RESULTS

ANIMAL STUDIES

In carrageenin-induced hind paw edema in rats, DJW, at a dose as high as 8,000 mg/kg, showed insignificant anti-inflammatory effect after carrageenin injection even at 3 h where the highest percentage of inhibition of 21 (Table 3). Whereas, diclofenac, at a dose of 10 mg/kg, significantly inhibited paw edema formation at 1, 3 and 5 h after carrageenin injection with the percentages of 57, 65 and 43, respectively. In order to test possible delayed effects of DJW, it was given 2 and 4 h prior to carrageenin injection. However, it was found that DJW still exerted insignificant anti-inflammatory effect (data not shown).

Table 4 shows the results of cotton pellet-induced granuloma formation in rats. A 10 mg/kg dose of diclofenac produced a significant inhibition of the granuloma formation (21%) as did a 5 mg/kg dose of prednisolone (39%). On the contrary, DJW at a dose as high as 8,000 mg/kg had no antigranuloma formation. The transudative weight of the control group was found to be 165.33±10.67 mg. A 10 mg/kg dose of diclofenac and a 5 mg/kg dose of prednisolone significantly reduced the weight of the transudate to 138.33±9.33 and 125.18±10.15 mg, respectively. In contrast, a 8,000 mg/kg dose of DJW did not show any effect on the transudate weight.

With respect to the body weight gain, in control group, it was 29.00±7.87 g, whereas, in diclofenac and DJW groups, they were 25.33±3.93 and 32.67±11.78 g, respectively (Table 5). Prednisolone, at a dose of 5 mg/kg, markedly reduced the body weight gain to 13.33±6.28 g. Dry thymus weight of rats in the control group was 43.55±9.12 mg/100g body weight (Table 5). Both diclofenac and DJW did not show any suppressive effect on the thymus weight of the rats (47.84±12.27 and 40.99±6.93 mg/100g body weight, respectively) when compared with the control group, whereas, prednisolone significantly reduced the thymus weight to 27.19±7.54 mg/100g body weight.

Significant elevation of alkaline phosphatase level in the serum of rats in control group (28.45 x 10^{-4}U of enzyme/mg of serum protein) was observed when compared with that of normal/non-implanted rats (20.83 x 10^{-4}U of enzyme/mg of serum protein) (Table 6). The increase in serum alkaline phosphatase caused by cotton pellet implantation was significantly reduced from control level to normal level by prednisolone at the dose of 5 mg/kg (21.00 x 10^{-4}U of enzyme/mg of serum protein), whereas, both diclofenac at the dose of 10 mg/kg and DJW at the dose of 8,000 mg/kg exhibited insignificant effect (22.26 x 10^{-4} and 21.98 x 10^{-4}U of enzyme/mg of serum protein, respectively).

The results on licking response in the early phase of the formalin test are shown in Table 7. DJW, at doses of 250, 1,000, and 4,000 mg/kg, significantly inhibited licking response from control group with the percentages of 56, 45 and 55 respectively. Codeine (50 mg/kg) and diclofenac (10 mg/kg) also showed inhibitory effect on licking response of 54% and 73%, respectively. Inhibition of licking response of the test drugs in the late phase of the formalin test is shown in Table 8. Similar to the early phase, codeine and diclofenac still exerted inhibitory effect on licking response (67% and 95%, respectively), except that the inhibitory effect of diclofenac was nearly complete. At doses of 250, 1,000, and 4,000 mg/kg, DJW exhibited significant analgesic activity in a dose dependent manner with the percentages of inhibition of 40, 74 and 88, respectively.

Table 3. Effects of DJW and diclofenac in carrageenin-induced paw edema model.

Drug	Dose (mg/kg)	Time after carrageenin injection					
		1h		3h		5h	
		EV (ml)	EI (%)	EV (ml)	EI (%)	EV (ml)	EI (%)
Control	-	0.14±0.03	-	0.52±0.08	-	0.37±0.07	-
Diclofenac	10	0.06±0.03*	57	0.18±0.06*	65	0.21±0.09*	43
DJW	8,000	0.15±0.06	0	0.41±0.12	21	0.34±0.15	8

Data represent mean±S.D. (n = 6). Control = received 5% Tween 80 only. *Significantly different from control ($p < 0.05$). EV = edema volume, EI = edema inhibition.

Table 4. Effects of DJW, prednisolone and diclofenac on granuloma formation and transudation in cotton pellet-induced granuloma model.

Group	Dose (mg/kg)	Granuloma wet weight (mg)	Granuloma dry weight (mg)	Transudative weight (mg)	Granuloma weight (mg/mg cotton)	GI (%)
Control	-	211.89±13.49	46.56±3.13	165.33±10.67	1.35±0.17	-
Prednisolone	5	161.27±10.92*	36.08±3.72*	125.18±4.14*	0.83±0.20*	39
Diclofenac	10	178.88±12.03*	40.56±4.14*	138.33±9.33*	1.06±0.22*	21
DJW	8,000	210.43±27.18	45.81±3.97	164.63±23.34	1.30±0.18	4

Data represent mean±S.D. (n = 6). Control = received 5% Tween 80 only. GI = granuloma inhibition. *Significantly different from control ($p < 0.05$).

Table 5. Effects of DJW, prednisolone and diclofenac on body weight and dry thymus weight in cotton pellet-induced granuloma model.

Group	Dose (mg/kg)	Body weight (g)			Dry thymus weight (mg/100g)
		Initial	Final	Gain	
Control	-	193.00±5.62	222.00±4.56	29.00±7.87	43.55±9.12
Prednisolone	5	195.67±6.98	209.00±9.44*	13.33±6.28*	27.19±7.54*
Diclofenac	10	194.67±6.41	220.00±6.32	25.33±3.93	47.84±12.27
DJW	8,000	191.33±5.01	224.00±9.72	32.67±11.78	40.99±6.93

Data represent mean±S.D. (n = 6). Control = received 5% Tween 80 only. *Significantly different from control ($p < 0.05$).

Table 6. Effects of DJW, prednisolone and diclofenac on serum alkaline phosphatase in cotton pellet-induced granuloma model.

Group	Dose (mg/kg)	Serum alkaline phosphatase activity (U of enzyme/mg of serum protein x 10^{-4})
Normal	-	20.83±1.28*
Control	-	28.45±4.73
Prednisolone	5	21.00±1.66*
Diclofenac	10	22.26±5.02
DJW	8,000	21.98±10.12

Data represent mean±S.D. (n = 6). Normal = nonimplanted group. Control = implanted group, received 5% Tween 80 only. *Significantly different from control ($p < 0.05$).

Table 7. Effects of DJW, codeine and diclofenac in the early phase of the formalin test in mice.

Group	Dose (mg/kg)	Licking time (min)	Inhibition of licking response (%)
Control	-	2.55±0.40	-
Codeine	50	1.16±0.11*	55
Diclofenac	10	0.68±0.31*	73
DJW	250	1.13±0.06*	56
DJW	1,000	1.41±0.35*	45
DJW	4,000	1.14±0.30*	55

Data represent mean±S.D. (n=6). *Significantly different from control (p <0.05).

Table 8. Effects of DJW, codeine and diclofenac in the late phase of the formalin test in mice.

Group	Dose (mg/kg)	Licking time (min)	Inhibition of licking response (%)
Control	-	2.78±0.38	-
Codeine	50	0.92±0.41*	67
Diclofenac	10	0.15±0.20*	95
DJW	250	1.66±0.29*	40
DJW	1,000	0.71±0.32*	74
DJW	4,000	0.33±0.21*	88

Data represent mean±S.D. (n=6). *Significantly different from control (p <0.05).

CLINICAL TRIAL

DJW and its placebo capsules were prepared in 4 separate lots. The quality control and standardization performed before prescribing are shown in Table 9. All variables were in allowable ranges recommended by the Food and Drug Administration of Thailand. The screening for microorganisms and aflatoxin of cane sugar used as placebo were also performed and passed as well. A total of 429 patients were recruited into this study, of whom 229 patients were excluded (Figure 1). The remaining 200 patients were randomized into DJW and diclofenac groups, 100 patients per group. In DJW group, 4 patients withdrew from the study due to ineffectiveness (n=3) and transportation problem (n=1), 1 patient lost to follow up and 1 patient had a traffic accident during the study. In diclofenac group, 3 patients lost to follow up and 3 patients were withdrawn due to the accidents. Thus, the completers in each group were 94 patients. The two treatment groups were not significantly different in demographic data e.g., sex, age, weight, height, duration of OA, location of OA (Table 10) and base-line data for the major outcome assessment e.g., VAS, Lequesne's functional index and time for climbing up the stairs (Table 11). The radiographic findings at entry (Table 12) were not different between both groups. Previous OA treatments of the patients and their therapeutic outcome are shown in Table 13 and 14, respectively. All patients had been treated by at least one treatment procedure before entry into this study. The most common procedures were oral medications (e.g., paracetamol, NSAIDs, muscle relaxants, etc.) followed by topical medications (e.g., various types of balm and gel) and intramuscular injection of NSAIDs, respectively. Most patients experienced temporary improvement from the previous treatments. The concomitant treatments of coexisting disorders among the patients are shown in Table 15. More than 50% of the patients used no concomitant treatments during this study. The most common drug therapy used in concomitant treatment was cardiovascular drugs, especially antihypertensives. However, the proportions of patients used concomitant treatments in both groups were not significantly different. During the study, the rates of compliance with medications in DJW group were 94%, whereas, those in diclofenac group were 96%.

