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SHORT COMMUNICATION

The Long-Term Safety of S-Flurbiprofen Plaster for Osteoarthritis Patients: An Open-Label, 52-Week Study

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Abstract

Background and objectives The newly developed S-flurbiprofen plaster (SFPP) is a tape-type patch that shows innovative percutaneous absorption. This study was designed to evaluate the safety of a long-term 52-week SFPP application to osteoarthritis (OA) patients.

Methods This was a multi-center, open-label, uncontrolled prospective study that included 201 OA patients. SFPP at 40 mg/day was applied to the site of pain in 101 patients and at 80 mg/day (2 patches) in 100 patients at a total of 301 sites for 52 weeks. The affected sites assessed included the knee (192), lumbar spine (66), cervical spine (26), and others (17). Drug safety was evaluated by medical examination, laboratory tests, and examination of vital signs. Efficacy was evaluated by the patient's and clinician's global assessments and clinical symptoms.

Results Most patients (80.1 %) completed the 52-week SFPP application. The majority of drug-related adverse events (AEs) included mild dermatitis at the application sites and occurred in 46.8 % of the sites. No photosensitive dermatitis was observed. Systemic AEs occurred in 9.0 % of the patients; a serious AE (gastric ulcer hemorrhage) occurred in one patient. No clinically significant changes in the laboratory tests and vital signs were observed. The efficacy evaluation showed an improvement from 2 weeks after the SFPP application, which continued during the 52 weeks' treatment.

Conclusions No apparent safety concerns were observed, even during the long-term SFPP application. Therefore, SFPP could be an additional pharmacotherapy in OA treatment.

Key Points

The S-flurbiprofen plaster (SFPP) with an innovative percutaneous absorption was developed for the treatment of osteoarthritis (OA) commonly seen in the elderly.

Long-term 52-week application of SFPP was well tolerated in the OA patients, who had a mean age of 66.3 years.

1 Introduction

Osteoarthritis (OA) is strongly linked to aging, and characterized by chronic pain, inflammation, and impaired overall functioning, significantly affecting quality of life [1, 2]. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the pharmacotherapy of OA [3]. Although oral NSAIDs in particular have been used as first-line therapy for many years, concerns about adverse reactions related to class effects of NSAIDs such as gastrointestinal injuries and related hemorrhage are increasingly seen in the elderly patient [4–6]

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In recent years, the efficacy of topical NSAIDs is increasingly recognized and, currently, several clinical practice guidelines highly recommend topical NSAIDs over oral formulations [7–12].

S-flurbiprofen plaster (SFPP) is a tape-type patch that contains S-flurbiprofen (SFP)the active ingredient of flurbiprofen (FP), which has a potent cyclooxygenase (COX)-inhibitory effect—and has been developed to achieve improved percutaneous absorption of SFP and its penetration into deep tissues. A clinical pharmacology study of SFPP in knee OA patients showed high penetration of SFP into the synovial tissue [13]. In addition, 2-week randomized controlled studies demonstrated the superior clinical efficacy of SFPP over that of the placebo [14]) and an FP patch [15], which suggested that SFPP might be useful for the short-term treatment of OA.

Systemic exposure to SFP following the application of 80 mg/day of SFPP (two patches/day) for 7 days was estimated to be comparable to that of oral formulations of FP [14]. Adverse reactions considered as a class effect of NSAIDs include gastrointestinal, renal, and cardiac disorders [16]. These adverse reactions rarely occurred in the 2-week SFPP studies [14, 15]. However, in clinical practice, topical NSAIDs are commonly used as long-term treatments, including their intermittent use in several OA treatment paradigms. Thus, here, we evaluated the safety of SFPP applied to OA patients at doses up to 80 mg/day for 52 weeks.

2 Method

2.1 Study Design and Participant Selection

This was a phase III, multi-center, open-label, uncontrolled prospective study conducted between May 2012 and December 2013 at 11 study sites in Japan. The Declaration of Helsinki and Good Clinical Practice guidelines were followed throughout the study. The protocol and informed consent form were approved by the institutional review board at each participating study site. (Trial registration: JapicCTI-121840.)

Osteoarthritis patients with moderate or severe pain in a major joint, and who were ≥20 years of age and had provided written informed consent were included. The diagnosis of OA was based on both radiographic evidence and clinical symptoms determined by the clinician.

Patients who had three or more symptomatic OA sites were excluded. Patients were also excluded if they had diseases or required treatments that might affect the safety or efficacy assessment of NSAIDs, i.e., complication of gastrointestinal ulcers or other joint diseases such as rheumatoid arthritis. In principle, the concomitant use of oral NSAIDs and other analgesics as well as that of antiulcer and gastrointestinal agents was prohibited.

SFPP is a tape-type patch, 10 cm × 14 cm, containing 40 mg of SFP per patch (Tokuhon Corporation, Tokyo Japan). The condition of the OA sites from the whole body were assessed by a clinician, and one or two painful sites were selected for the study. SFPP was applied at a daily dose of one patch per site to be assessed for 52 weeks. The site to be assessed was not changed during the study.

2.2 Study Assessments

Drug safety was assessed by medical examination by the clinician; blood and urine tests (blood cell count, hepatic function, and renal function); and blood pressure and pulse rate at Day1 (before the application; baseline), 2 and 4 weeks after the application, and every 4 weeks thereafter until 52 weeks.

