (Table I) and the secondary (24%) forms of knee OA with different levels of disease severity. Many internal and external factors could interfere with ASU therapeutic efficacy, because of comorbidities, concomitant medication, patient's weight, age, profession and physical activity. Diagnosis of knee OA based on X-ray and physician's judgment, prescribed treatment and monitoring of therapy were performed by 99 trained and instructed rheumatologists, however, all these procedures were not strictly controlled by the research team. Investigators simply compiled anonymous data submitted by physicians. Another weakness of this study was lack of either placebo or comparator drugs. It is clear, that the design of our study does not fulfill all recommendations from the current guidelines on clinical investigation of medicinal products used in the treatment of osteoarthritis [<http://www.ema.europa.eu>] [20]. Overlooking issues of a study design, the treatment effect was large and we were able to show a strong evidence of ASU efficacy during a “usual care” of OA. Interestingly, an improvement of knee function and a decrease in pain intensity in both groups of the compliant and not fully compliant patients at visit 3 vs. the visit 0 were statistically significant, and a better clinical effect was observed in the population of compliant patients as expected.

The results obtained in the survey confirm the efficacy and safety of oral ASU as a SYSADOA. However, we cannot exclude the possibility that assessment of the effectiveness of treatment with ASU might be slightly quantitatively overrated. First of all, we should consider a phenomenon similar to the placebo effect called “experimental subordination” [21] as well as the “Haw-



thorne effect”, whereby a patient’s performance changes because a person is being studied [22]. Some patients driven by kindness and gratitude for physician’s efforts and attention tend to exaggerate benefits of treatment. Moreover, spontaneous improvements and fluctuations of symptoms in osteoarthritis cannot be neglected [23]. In our opinion and according to other authors [24], phenomena similar to the placebo effect or “subordination – politeness” effects decrease with increasing sample size and if the treatment effect is large [19]. The treatment effect in our group of 4186 patients was large and detectable in all evaluated parameters including decreased use of analgesics and NSAIDs. Some differences in outcomes observed between subgroups of patients (obese vs. not obese, 65 years of age and older, not fully compliant vs. compliant) deny the existence of any substantial placebo-like effect or subordination phenomenon. Since overweight or obesity contributes to the development of knee OA and strengthens clinical symptoms of the disease [25], it seems to be expected, that our obese patients reported the greatest pain at baseline and a reduction of pain intensity during treatment not only due to being polite. In addition, were “not fully compliant” patients “subordinated”?

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In summary, we conclude, that in our real-life study we were able to confirm, that the vast majority of patients adherent to the ASU treatment for 6 months showed gradual and substantial alleviation of joint pain, functional ability improvement and the reduction in NSAIDs intake. The results of our survey support recommendations [2] indicating the usefulness of ASU in a routine symptomatic treatment of knee OA.

### Acknowledgements

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A full list of the rheumatologists who contributed to this survey and generated the data will be available at <http://www.spartanska.pl/reumatologia>.

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