During four weeks of treatment, mean changes in body weight at the end of the study compared to their base-line values in diclofenac group were significantly different from DJW

group [+0.64±0.10 versus +0.08±0.10 kg, ITT (intent-to-treat) analysis and +0.65±0.10 kg versus +0.07±0.10 kg, analysis on completers]. These significant differences were observed as early as week 1 and continued throughout the study (data not presented).

Mean changes in blood pressure during four weeks of treatment did not differ between both groups. Except at week 3, systolic blood pressure in DJW group was significantly lower than that of diclofenac group (-9.09±1.66 versus –3.76±1.69 mmHg, ITT analysis and –8.73±1.69 versus –3.60±1.78 mmHg, analysis on completers), as did diastolic blood pressure (-4.58±0.80 versus –1.30±0.73 mmHg, ITT analysis and –4.29±0.80 versus –1.52±0.77 mmHg, analysis on completers). Although mean changes in blood pressure at the remaining time-points were not statistically different between both groups, DJW group demonstrated a tendency of greater reduction than diclofenac group (data not shown).

In both an ITT analysis and analysis on completers, VAS assessing pain and stiffness at each time-point decreased significantly when compared to their own base-line values (within group analysis), as did Lequesne's functional index and time for climbing up the stairs (Table 16-17 and Figure 2-13). The percentages of improvement in VAS assessing pain and stiffness were higher than 65% in both groups, whereas, the percentages of improvement in Lequesne's functional index and time for climbing up the stairs were approximately 40% and 20%, respectively.

When the statistical analysis between groups was performed, the mean changes in VAS assessing pain during climbing up and down the stairs, night pain, resting pain, total pain, and time for climbing up the stairs did not differ significantly between both groups (Table 18-19 and Figure 14-25). Nonetheless, the mean changes in VAS assessing walking pain, standing pain, and stiffness were significantly different during week 0-1, whereas, the differences in mean changes in Lequesne's functional index were found during week 0-1 and week 0-2. Afterwards, the mean changes in these variables became indifferent throughout the study.

The physician's and patients' overall opinions of improvement, as measured on VAS, are shown in Table 20 and Figure 26-27. Regardless of ITT or completer data sets, the physician's overall opinion of improvement at each time point did not significantly differ between the two groups. However, the differences between groups (DJW versus diclofenac group) were found in patients' overall opinion at week 1 (32.58±23.18 versus 37.48±18.59, ITT analysis and

32.84±23.35 versus 37.55±18.70, analysis on completers), but no differences in patients' overall opinion were demonstrated at the remaining time-points.

The percentages of patients experienced adverse events during the study are shown in Table 21. Most patients in both groups experienced no adverse events (72% and 73% for DJW and diclofenac groups, respectively). The most common adverse events occurred in DJW and diclofenac groups were raised blood pressure (16% and 19%), central nervous system symptoms including dizziness, somnolence and drowsiness (16% and 11%), and gastrointestinal symptoms including nausea/vomiting, dyspepsia, diarrhea and constipation (12% and 5%). The less common adverse events were increased appetite, cramp, rash, flu and accident. However, the percentages of patients experienced each adverse event in both groups were not significantly different. Furthermore, changes in biochemical (creatinine, uric acid, total bilirubin, direct bilirubin and alkaline phosphatase) and hematological (hemoglobin, hematocrit, white blood cell count and platelet count) parameters between pre- and post-treatment were not clinically different in both groups (data not shown).

Table 22 shows the number of patients considered to be responders at the end of the study (week 4) and at 1 and 2 months after treatment. At the end of the study, from 100 patients per treatment group, there were 73 responders in DJW group and 78 responders in diclofenac group and there were no significant differences between groups (p = 0.41). By telephone interview at 1 month after treatment, the number of remaining responders in DJW group (33 patients from 66 evaluated responders) was significantly higher (p = 0.046) than that in diclofenac group (23 patients from 66 evaluated responders). The number of evaluated responders during follow up period in both groups were decreased because some previous responders were unable to be evaluated due to loss to follow up or using NSAIDs for other purposes. By the final telephone interview (2 months after treatment), the number of remaining responders in DJW group (20 patients) was much more than that in diclofenac group (8 patients) with significant difference (p < 0.01). Two evaluated responders from the last interview in each group were lost to follow up at this final interview.

In summary, in animal studies, DJW exhibited analgesic effect in both phases of the formalin test without anti-inflammatory effect in carrageenin-induced rat paw edema model and in cotton pellet-induced granuloma model. In clinical trial, VAS assessing pain and stiffness,

Lequesne's functional index and time for climbing up the stairs at each time point of DJW and diclofenac groups decreased significantly when compared to their own base-line values. The mean changes in all VAS assessing pain, except for walking and standing pain, did not differ significantly between both groups. The differences in mean changes in VAS assessing walking pain, standing pain and stiffness were found only during week 0-1, whereas, those in Lequesne's functional index were found during week 0-1 and week 0-2. At the end of the study, the number of responders were not significantly different between the two groups, whereas, at 1 and 2 months after treatment, the remaining responders in DJW group were significantly higher than that in diclofenac group.

Table 9. The quality control and standardization of DJW.

Lot No.[1]	%Weight variation[2] (mean±S.D.)	Microorganism contamination						Aflatoxin contamination[10] (ppb)
		Viable count[3] (CFU/g)	Total coliform[4] (MPN/100 g)	Fecal coliform[5] (MPN/100 g)	Enterobacteria[6]	Clostridium spp, Salmonella spp[7], Staphylococcus aureus[8]	Fungus[9]	
1	4.45±2.97	1,500	0	0	NF[11]	NF	NF	17.80
2	0.64±0.57	2,600	0	0	NF	NF	NF	18.30
3	0.78±0.44	3,300	0	0	NF	NF	NF	16.43
4	0.75±0.54	100	0	0	NF	NF	NF	13.95

[1]The mean disintegration time of DJW capsules was 21 min at room temperature (29^{0}C) and 10 min at 40^{0}C, must not more than 30 min. [2](mean weight of DJW 20 capsules-500 mg)/500 mg x 100, must not more than 15%. [3]Aerobic bacteria, CFU = colony forming unit, must not more than 500,000 CFU/g. [4]All species of coliform, MPN = most probable number, must not more than 5,000 CFU/g. [5]Coliform found in feces (E. coli), must not more than 50 CFU/g. [6]Must not more than 5,000 CFU/g. [7]Must not found in 10 g sample. [8]Must not found in 1 g sample. [9]Must not more than 5,000 CFU/g. [10]Must not more than 20 part per billion (ppb). [11]NF = not found.