The relationship between SFPP and an adverse event (AE) was assessed using a 4-point scale ("related," "probably related," "possibly related," and "not related") by the clinician. All the "related," "probably related," and "possibly related" scores were defined as "Drug-related AE." In addition, the severity of each AE was determined on a 3-point scale (mild = treatment not required or daily living not affected, moderate = some treatment required or daily living affected, and severe = particular emergency treatment required or daily living complicated). Since SFPP is a topical formulation, AEs were assessed separately for local AEs at the application sites (skin symptoms) and systemic AEs, except those at the application sites.

The efficacy of SFPP in the outpatients was assessed by the patient's and clinician's global assessments as well as clinical symptoms (CS) at 2 weeks before the application (screening), Day1 (before the application; baseline), 2 and 4 weeks after the application, and every 4 weeks thereafter until 52 weeks. The patient's and clinician's global assessments consisted of a 5-point scale (marked, moderate, mild, not changed, and worse). The severity of CS was assessed for seven parameters (exercise pain, rest pain, local tenderness, swelling, local heat sensation, limitation of range of motion, and disability of activities of daily living [ADL]) on a 4-point scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe), which allowed for the calculation of the total clinical symptoms (tCS) score.

2.3 Statistical Analysis

The planned sample size was set to 100 patients in each treatment group to mainly evaluate drug safety during the long-term application of SFPP.

All analyses were carried out according to the pre-specified statistical analysis plan using SAS® 9.2. The significance level was set at 5 % (two-sided). Missing data at the end of the study period were imputed using the last observation carried forward (LOCF) method; missing data at other time-points were not imputed.

The safety analyses were based on the safety population that comprised all the patients who had applied SFPP at least once and of whom safety data had been obtained after the SFPP application. The number and percentage of patients who had an AE were summarized using the Medical Dictionary for Regulatory Activities (MedDRA/J ver.16.1) terminologies (system organ class and preferred term). Continuous outcomes in the laboratory tests and vital signs were analyzed using a paired *t* test.

Efficacy analyses were based on the full analysis set (FAS) that comprised all the patients who had applied SFPP at least once and for whom the efficacy data had been obtained after the SFPP application. For the efficacy outcomes, the descriptive statistics were summarized by the treatment group and each time-point, and the tCS was analyzed using a paired *t* test.

Table 2 Sites assessed

Site	Total $n = 301$	SFPP 40 mg $n = 101$	SFPP 80 mg $n = 200$
Single sites, *n* (%)			
Knee	192 (63.8)	46 (45.5)	146 (73.0)
Lumbar spine	66 (21.9)	39 (38.6)	27 (13.5)
Cervical spine	26 (8.6)	11 (10.9)	15 (7.5)
Shoulder	9 (3.0)	3 (3.0)	6 (3.0)
Elbow	3 (1.0)	1 (1.0)	2 (1.0)
Hip	2 (0.7)		2 (1.0)
Hallux	1 (0.3)	1 (1.0)	
Thoracic spine	1 (0.3)		1 (0.5)
Ankle	1 (0.3)		1 (0.5)

	SFPP 80 mg $n = 100$
Combination sites, *n* (%)	
Both knees	66 (66.0)
Lumbar and cervical spine	12 (12.0)
Knee and lumbar spine	11 (11.0)
Others	11 (11.0)

3 Results

3.1 Patient Disposition

The patient demographic characteristics are listed in Table 1. The study included 201 OA patients. The study population comprised 50 males and 151 females aged 66.3 ± 11.8 years (mean ± standard deviation) and a body mass index (BMI) of 24.76 ± 3.86 kg/m^2. The sites assessed are given in Table 2. A total of 301 sites were assessed for the 201 patients since two sites had to be assessed for the 100 patients in SFPP 80-mg group. The site with the most assessments was the knee ($n = 192$, 63.8 %) followed by the lumbar spine ($n = 66$, 21.9 %). The combination of both knees was the most common site combination in the SFPP 80-mg group ($n = 66$, 66.0 %).

A total of 201 patients received the study drug (SFPP), of whom 161 completed the study (Fig. 1). Fourteen patients discontinued from the study as the result of an AE. The application periods of SFPP and the patient disposition per treatment group for each period are listed in Table 3. Of the 201 patients, 161 applied SFPP for 52 weeks or longer. Of these, 92.5 % (186/201 patients) had more than 80 % application rate (the actual total number of patches during the application period/the prescribed number of patches during the application period).

3.2 Safety Evaluations

Skin symptoms that occurred at least once during each application period were observed at 141 of the 301 application sites (Table 4). These included application site

Table 1 Patient demographic characteristics

	Total $n = 201$	SFPP 40 mg $n = 101$	SFPP 80 mg $n = 100$
Age (years), mean ± SD	66.3 ± 11.8	66.2 ± 12.1	66.4 ± 11.5
Gender, *n* (%)			
Male	50 (24.9)	29 (28.7)	21 (21.0)
Female	151 (75.1)	72 (71.3)	79 (79.0)
Weight (kg), mean ± SD	60.46 ± 11.55	59.11 ± 10.54	61.82 ± 12.38
BMI (kg/m^2), mean ± SD	24.76 ± 3.86	24.21 ± 3.06	25.32 ± 4.48

SD standard deviation, *BMI* body mass index

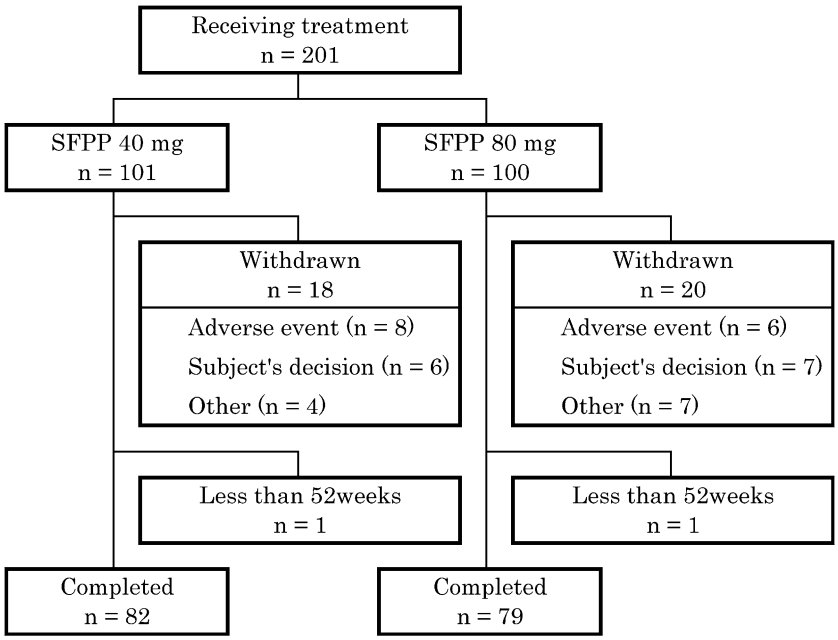

Fig. 1 Patient disposition. *SFPP* S-flurbiprofen plaster

Table 3 Application periods for the S-flurbiprofen plaster (SFPP)

Application periods (weeks), *n* (%)	All subjects *n* = 201	SFPP 40 mg *n* = 101	SFPP 80 mg *n* = 100
0–11	7 (3.5)	4 (4.0)	3 (3.0)
12–23	15 (7.5)	7 (6.9)	8 (8.0)
24–35	11 (5.5)	5 (5.0)	6 (6.0)
36–51	7 (3.5)	3 (3.0)	4 (4.0)
52–	161 (80.1)	82 (81.2)	79 (79.0)

Table 4 Drug-related adverse events at the application sites (skin symptoms)

	Total *n* = 301	Knee *n* = 192	Lumbar spine *n* = 66	Cervical spine *n* = 26	Other[a] *n* = 17
Drug-related AEs, *n* (%)	141 (46.8)	94 (49.0)	30 (45.5)	11 (42.3)	6 (35.3)
Application site dermatitis	88 (29.2)	62 (32.3)	14 (21.2)	6 (23.1)	6 (35.3)
Application site eczema	32 (10.6)	21 (10.9)	8 (12.1)	3 (11.5)	
Application site erythema	17 (5.6)	10 (5.2)	4 (6.1)	3 (11.5)	
Application site pruritus	10 (3.3)	2 (1.0)	6 (9.1)	2 (7.7)	
Application site discoloration	3 (1.0)	3 (1.6)			

AEs adverse events

[a] Shoulder, elbow, hip, hallux, thoracic spine, and ankle

dermatitis, eczema, and erythema, and were mild and moderate in severity in 126 and 15 sites, respectively. None of the AEs at the sites were rated as severe. AEs at 128 sites were resolved by interruption of SFPP or by drug treatment, which allowed for study continuation until the end of the study period. The AEs at the remaining 13 sites necessitated discontinuation of the study; however, these AEs were resolved after the study discontinuation.

Systemic drug-related AEs occurred in 18 of the 201 patients (Table 5). Gastrointestinal disorders, such as gastritis and abdominal discomfort, were observed in nine patients and laboratory abnormalities, such as increased blood urea, were observed in seven patients. In addition, hepatic function disorder, colon adenomatous polyp, and generalized dermatitis were observed in one patient each. Among the nine patients in whom gastrointestinal disorders

were observed, severe gastric ulcer hemorrhage was observed in one patient, whereas the symptoms were mild in the other patients. The patient with the gastric ulcer hemorrhage complication underwent endoscopic hemostasis because of the occurrence of nausea and hematemesis at 129 days after the SFPP application. The patient discontinued the study at 22 days after symptom onset, and received treatment with proton pump inhibitors. The symptoms were resolved 81 days thereafter. Although gastric ulcer hemorrhage was observed in the patient suffering from atrophic gastritis due to a *Helicobacter pylori* infection, a possible relation between SFPP and gastric ulcer hemorrhage could not be excluded.

3.3 Laboratory Tests and Vital Signs

The blood urea nitrogen (BUN) levels increased in the two treatment groups 2 weeks after the SFPP application compared with those at baseline; however, they stabilized thereafter. The maximum mean change from baseline was 1.91 mg/dL for the SFPP 40-mg group (baseline, 15.11 mg/dL) and 1.89 mg/dL for the SFPP 80-mg group (baseline, 16.12 mg/dL). The creatinine levels increased 44 weeks after the SFPP application compared with those at baseline. The maximum mean change from baseline was 0.019 mg/dL for the SFPP 40-mg group (baseline, 0.678 mg/dL) and 0.022 mg/dL for the SFPP 80-mg group (baseline, 0.678 mg/dL) (Table 6).

Statistically significant changes were found in some of the laboratory parameters and vital signs assessed; however, these changes were not clinically significant.