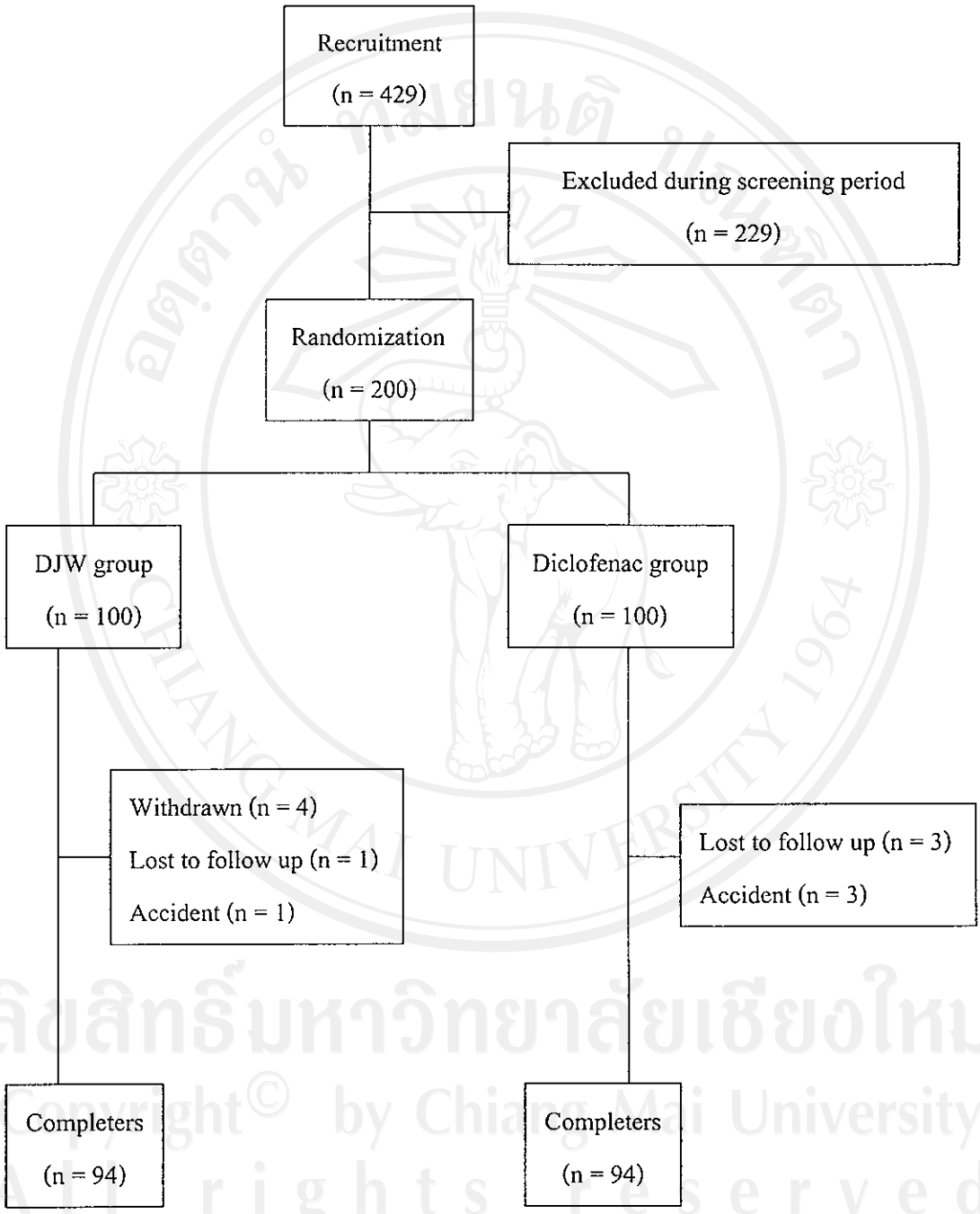


Figure 1. Flow chart of patients participating the clinical trial.

Table 10. Demographic data of participants evaluated at the end of run-in period (week 0).

Characteristic	Treatment groups		*p* value
	DJW	Diclofenac	
n (M:F)	100 (22:78)	100 (19:81)	NS[1]
Age (y)*	62.66 (9.46)	62.38 (8.22)	NS[1]
Body weight (kg)*	60.47 (10.34)	60.13 (10.89)	NS[1]
Height (m)*	1.51 (0.07)	1.51 (0.07)	NS[1]
BMI (kg/m^2)*	26.52 (4.38)	26.35 (3.85)	NS[1]
Duration of OA (y)*	5.46 (5.48)	4.79 (4.24)	NS[1]
Localization of OA			NS[2]
Right knee	17	17	
Left knee	14	14	
Both knee	69	69	

*Data represent mean (SD). NS: no statistical significance. Statistical analysis: [1]Student's t-test or [2]chi-square test.

Table 11. Base-line data for the major outcome assessments of participants evaluated at the end of run-in period (week 0).

Characteristic	Treatment groups: DJW (n=100)	Treatment groups: Diclofenac (n=100)	*p* value
VAS assessing pain (mm)*			
Walking pain	64.53 (24.92)	64.78 (25.14)	NS[1]
Standing pain	52.42 (25.87)	53.52 (24.69)	NS[1]
Pain during climbing up and down the stairs	63.08 (20.87)	62.69 (23.21)	NS[1]
Night pain	50.15 (26.74)	48.45 (28.18)	NS[1]
Resting pain	38.48 (22.09)	37.12 (26.08)	NS[1]
Total pain[a]	268.65 (88.87)	266.55 (89.33)	NS[1]
Pain during the most painful knee movement	82.25 (16.15)	81.17 (16.56)	NS[1]
VAS assessing stiffness			
Morning stiffness	53.53 (27.38)	58.32 (26.40)	NS[1]
Stiffness after rest	68.52 (22.76)	70.45 (22.32)	NS[1]
Total stiffness[b]	122.05 (41.98)	128.76 (42.34)	NS[1]
Lequesne's functional index	14.20 (3.13)	14.80 (2.61)	NS[1]
Time for climbing up the stairs	13.44 (4.85)	13.32 (5.10)	NS[2]

*Data represent mean (SD). [a]summation of VAS assessing walking pain, standing pain, pain during climbing up and down the stairs, night pain and resting pain, [b]summation of VAS assessing morning stiffness and stiffness after rest. NS: no statistical significance. Statistical analysis: [1]Wilcoxon rank-sum test or [2]student's t-test.

Table 12. The radiographic findings at entry into the study.

Radiographic findings	Treatment groups		*p* value
	DJW (169 knees)	Diclofenac (169 knees)	
Kellgren and Lawrence X-ray grade [67]			NS
Grade 2	31	23	
Grade 3	71	80	
Grade 4	67	66	
Knee compartment with most severe changes of OA			NS
Medial tibiofemoral	131	135	
Lateral tibiofemoral	16	8	
Patellofemoral	22	26	

Statistical analysis: Chi-square test.

Table 13. Percentage of the patients received previous OA treatments prior to this study*.

Treatment procedures	Treatment groups	
	DJW (n = 100)	Diclofenac (n = 100)
Oral medication	96	98
Topical medication	86	91
Intramuscular injection of NSAIDs	61	68
Intraarticular injection/aspiration	22	32
Oral herbal medication	32	37
Topical herbal medication	33	29
Physical therapy	17	15
Traditional massage	33	24
Acupuncture	18	13
Miscellaneous	0	2

*Some patients may receive more than one previous OA treatment.

Table 14. Percentage of the patients self-rated the outcome of previous OA treatments.

Outcome of previous treatment	Treatment groups	
	DJW (n = 100)	Diclofenac (n = 100)
Worse	5	7
Same	16	18
Temporary improvement	76	73
Much better	3	2

Table 15. Percentage of the patients used concomitant drug therapy during the study*.

	Treatment groups		
	DJW (n = 100)	Diclofenac (n = 100)	*p* value
No concomitant drug therapy	60	53	NS
Cardiovascular drugs	29	36	NS
Anti-diabetics	7	11	NS
Lipid-lowering drugs	3	3	NS
Thyroid/anti-thyroid drugs	4	3	NS
Vitamins/minerals	3	3	NS
Bronchodilators	2	3	NS
Miscellaneous	5	5	NS

*More than one concomitant drug therapy might be used. Statistical analysis: Chi-square test or Fisher's exact test.

Table 16. Mean VAS assessing pain and stiffness, Lequesne's functional index and time for climbing up the stairs in intent-to-treat patients (n =100/group).

Variable	Treatment Group	Week 0	Week 1	Week 2	Week 3	Week 4	% improvement[a]
VAS assessing pain (mm)							
Walking pain	DJW	64.53 (24.92)	47.58* (25.33)	37.72* (25.00)	28.00* (23.25)	18.06* (20.76)	72.01
	Diclofenac	64.78 (25.14)	44.08* (23.43)	34.99* (22.07)	24.21* (21.00)	14.31* (16.10)	77.91
Standing pain	DJW	52.42 (25.87)	39.81* (26.09)	31.61* (24.89)	24.29* (22.98)	16.89* (20.59)	67.78
	Diclofenac	53.52 (24.69)	37.60* (24.06)	28.19* (22.40)	21.12* (21.16)	12.86* (16.69)	75.97
Pain during climbing up and down the stairs	DJW	63.08 (20.87)	46.31* (26.56)	36.40* (25.67)	28.16* (24.03)	18.41* (21.50)	70.81
	Diclofenac	62.69 (23.21)	43.90* (22.29)	32.61* (22.42)	24.59* (21.79)	15.83* (19.65)	74.75
Night pain	DJW	50.15 (26.74)	33.44* (27.27)	23.56* (22.79)	15.68* (18.14)	9.27* (15.04)	81.52
	Diclofenac	48.45 (28.18)	28.93* (22.82)	20.87* (19.56)	15.02* (17.87)	8.65* (14.68)	82.15
Resting pain	DJW	38.48 (22.09)	27.25* (21.99)	19.96* (19.98)	12.64* (15.56)	7.42* (13.09)	80.72
	Diclofenac	37.12 (26.08)	22.84* (20.62)	16.26* (18.19)	11.30* (16.40)	6.58* (13.96)	82.27
Total pain[b]	DJW	268.65 (88.87)	194.38* (105.06)	149.24* (103.19)	108.76* (92.54)	70.04* (83.94)	73.93
	Diclofenac	266.55 (89.33)	177.34* (85.49)	132.91* (84.50)	96.21* (81.94)	58.23* (70.43)	78.15
Pain during the most painful knee movement	DJW	82.25 (16.15)	63.31* (26.35)	49.77* (28.70)	37.69* (28.45)	26.81* (27.70)	67.40
	Diclofenac	81.17 (16.56)	56.79* (24.87)	43.64* (27.30)	33.10* (27.17)	22.84* (25.85)	71.86
VAS assessing stiffness (mm)							
Morning stiffness	DJW	53.53 (27.38)	36.61* (25.56)	28.04* (23.86)	19.66* (20.53)	12.34* (17.69)	76.95
	Diclofenac	58.32 (26.40)	38.73* (23.87)	28.52* (21.93)	20.19* (20.23)	12.90* (17.34)	77.88
Stiffness after rest	DJW	68.52 (22.76)	51.69* (24.93)	39.40* (25.31)	29.05* (24.60)	19.62* (23.06)	71.37
	Diclofenac	70.45 (22.32)	49.71* (24.68)	39.54* (24.97)	28.23* (24.17)	18.90* (20.60)	73.17
Total stiffness[c]	DJW	122.05 (41.98)	88.30* (45.93)	67.44* (46.25)	48.71* (42.82)	31.96* (38.84)	73.81
	Diclofenac	128.76 (42.34)	88.44* (43.84)	68.06* (43.03)	48.42* (41.97)	31.80* (36.07)	75.30
Lequesne's functional index (score)	DJW	14.20 (3.13)	11.60* (4.11)	11.05* (4.04)	9.93* (4.40)	8.92* (4.60)	37.18
	Diclofenac	14.80 (2.61)	10.89* (3.38)	10.65* (3.55)	9.59* (3.52)	8.64* (3.83)	41.62
Time for climbing up the stairs (s)	DJW	13.44 (4.85)	11.65* (4.75)	11.42* (4.67)	10.94* (4.73)	10.50* (4.38)	21.88
	Diclofenac	13.32 (5.10)	11.26* (5.12)	11.14* (5.72)	10.61* (5.51)	10.18* (4.46)	23.57