3.4 Efficacy Evaluations

In the patient's global assessment (Fig. 2a), the score "marked" appeared at 2 weeks after the SFPP application,

Table 5 Systemic adverse events

	Total $n = 201$	SFPP 40 mg $n = 101$	SFPP 80 mg $n = 100$
AE	168 (83.6)	82 (81.2)	86 (86.0)
Drug-related AE	18 (9.0)	6 (5.9)	12 (12.0)
SAE	8 (4.0)	3 (3.0)	5 (5.0)
Drug-related SAE[a]	1 (0.5)	1 (1.0)	
Drug-related AEs			
Gastrointestinal disorders			
Gastritis	4 (2.0)	1 (1.0)	3 (3.0)
Abdominal discomfort	2 (1.0)	1 (1.0)	1 (1.0)
Gastric ulcer hemorrhage[a]	1 (0.5)	1 (1.0)	
Gastric ulcer	1 (0.5)		1 (1.0)
Duodenal ulcer	1 (0.5)		1 (1.0)
Gastro-esophageal reflux disease	1 (0.5)		1 (1.0)
Abdominal pain upper	1 (0.5)		1 (1.0)
Dyspepsia	1 (0.5)		1 (1.0)
Investigations			
Blood urea increased	4 (2.0)	1 (1.0)	3 (3.0)
Blood creatinine increased	1 (0.5)	1 (1.0)	
Blood urine present	3 (1.5)	1 (1.0)	2 (2.0)
Protein urine present	1 (0.5)		1 (1.0)
Occult blood	1 (0.5)		1 (1.0)
Hepatobiliary disorders			
Hepatic function abnormal	1 (0.5)		1 (1.0)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)			
Colon adenoma	1 (0.5)		1 (1.0)
Skin and subcutaneous tissue disorders			
Dermatitis	1 (0.5)	1 (1.0)	

Values are given as *n* (%)

AE adverse event, *SAE* serious adverse event

[a] Gastric ulcer hemorrhage was a drug-related SAE

and the percentage of "marked" increased continuously until 52 weeks after the SFPP application, reaching 44.2 % (72/163 patients; 45.8 and 42.5 % for the SFPP 40-mg and 80-mg groups, respectively). The percentage of the improvement (the sum of "marked" and "moderate") was 72.4 % (118/163 patients; 73.5 % and 71.3 % for the SFPP 40- and 80-mg groups, respectively) at 52 weeks after the SFPP application.

Similarly, in the clinician's global assessment (Fig. 2b), the score "marked" appeared at 2 weeks after the SFPP application, and the percentage of "marked" increased continuously until 52 week after the SFPP application, reaching 46.0 % (75/163 patients; 45.8 % and 46.3 % for the SFPP 40-mg and 80-mg groups, respectively). The percentage of the improvement was 74.8 % (122/163 patients; 74.7 and 75.0 % for the SFPP 40- and 80-mg groups, respectively) 52 weeks after the SFPP application.

Figure 2c shows the time-course changes in the tCS per site to be assessed. The mean ± standard error of the tCS for all sites was 6.2 ± 0.1, 4.5 ± 0.1, and 1.8 ± 0.1 at baseline, 2 weeks, and 52 weeks after the SFPP application, thus improving the tCS by 4.4 ± 0.1 points at

Table 6 Time-course changes in the laboratory tests

Time of assessment	Number of patients	BUN (mg/dL)	Creatinine (mg/dL)
SFPP 40 mg			
Baseline	101	15.11 ± 0.36	0.678 ± 0.016
2 weeks	100	16.17 ± 0.40*	0.681 ± 0.015
4 weeks	100	16.56 ± 0.43*	0.682 ± 0.016
8 weeks	100	16.19 ± 0.43*	0.671 ± 0.015
12 weeks	97	16.46 ± 0.39*	0.687 ± 0.015
16 weeks	94	15.92 ± 0.40*	0.685 ± 0.016
20 weeks	92	15.86 ± 0.36	0.681 ± 0.016
24 weeks	89	16.46 ± 0.48*	0.683 ± 0.016
28 weeks	90	16.73 ± 0.43*	0.674 ± 0.016
32 weeks	85	16.41 ± 0.42*	0.673 ± 0.016
36 weeks	84	16.21 ± 0.39*	0.681 ± 0.016
40 weeks	84	16.45 ± 0.42*	0.676 ± 0.016
44 weeks	84	16.60 ± 0.40*	0.680 ± 0.017
48 weeks	84	16.58 ± 0.46*	0.684 ± 0.016
52 weeks	81	16.97 ± 0.51*	0.697 ± 0.016*
SFPP 80 mg			
Baseline	100	16.12 ± 0.37	0.678 ± 0.013
2 weeks	97	17.39 ± 0.43*	0.684 ± 0.014
4 weeks	98	17.70 ± 0.44*	0.690 ± 0.015
8 weeks	99	17.28 ± 0.35*	0.682 ± 0.013
12 weeks	96	17.13 ± 0.34*	0.685 ± 0.013
16 weeks	95	17.16 ± 0.40*	0.685 ± 0.014
20 weeks	90	17.15 ± 0.45*	0.683 ± 0.014
24 weeks	88	16.44 ± 0.42	0.683 ± 0.015
28 weeks	83	17.18 ± 0.39*	0.675 ± 0.015
32 weeks	83	17.23 ± 0.46*	0.691 ± 0.016
36 weeks	83	17.61 ± 0.51*	0.689 ± 0.015
40 weeks	82	17.58 ± 0.45*	0.692 ± 0.015
44 weeks	81	17.66 ± 0.47*	0.701 ± 0.016*
48 weeks	81	17.86 ± 0.51*	0.701 ± 0.017*
52 weeks	79	16.70 ± 0.45	0.701 ± 0.016*

Values are given as mean ± standard error

Normal ranges: BUN, 6–20 mg/dL; creatinine, 0.61–1.04 mg/dL (males) and 0.47–0.79 mg/dL (females)

BUN blood urea nitrogen

* $p < 0.05$

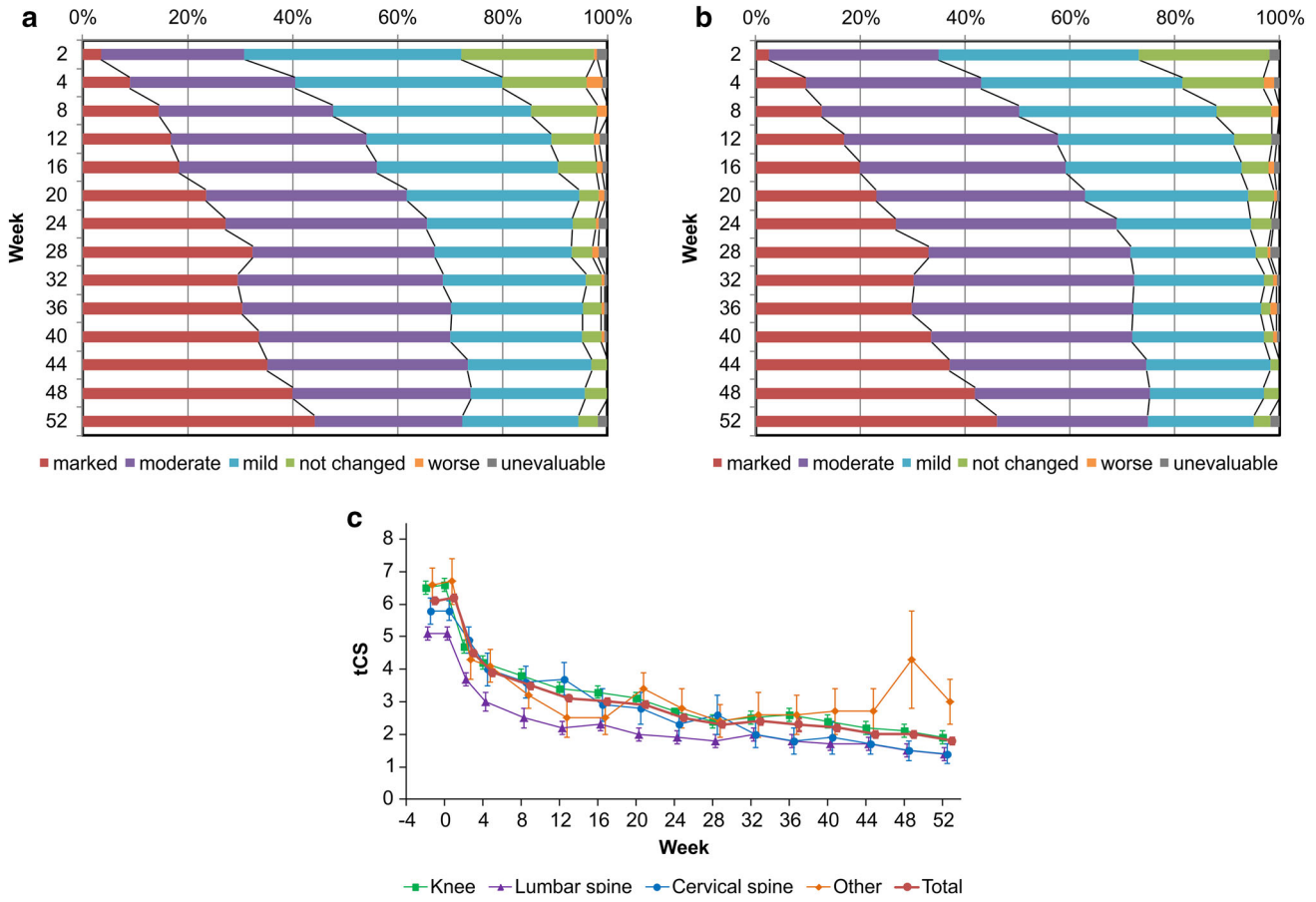

Fig. 2 **a** Patient's global assessment; **b** Clinician's global assessment; **c** time-course changes in the total clinical symptoms score (tCS, mean ± standard error). *p* values were calculated using a paired *t* test (two-sided, 5 % significance level). Significant improvements from baseline were observed at all assessment time-points except at the 48-week time-point of "other." *tCS* total clinical symptoms

52 weeks. The tCS improved significantly from 2 weeks after the SFPP application, and improved continuously until 52 weeks after the application for all sites assessed. In addition, the CS improved for all seven parameters compared to that at baseline (Table 7).

4 Discussion

In this study, the percentage of patients who continuously applied SFPP for 52 weeks (the completion rate) was high (80.1 %), which was much higher than the 50 % completion rate of previous long-term (52 weeks) studies of topical NSAIDs in OA patients [17, 18]. Although these patients were expected to be in the consistent systemic exposure (consistently high blood concentration of SFP) with the higher adherence of SFPP throughout the study. Only 7.0 % (14/201 patients) discontinued the study due to AEs. From these results, the present study suggested a relatively better safety profile for SFPP.