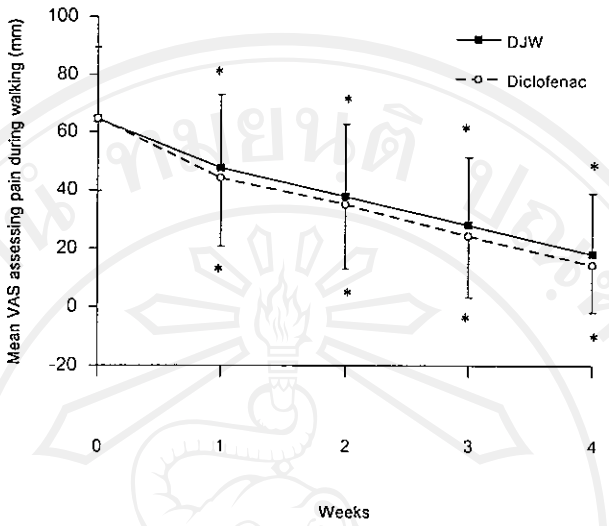
Data represent mean (SD). [a]Calculated by ($mean_{week\ 0} - mean_{week\ 4}$) x $100/mean_{week\ 0}$, [b]summation of VAS assessing walking pain, standing pain, pain during climbing up and down the stairs, night pain and resting pain, [c]summation of VAS assessing morning stiffness and stiffness after rest. *$p<0.05$ versus baseline value.

Table 17. Mean VAS assessing pain and stiffness, Lequesne's functional index and time for climbing up the stairs in completers (n = 94/group).

Variable	Treatment Group	Week 0	Week 1	Week 2	Week 3	Week 4	% improvement[a]
VAS assessing pain (mm)							
Walking pain	DJW	64.06 (25.22)	46.95* (25.23)	36.61* (24.31)	26.33* (21.66)	15.76* (17.62)	75.40
	Diclofenac	65.15 (25.43)	43.93* (23.85)	34.84* (22.10)	23.56* (20.73)	13.03* (14.68)	80.00
Standing pain	DJW	51.56 (25.64)	38.30* (25.03)	29.63* (22.99)	21.88* (19.86)	14.01* (15.53)	72.83
	Diclofenac	52.88 (24.48)	36.36* (22.92)	27.03* (21.39)	19.64* (19.53)	10.86* (13.05)	79.46
Pain during climbing up and down the stairs	DJW	62.96 (21.04)	45.38* (26.29)	34.96* (24.73)	26.60* (22.18)	15.90* (17.97)	74.75
	Diclofenac	62.91 (23.44)	43.68* (22.08)	32.19* (21.60)	23.78* (20.51)	14.47* (17.48)	77.00
Night pain	DJW	48.70 (26.62)	32.18* (27.49)	21.83* (22.26)	13.71* (16.48)	6.89* (11.49)	85.85
	Diclofenac	48.85 (28.45)	28.32* (22.39)	19.80* (18.45)	13.57* (16.04)	6.80* (11.14)	86.08
Resting pain	DJW	38.44 (22.39)	26.68* (22.03)	19.02* (19.49)	11.23* (13.94)	5.68* (10.07)	85.22
	Diclofenac	36.63 (25.75)	21.73* (19.21)	14.87* (15.89)	9.60* (13.03)	4.57* (8.50)	87.52
Total pain[b]	DJW	265.73 (89.86)	189.48* (103.97)	142.04* (98.65)	99.42* (82.05)	58.23* (65.09)	78.09
	Diclofenac	266.42 (90.25)	174.01* (83.27)	128.73* (79.08)	90.15* (73.12)	49.74* (53.71)	81.33
Pain during the most painful knee movement	DJW	81.68 (16.39)	61.99* (26.31)	47.59* (27.91)	34.90* (26.63)	23.32* (24.32)	71.45
	Diclofenac	81.25 (16.12)	55.94* (24.39)	42.88* (26.63)	31.82* (25.95)	20.90* (23.74)	74.28
VAS assessing stiffness (mm)							
Morning stiffness	DJW	52.97 (27.58)	35.45* (24.72)	26.47* (22.16)	17.59* (17.32)	9.80* (12.16)	81.50
	Diclofenac	58.19 (26.87)	37.98* (23.32)	27.66* (20.96)	18.86* (18.48)	11.11* (14.19)	80.91
Stiffness after rest	DJW	67.35 (22.86)	49.72* (24.12)	36.97* (23.35)	26.21* (21.02)	16.18* (17.33)	75.98
	Diclofenac	70.63 (21.41)	48.61* (23.56)	37.96* (23.70)	26.45* (22.44)	16.52* (17.09)	76.61
Total stiffness[c]	DJW	120.31 (42.09)	85.18* (44.23)	63.44* (42.55)	43.79* (35.87)	25.97* (27.29)	78.41
	Diclofenac	128.82 (42.15)	86.59* (42.26)	65.62* (41.05)	45.31* (38.52)	27.63* (29.39)	78.55
Lequesne's functional index (score)	DJW	14.05 (3.11)	11.27* (3.96)	10.72* (3.84)	9.54* (4.13)	8.47* (4.25)	39.71
	Diclofenac	14.79 (2.66)	10.65* (3.32)	10.47* (3.50)	9.33* (3.41)	8.32* (3.67)	43.74
Time for climbing up the stairs (s)	DJW	13.31 (4.80)	11.29* (4.35)	11.04* (4.24)	10.55* (4.26)	10.08* (3.78)	24.27
	Diclofenac	13.24 (5.08)	10.97* (4.83)	10.86* (5.56)	10.35* (5.36)	9.88* (4.15)	25.37

Data represent mean (SD). [a]Calculated by ($mean_{week\ 0} - mean_{week\ 4}$) x 100/$mean_{week\ 0}$, [b]summation of VAS assessing walking pain, standing pain, pain during climbing up and down the stairs, night pain and resting pain, [c]summation of VAS assessing morning stiffness and stiffness after rest. *$p<0.05$ versus baseline value.

A. Intent-to-treat analysis



B. Analysis on completers

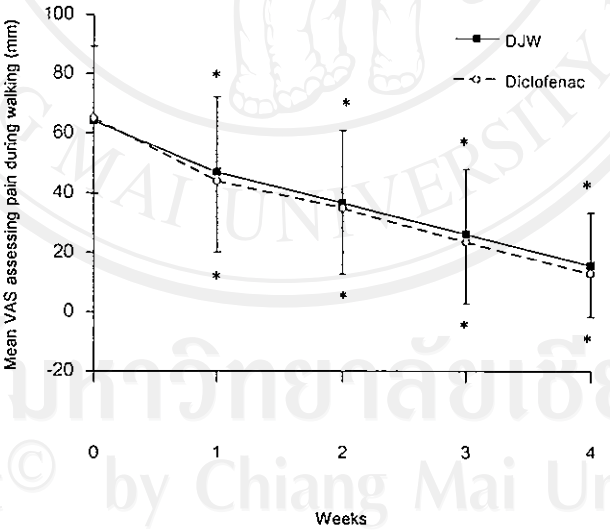
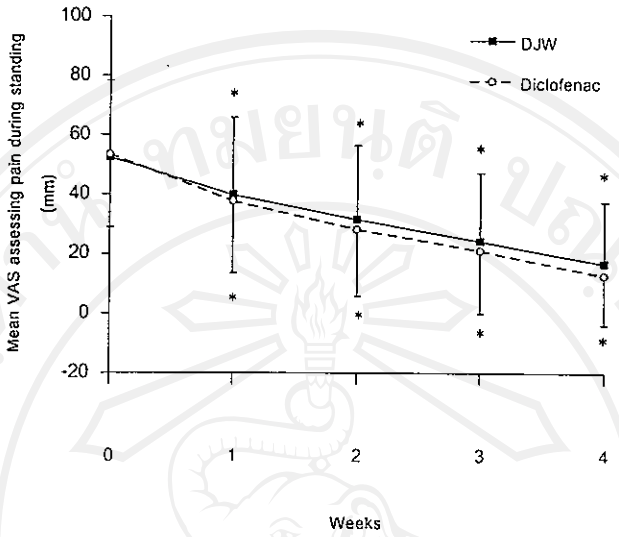


Figure 2. Mean VAS assessing pain during walking in each treatment group evaluated at the end of run-in period (week 0) and during treatment. Data represent mean±SD. *$p < 0.05$ compared to base-line value (Wilcoxon's signed-rank test).

A. Intent-to-treat analysis



B. Analysis on completers

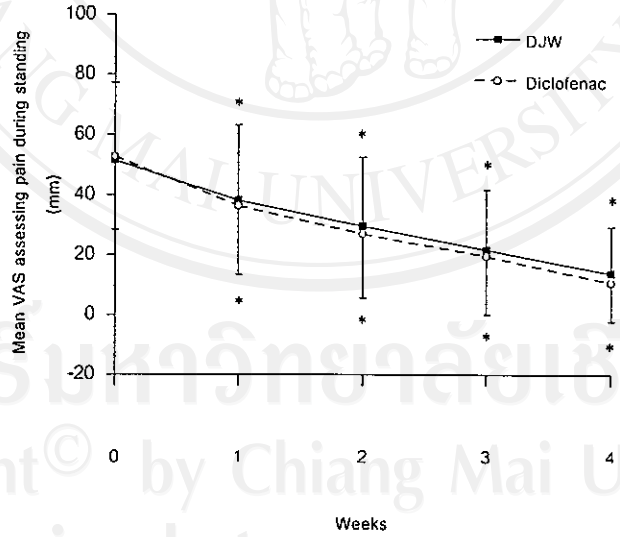
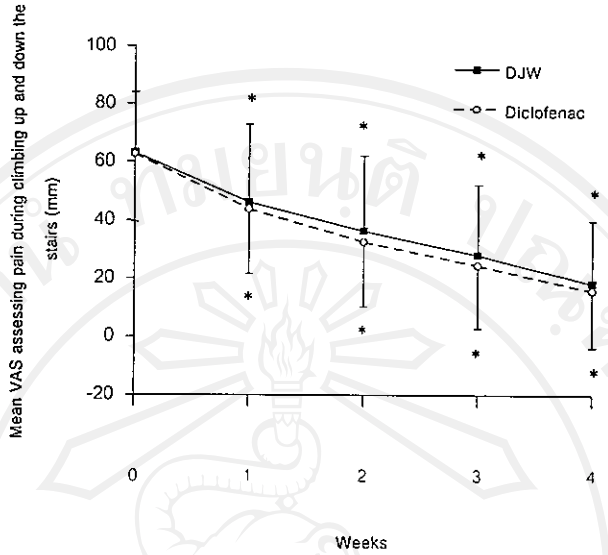


Figure 3. Mean VAS assessing pain during standing in each treatment group evaluated at the end of run-in period (week 0) and during treatment. Data represent mean±SD. *$p < 0.05$ compared to base-line value (Wilcoxon's signed-rank test).

A. Intent-to-treat analysis



B. Analysis on completers

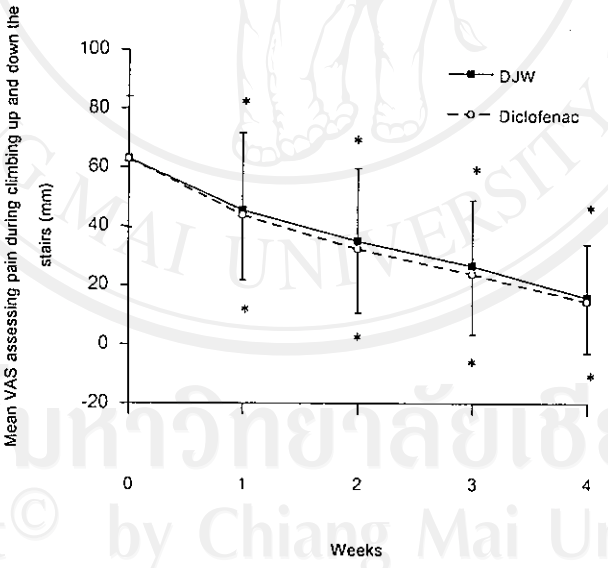
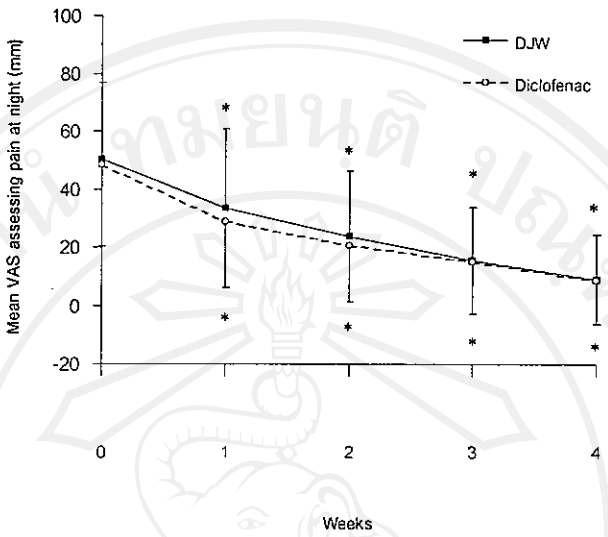


Figure 4. Mean VAS assessing pain during climbing up and down the stairs in each treatment group evaluated at the end of run-in period (week 0) and during treatment. Data represent mean±SD. *$p < 0.05$ compared to base-line value (Wilcoxon's signed-rank test).

A. Intent-to-treat analysis



B. Analysis on completers

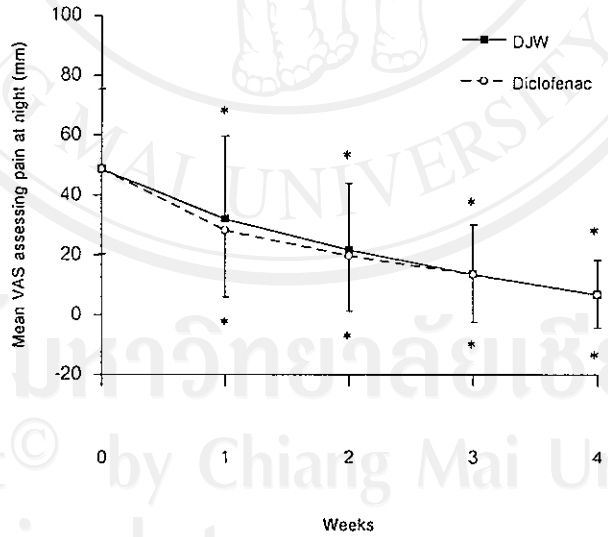
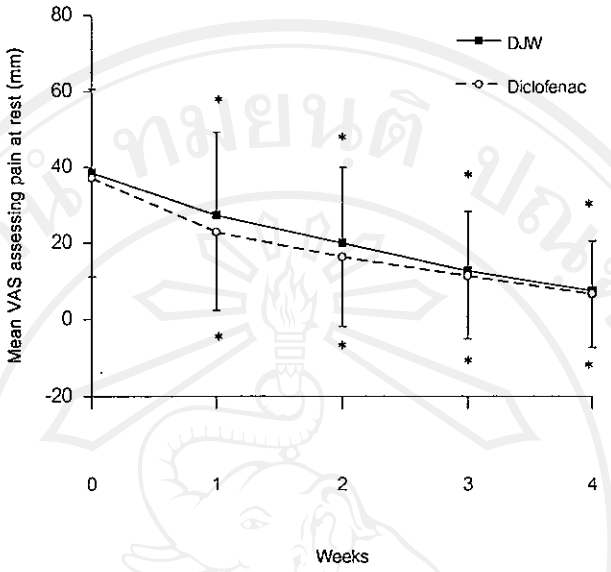


Figure 5. Mean VAS assessing pain at night in each treatment group evaluated at the end of run-in period (week 0) and during treatment. Data represent mean±SD. *$p < 0.05$ compared to base-line value (Wilcoxon's signed-rank test).