In the safety assessment of SFPP, the most common drug-related AEs were skin symptoms at the application sites, and most of the drug-related systemic AEs were not considered clinically significant.

The incidence of drug-related AEs causing gastrointestinal symptoms, which are a class effect of NSAIDs, was 3.0 % (3/101 patients) and 6.0 % (6/100 patients) in the SFPP 40-mg and 80-mg groups, respectively. Of the nine patients with gastrointestinal symptoms, gastrointestinal ulcer was found in two patients; however, the other seven patients experienced only mild symptoms such as gastritis, and no study discontinuations due to drug-related AEs occurred. Therefore, the risk of gastrointestinal disorders caused by SFPP was considered lower than with oral administration [19, 20]. The following two phenomena are reported in gastrointestinal disorders associated with oral NSAIDs: a decrease in endogenous prostaglandins (PGs) in the gastric mucosa induced by inhibition of plasma COX, and a direct effect of NSAIDs on the gastric mucosal epithelial cells [21–23]. SFP, which exhibits non-selective

Table 7 Time-course changes in the clinical symptoms score

Time of assessment	Number of sites	Total	Pain				Inflammation			Limitation of range of motion	Disability of activities of daily living
			Total	Exercise pain	Rest pain	Local tenderness	Total	Swelling	Local heat sensation		
−2 weeks	299	6.1 ± 0.1	3.5 ± 0.1	1.9 ± 0.0	0.5 ± 0.0	1.0 ± 0.0	0.8 ± 0.1	0.7 ± 0.0	0.1 ± 0.0	0.8 ± 0.0	1.1 ± 0.0
Baseline	301	6.2 ± 0.1	3.5 ± 0.1	2.0 ± 0.0	0.5 ± 0.0	1.1 ± 0.0	0.8 ± 0.1	0.7 ± 0.0	0.1 ± 0.0	0.8 ± 0.0	1.1 ± 0.0
2 weeks	294	4.5 ± 0.1	2.5 ± 0.1	1.4 ± 0.0	0.3 ± 0.0	0.8 ± 0.0	0.5 ± 0.0	0.5 ± 0.0	0.0 ± 0.0	0.6 ± 0.0	0.9 ± 0.0
4 weeks	296	3.9 ± 0.1	2.0 ± 0.1	1.2 ± 0.0	0.2 ± 0.0	0.6 ± 0.0	0.5 ± 0.0	0.4 ± 0.0	0.0 ± 0.0	0.6 ± 0.0	0.8 ± 0.0
8 weeks	298	3.5 ± 0.1	1.8 ± 0.1	1.1 ± 0.0	0.2 ± 0.0	0.5 ± 0.0	0.4 ± 0.0	0.4 ± 0.0	0.0 ± 0.0	0.5 ± 0.0	0.7 ± 0.0
12 weeks	289	3.1 ± 0.1	1.6 ± 0.1	1.0 ± 0.0	0.2 ± 0.0	0.4 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.0 ± 0.0	0.5 ± 0.0	0.7 ± 0.0
16 weeks	283	3.0 ± 0.1	1.5 ± 0.1	0.9 ± 0.0	0.2 ± 0.0	0.4 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.0 ± 0.0	0.5 ± 0.0	0.7 ± 0.0
20 weeks	271	2.9 ± 0.1	1.4 ± 0.1	0.8 ± 0.0	0.2 ± 0.0	0.4 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.0 ± 0.0	0.5 ± 0.0	0.6 ± 0.0
24 weeks	264	2.5 ± 0.1	1.2 ± 0.1	0.8 ± 0.0	0.1 ± 0.0	0.3 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.0 ± 0.0	0.5 ± 0.0	0.6 ± 0.0
28 weeks	256	2.3 ± 0.1	1.1 ± 0.1	0.7 ± 0.0	0.1 ± 0.0	0.3 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.0 ± 0.0	0.5 ± 0.0	0.5 ± 0.0
32 weeks	250	2.4 ± 0.1	1.2 ± 0.1	0.8 ± 0.0	0.1 ± 0.0	0.3 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.0 ± 0.0	0.4 ± 0.0	0.5 ± 0.0
36 weeks	249	2.3 ± 0.2	1.2 ± 0.1	0.7 ± 0.0	0.1 ± 0.0	0.3 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.0 ± 0.0	0.4 ± 0.0	0.5 ± 0.0
40 weeks	247	2.2 ± 0.1	1.1 ± 0.1	0.7 ± 0.0	0.1 ± 0.0	0.3 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.0 ± 0.0	0.4 ± 0.0	0.5 ± 0.0
44 weeks	245	2.0 ± 0.1	1.1 ± 0.1	0.7 ± 0.0	0.1 ± 0.0	0.3 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.0 ± 0.0	0.3 ± 0.0	0.4 ± 0.0
48 weeks	245	2.0 ± 0.1	1.0 ± 0.1	0.6 ± 0.0	0.1 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.0 ± 0.0	0.4 ± 0.0	0.4 ± 0.0
52 weeks	237	1.8 ± 0.1	1.0 ± 0.1	0.6 ± 0.0	0.1 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.0 ± 0.0	0.3 ± 0.0	0.4 ± 0.0