A. Intent-to-treat analysis



B. Analysis on completers

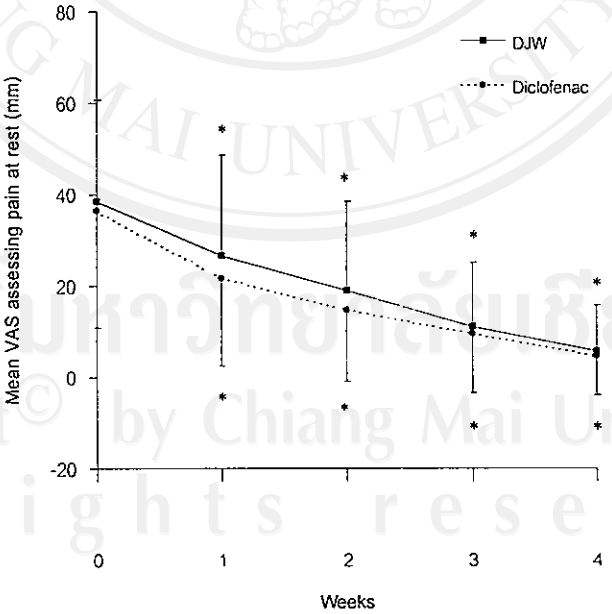
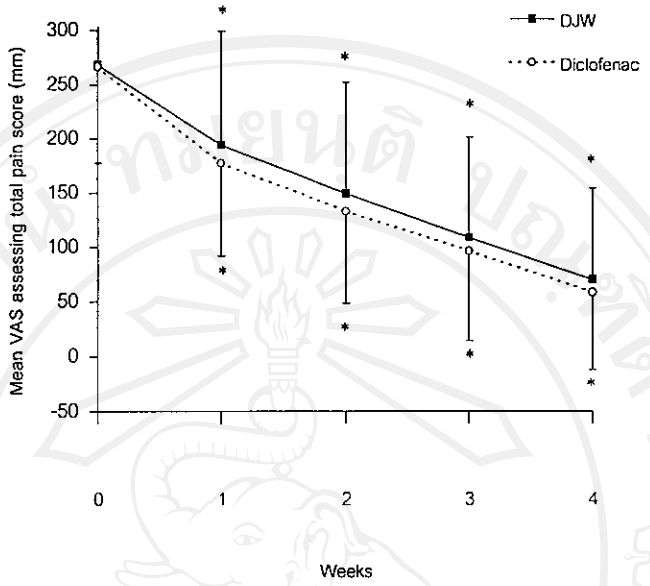


Figure 6. Mean VAS assessing pain at rest in each treatment group evaluated at the end of run-in period (week 0) and during treatment. Data represent mean±SD. *$p < 0.05$ compared to base-line value (Wilcoxon's signed-rank test).

A. Intent-to-treat analysis



B. Analysis on completers

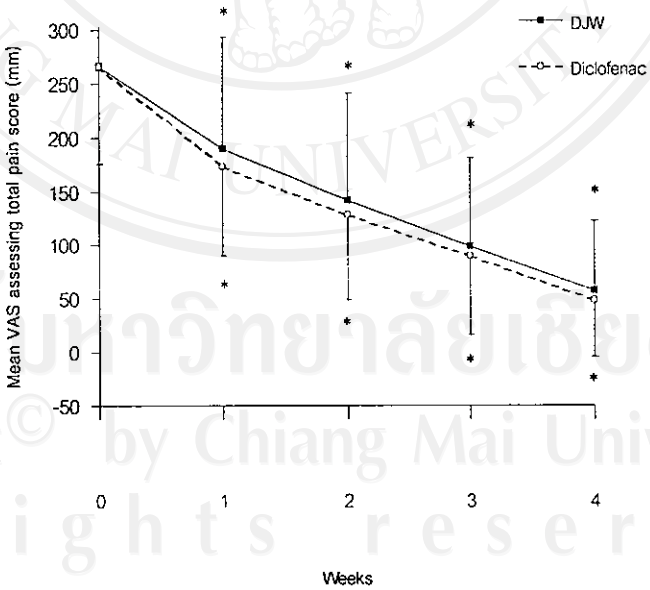
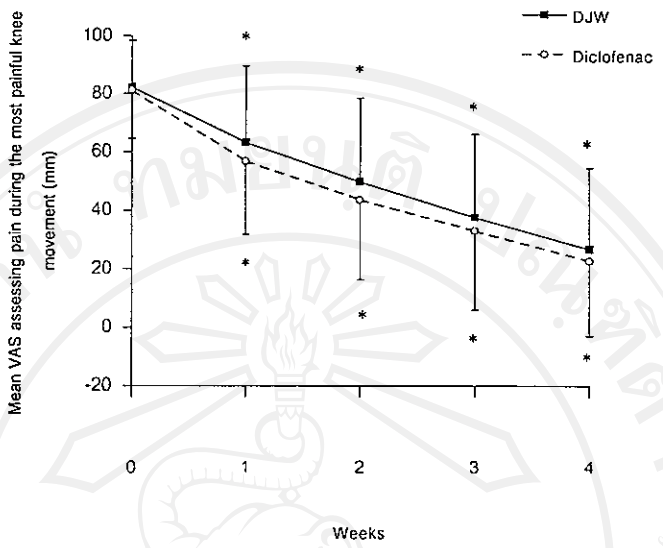


Figure 7. Mean VAS assessing total pain score in each treatment group evaluated at the end of run-in period (week 0) and during treatment. Data represent mean±SD. *$p < 0.05$ compared to base-line value (Wilcoxon's signed-rank test).

A. Intent-to-treat analysis



B. Analysis on completers

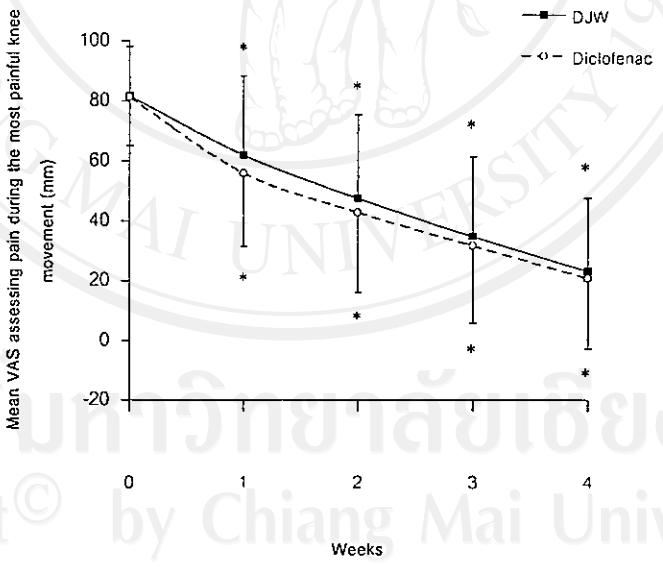
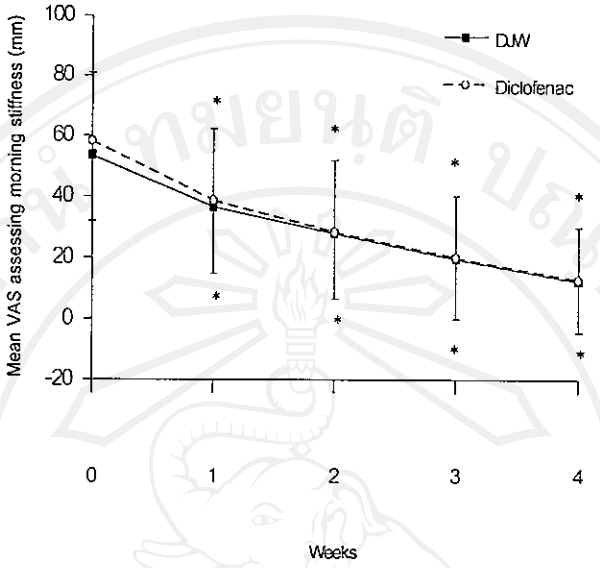


Figure 8. Mean VAS assessing pain during the most painful knee movement in each treatment group evaluated at the end of run-in period (week 0) and during treatment. Data represent mean±SD. *$p < 0.05$ compared to base-line value (Wilcoxon's signed-rank test).

A. Intent-to-treat analysis



B. Analysis on completers

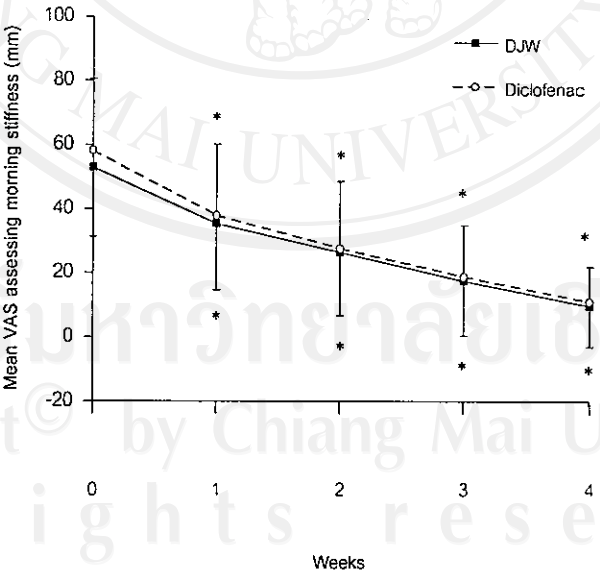
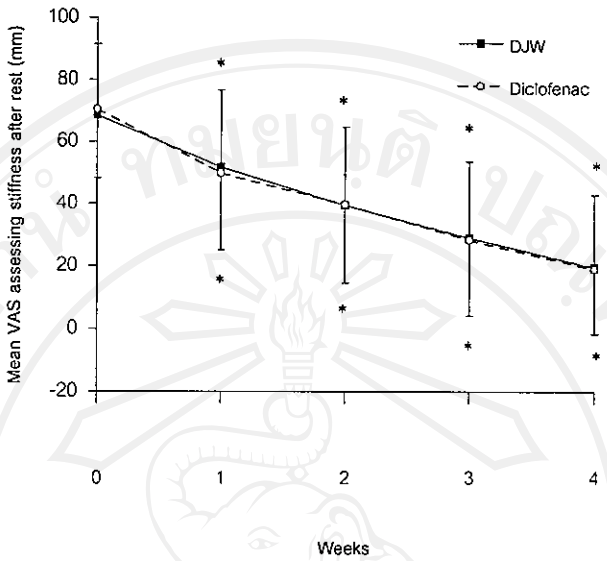


Figure 9. Mean VAS assessing morning stiffness in each treatment group evaluated at the end of run-in period (week 0) and during treatment. Data represent mean±SD. *$p < 0.05$ compared to base-line value (Wilcoxon's signed-rank test).

A. Intent-to-treat analysis



B. Analysis on completers

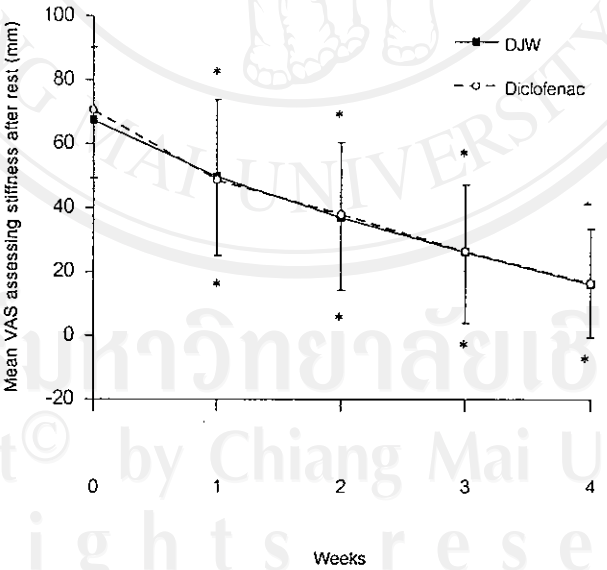
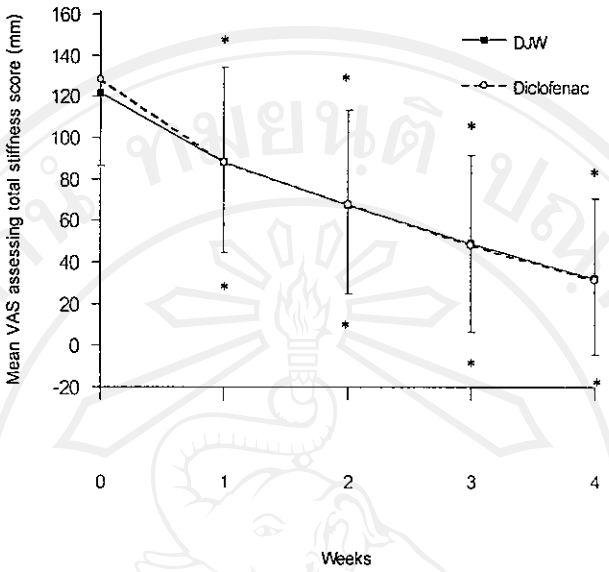


Figure 10. Mean VAS assessing stiffness after rest in each treatment group evaluated at the end of run-in period (week 0) and during treatment. Data represent mean±SD. *$p < 0.05$ compared to base-line value (Wilcoxon's signed-rank test).

A. Intent-to-treat analysis



B. Analysis on completers

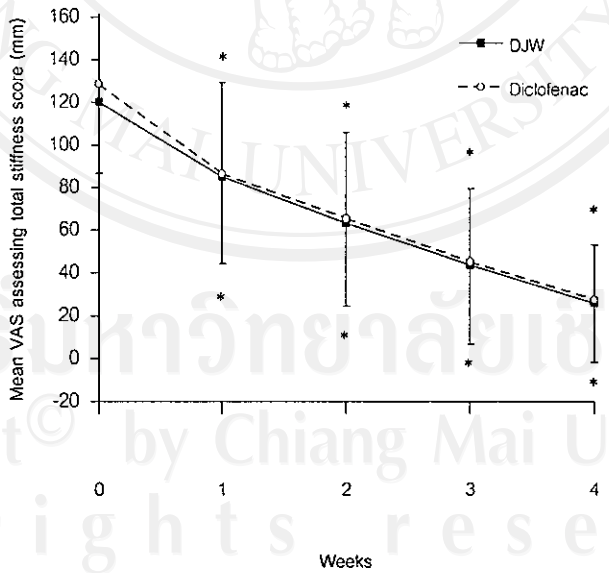
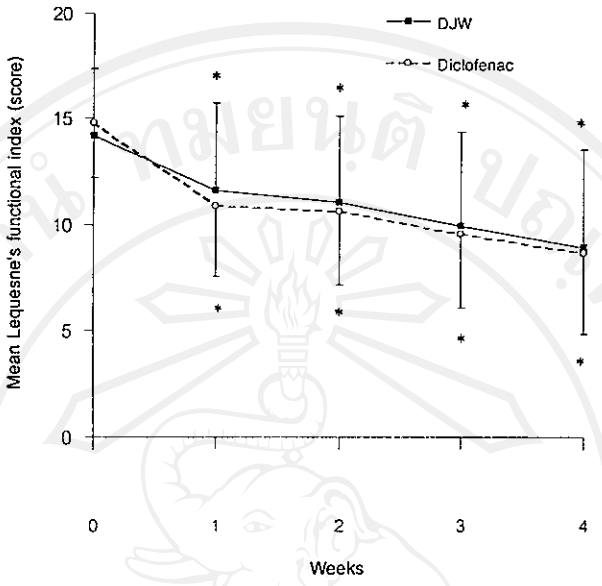


Figure 11. Mean VAS assessing total stiffness score in each treatment group evaluated at the end of run-in period (week 0) and during treatment. Data represent mean±SD. *$p < 0.05$ compared to base-line value (Wilcoxon's signed-rank test).

A. Intent-to-treat analysis



B. Analysis on completers

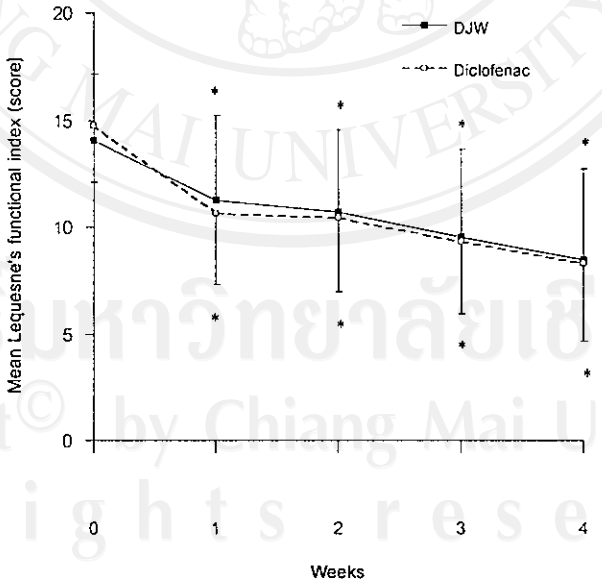
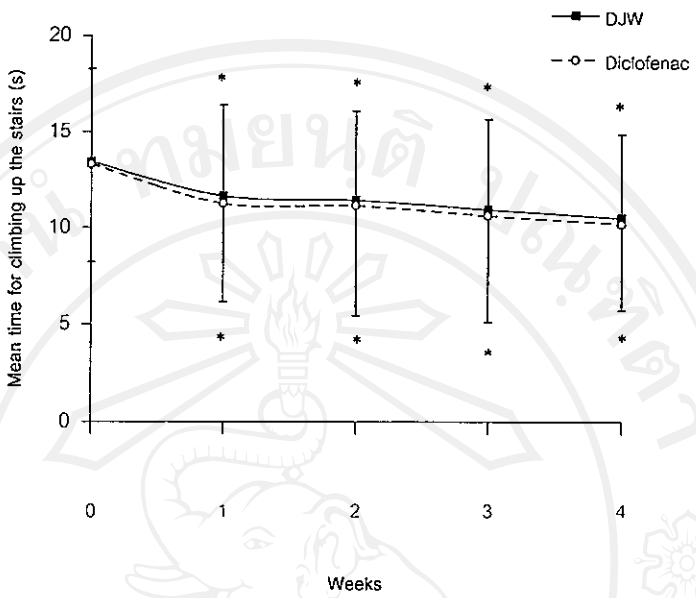


Figure 12. Mean Lequesne's functional index in each treatment group evaluated at the end of run-in period (week 0) and during treatment. Data represent mean±SD. *$p < 0.05$ compared to base-line value (Wilcoxon's signed-rank test).