Values are given as mean ± standard error

p values were calculated using a paired *t* test (two-sided, 5 % significance level). Significant improvements from baseline were observed for all parameters at all assessment time points

inhibition of COX-1 ($IC_{50} = 8.97$ nM) and COX-2 ($IC_{50} = 2.94$ nM) [24], induces gastrointestinal disorders by acting on the gastric mucosal cells. However, the transdermal administration of SFP did not induce gastric ulcer at exposures up to seven times the maximum plasma concentration (C_{max}) and ten times the area under the concentration-time curve (AUC) after oral administration to rats [14]; therefore, the effects on the digestive organs might be avoided by the transdermal administration of SFP. Similarly, there were no drug-related AEs causing renal disorders. A significant but small increase in BUN levels was observed in previous 2-week SFPP application studies [14, 15]. Therefore, in the present study, we assessed the changes in the laboratory values of renal function-related parameters. Similar to these previous 2-week SFPP application studies, in the current study, a statistically significant increase in BUN levels was observed 2 weeks after the SFPP application, which did not increase further during the prolonged application periods. In addition, the creatinine levels significantly increased from 44 weeks after the SFPP application, although only slight changes in the mean values were observed and these values were within the normal range; therefore, we believe this finding does not suggest a clinically significant effect of SFPP on renal function.

Although patients with cardiovascular diseases, including a past history, were enrolled, no drug-related AEs classified as cardiovascular disorders are observed.

Statistically significant changes were found in some of the blood tests, urinalysis results, blood pressure, and pulse rate, although these changes were considered clinically insignificant.

In the present study, the major drug-related systemic AEs were also gastrointestinal disorders. Laboratory abnormalities were observed for a small number of patients, although these changes were observed for racemic flurbiprofen tablets [19, 20]; therefore, no new drug-related AEs were observed in the present study.

Some topical NSAIDs are known to cause serious photosensitive dermatitis [25, 26], while FP is known to pose no such risk. The benzophenone moiety in chemical structures has been shown to contribute to photoallergic reactions [27, 28]. SFP does not contain a benzophenone moiety. In the current study, SFPP was applied to various sites for 52 weeks without restrictions such as protection from sunlight, and no photosensitivity dermatitis-related AEs were observed. Therefore, SFPP may be used safely without concern for photosensitivity dermatitis.

As application of SFPP was started without any washout period of former NSAIDs, we expected that the apparent improvement of SFPP seemed to be very difficult. Suprisingly, both the patient's and clinician's global assessments showed apparent improvements as early as 2 weeks after the SFPP application, and the improvement rates continued to increase over the following weeks until the end of the study. However, our study had major limitations such as a lack of a control group and randomization. The result of efficacy only showed the possibility and further studies including control groups would be necessary to confirm the immediate and long-lasting effects of SFPP.

Since the number of elderly persons in Japan will continue to increase in the near future, prevention of "locomotive syndrome," deterioration in locomotive function associated with locomotor disability, and extension of healthy life expectancy are challenges to be faced [29, 30]. OA, the most common joint disease, is an important disease underlying locomotive syndrome. Arthralgia due to OA worsens locomotive function. Hopefully, SFPP could open new avenues for preventing the progression of functional disorders in OA patients.

5 Conclusion

SFPP did not cause safety concerns during its continuous application for up to 52 weeks in OA patients. Therefore, SFPP could be an additional pharmacotherapy in the treatment of OA.

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Compliance with Ethical Standards

Conflict of interests Taisho Pharmaceutical Co., Ltd. was involved in the design of the study, its conduct, and the data analysis. I. Yataba, N. Otsuka, and I. Matsushita are employees of Taisho Pharmaceutical Co., Ltd. H. Matsumoto has received consultancy fees from Taisho Pharmaceutical Co., Ltd. Y. Hoshino had received consultancy fees from Taisho Pharmaceutical Co., Ltd. while in a previous affiliation.

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Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee at each participating study site and with the 1964 Helsinki Declaration and Good Clinical Practice guidelines.

Informed consent Informed consent was obtained from all individual participants included in the study.

Author contributions All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version for publication. I. Yataba and N.

Otsuka had full access to all of the study data and take responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design: I. Yataba, N. Otsuka, I. Matsushita, H. Matsumoto, and Y. Hoshino. Data acquisition: I. Yataba. Data analysis and interpretation: I. Yataba, N. Otsuka, I. Matsushita, H. Matsumoto, and Y. Hoshino.

References

1. Muraki S, Akune T, Oka H, En-yo Y, Yoshida M, Saika A, et al. Association of radiographic and symptomatic knee osteoarthritis with health-related quality of life in a population-based cohort study in Japan: the ROAD study. Osteoarthritis Cartilage. 2010;18:1227–34. doi:10.1016/j.joca.2010.06.001.
2. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. Ann Rheum Dis. 2001;60:91–7. doi:10.1136/ard.60.2.91.
3. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Ann Intern Med. 2015;162:46–54. doi:10.7326/M14-1231.
4. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. N Engl J Med. 1999;340:1888–99.
5. Zullo A, Hassan C, Campo SM, Morini S. Bleeding peptic ulcer in the elderly: risk factors and prevention strategies. Drugs Aging. 2007;24:815–28.
6. Barkin RL, Beckerman M, Blum SL, Clark FM, Koh EK, Wu DS. Should nonsteroidal anti-inflammatory drugs (NSAIDs) be prescribed to the older adult? Drugs Aging. 2010;27:775–89. doi:10.2165/11539430-000000000-00000.
7. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage. 2014;22:363–88. doi:10.1016/j.joca.2014.01.003.
8. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012;64:465–74. doi:10.1002/acr.21596.
9. Brown GA. AAOS clinical practice guideline: treatment of osteoarthritis of the knee: evidence-based guideline, 2nd edition. J Am Acad Orthop Surg. 2013;21:577–9. doi:10.5435/JAAOS-21-09-577.
10. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis. 2003;62:1145–55. doi:10.1136/ard.2003.011742.
11. National Institute for Health and Care Excellence. Osteoarthritis: Care and management in adults, https://www.nice.org.uk/guidance/CG177;2014. Last accessed 25 April 2016.
12. Stanos S. Osteoarthritis guidelines: a progressive role for topical NSAIDs. J Am Osteopath Assoc. 2013;113:123–7.
13. Yataba I, Otsuka N, Matsushita I, Kamezawa M, Yamada I, Sasaki S, et al. Plasma pharmacokinetics and synovial concentrations of S-flurbiprofen plaster in humans. Eur J Clin Pharmacol. 2016;72:53–9. doi:10.1007/s00228-015-1960-6.
14. Medicine Interview Form of LOQOA® tape 40. Revised in January 2016 (Version 3). Opened in the Website of Pharmaceuticals and Medical Devices Agency, Japan. Available at http://www.pmda.go.jp/. Last accessed 25 April 2016.
15. Yataba I, Otsuka N, Matsushita I, Matsumoto H, Hoshino Y. Efficacy of S-flurbiprofen plaster in knee osteoarthritis treatment: results from a phase III, randomized, active-controlled, adequate and well-controlled trial. Mod Rheumatol. 2016;. doi:10.1080/14397595.2016.1176624.
16. Brune K, Patrignani P. New insights into the use of currently available non-steroidal anti-inflammatory drugs. J Pain Res. 2015;8:105–18. doi:10.2147/JPR.S75160.
17. Peniston JH, Gold MS, Alwine LK. An open-label, long-term safety and tolerability trial of diclofenac sodium 1% gel in patients with knee osteoarthritis. Phys Sportsmed. 2011;39:31–8. doi:10.3810/psm.2011.09.1918.
18. Shainhouse JZ, Grierson LM, Naseer Z. A long-term, open-label study to confirm the safety of topical diclofenac solution containing dimethyl sulfoxide in the treatment of the osteoarthritic knee. Am J Ther. 2010;17:566–76. doi:10.1097/MJT.0b013e3181d169b5.
19. Ansaid® (flurbiprofen) [package insert]. New York, NY, US: Pharmacia Upjohn company, Division of Pfizer, Inc.; 2010.
20. Froben 100 mg Tablets (flurbiprofen) [package insert]. Maidenhead, Berkshire, UK: BGP Products, Ltd.; 2015.
21. Tomisato W, Tsutsumi S, Hoshino T, Hwang HJ, Mio M, Tsuchiya T, et al. Role of direct cytotoxic effects of NSAIDs in the induction of gastric lesions. Biochem Pharmacol. 2004;67:575–85.
22. Tomisato W, Tanaka K, Katsu T, Kakuta H, Sasaki K, Tsutsumi S, et al. Membrane permeabilization by non-steroidal anti-inflammatory drugs. Biochem Biophys Res Commun. 2004;323:1032–9.
23. Sinha M, Gautam L, Shukla PK, Kaur P, Sharma S, Singh TP. Current perspectives in NSAID-induced gastropathy. Mediators Inflamm. 2013;2013:258209. doi:10.1155/2013/258209.
24. Sugimoto M, Toda Y, Hori M, Mitani A, Ichihara T, Sekine S, et al. Analgesic effect of the newly developed S(+)-flurbiprofen plaster on inflammatory pain in a rat adjuvant-induced arthritis model. Drug Dev Res. 2016;77:20–8. doi:10.1002/ddr.21288.
25. European Medicines Agency. Assessment report for ketoprofen containing medicinal products (topical formulations). 2010. http://www.ema.europa.eu/ema. Last accessed 25 April 2016.
26. Guy RH, Kuma H, Nakanishi M. Serious photocontact dermatitis induced by topical ketoprofen depends on the formulation. Eur J Dermatol. 2014;24:365–71. doi:10.1684/ejd.2014.2332.
27. Nakazawa T, Shimo T, Chikamatsu N, Igarashi T, Nagata O, Yamamoto M. Study on the mechanism of photosensitive dermatitis caused by ketoprofen in the guinea pig. Arch Toxicol. 2006;80:442–8. doi:10.1007/s00204-006-0063-7.
28. Seto Y, Ohtake H, Kato M, Onoue S. Phototoxic risk assessments on benzophenone derivatives: photobiochemical assessments and dermal cassette-dosing pharmacokinetic study. J Pharmacol Exp Ther. 2015;354:195–202. doi:10.1124/jpet.115.223644.
29. Nakamura K. A "super-aged" society and the "locomotive syndrome". J Orthop Sci. 2008;13:1–2. doi:10.1007/s00776-007-1202-6.
30. Nakamura K. The concept and treatment of locomotive syndrome: its acceptance and spread in Japan. J Orthop Sci. 2011;16:489–91. doi:10.1007/s00776-011-0108-5.