A. Intent-to-treat analysis



B. Analysis on completers

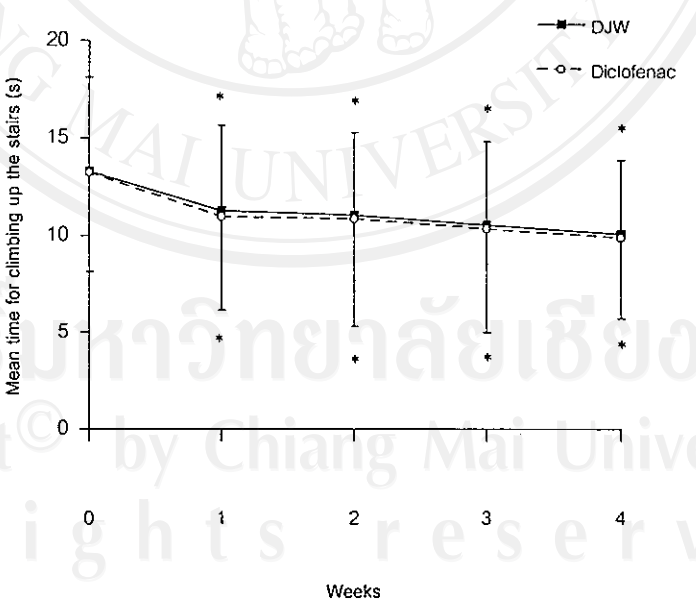


Figure 13. Mean time for climbing up the stairs in each treatment group evaluated at the end of run-in period (week 0) and during treatment. Data represent mean±SD. *$p < 0.05$ compared to base-line value (Wilcoxon's signed-rank test).

Table 18. Mean changes of VAS assessing pain and stiffness, Lequesne's functional index and time for climbing up the stairs in intent-to-treat patients (n = 100/group).

Variable	Treatment Group	Week 0-1	Week 0-2	Week 0-3	Week 0-4
VAS assessing pain (mm)					
Walking pain	DJW	-16.96 (1.68)	-26.82 (1.97)	-36.54 (2.31)	-46.48 (2.41)
	Diclofenac	-20.70[†](1.60)	-29.80 (1.95)	-40.58 (2.26)	-50.47 (2.38)
Standing pain	DJW	-12.61 (1.80)	-20.81 (2.23)	-28.13 (2.28)	-35.53 (2.34)
	Diclofenac	-15.93[†](1.33)	-25.33 (1.83)	-32.41 (2.04)	-40.66 (2.25)
Pain during climbing up and down the stairs	DJW	-16.78 (1.95)	-26.68 (2.30)	-34.93 (2.26)	-44.67 (2.22)
	Diclofenac	-18.79 (1.40)	-30.08 (1.91)	-38.11 (2.04)	-46.86 (2.35)
Night pain	DJW	-16.71 (2.32)	-26.60 (2.25)	-34.47 (2.42)	-40.88 (2.59)
	Diclofenac	-19.52 (1.98)	-27.58 (2.30)	-33.43 (2.51)	-39.80 (2.81)
Resting pain	DJW	-11.23 (1.24)	-18.52 (1.46)	-25.84 (1.86)	-31.06 (2.02)
	Diclofenac	-14.28 (1.34)	-20.86 (1.91)	-25.82 (2.07)	-30.54 (2.38)
Total pain[a]	DJW	-74.27 (6.53)	-119.42 (7.42)	-159.90 (7.85)	-198.61 (8.51)
	Diclofenac	-89.21 (5.25)	-133.64 (7.02)	-170.34 (7.65)	-208.33 (9.03)
Pain during the most painful knee movement	DJW	-18.94 (2.11)	-32.48 (2.63)	-44.56 (2.77)	-55.44 (2.67)
	Diclofenac	-24.38 (2.10)	-37.53 (2.51)	-48.07 (2.57)	-58.33 (2.59)
VAS assessing stiffness (mm)					
Morning stiffness	DJW	-16.93 (1.98)	-25.50 (2.24)	-33.87 (2.46)	-41.19 (2.58)
	Diclofenac	-19.59[†](1.69)	-29.80 (2.10)	-38.13 (2.47)	-45.42 (2.63)
Stiffness after rest	DJW	-16.83 (1.97)	-29.12 (2.41)	-39.48 (2.50)	-48.91 (2.54)
	Diclofenac	-20.74[†](1.72)	-30.91 (2.07)	-42.22 (2.29)	-51.55 (2.40)
Total stiffness[b]	DJW	-33.76 (3.48)	-54.62 (4.02)	-73.35 (4.21)	-90.10 (4.27)
	Diclofenac	-40.33[†](3.05)	-60.71 (3.72)	-80.35 (4.21)	-96.97 (4.47)
Lequesne's functional index (score)	DJW	-2.60 (0.34)	-3.15 (0.32)	-4.28 (0.37)	-5.29 (0.38)
	Diclofenac	-3.92[†](0.31)	-4.16[†](0.32)	-5.22 (0.36)	-6.16 (0.40)
Time for climbing up the stairs (s)	DJW	-1.79 (0.33)	-2.02 (0.31)	-2.50 (0.32)	-2.94 (0.32)
	Diclofenac	-2.05 (0.31)	-2.18 (0.34)	-2.71 (0.34)	-3.13 (0.33)

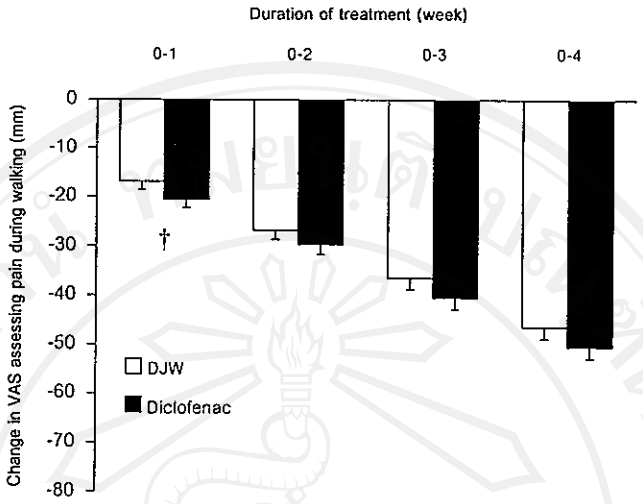
Data represent mean (SD). [a]Summation of VAS assessing walking pain, standing pain, pain during climbing up and down the stairs, night pain and resting pain, [b]summation of VAS assessing morning stiffness and stiffness after rest. [†]$p<0.05$ versus DJW group at the same duration of treatment.

Table 19. Mean changes of VAS assessing pain and stiffness, Lequesne's functional index and time for climbing up the stairs in completers (n = 94/group).

Variable	Treatment Group	Week 0-1	Week 0-2	Week 0-3	Week 0-4
VAS assessing pain (mm)					
Walking pain	DJW	-17.11 (1.75)	-27.45 (2.04)	-37.73 (2.36)	-48.30 (2.40)
	Diclofenac	-21.23†(1.64)	-30.31 (1.98)	-41.60 (2.26)	-52.12 (2.32)
Standing pain	DJW	-13.26 (1.85)	-21.94 (2.29)	-29.68 (2.30)	-37.55 (2.30)
	Diclofenac	-16.52†(1.37)	-25.85 (1.87)	-33.23 (2.06)	-42.02 (2.25)
Pain during climbing up and down the stairs	DJW	-17.59 (2.03)	-28.01 (2.36)	-36.70 (2.24)	-47.06 (2.09)
	Diclofenac	-19.23 (1.43)	-30.72 (1.93)	-39.13 (2.04)	-48.44 (2.34)
Night pain	DJW	-16.52 (2.41)	-26.87 (2.32)	-35.00 (2.47)	-41.81 (2.63)
	Diclofenac	-20.53 (2.06)	-29.05 (2.36)	-35.27 (2.54)	-42.04 (2.82)
Resting pain	DJW	-11.77 (1.29)	-19.43 (1.50)	-27.21 (1.88)	-32.76 (2.01)
	Diclofenac	-14.90 (1.39)	-21.76 (1.98)	-27.04 (2.13)	-32.06 (2.43)
Total pain[a]	DJW	-76.25 (6.78)	-123.69 (7.52)	-166.31 (7.67)	-207.50 (8.03)
	Diclofenac	-92.41 (5.32)	-137.69 (7.02)	-176.27 (7.46)	-216.68 (8.69)
Pain during the most painful knee movement	DJW	-19.68 (2.21)	-34.09 (2.70)	-46.78 (2.78)	-58.35 (2.54)
	Diclofenac	-25.31 (2.16)	-38.37 (2.54)	-49.43 (2.56)	-60.35 (2.51)
VAS assessing stiffness (mm)					
Morning stiffness	DJW	-17.52 (2.07)	-26.50 (2.32)	-35.38 (2.51)	-43.17 (2.59)
	Diclofenac	-20.20†(1.74)	-30.53 (2.16)	-39.32 (2.53)	-47.08 (2.66)
Stiffness after rest	DJW	-17.62 (2.06)	-30.38 (2.47)	-41.14 (2.48)	-51.17 (2.43)
	Diclofenac	-22.03†(1.74)	-32.67 (2.07)	-44.19 (2.21)	-54.11 (2.24)
Total stiffness[b]	DJW	-35.14 (3.63)	-56.88 (4.10)	-76.52 (4.15)	-94.34 (4.05)
	Diclofenac	-42.23†(3.12)	-63.20 (3.77)	-83.51 (4.17)	-101.19 (4.31)
Lequesne's functional index (score)	DJW	-2.78 (0.35)	-3.32 (0.33)	-4.51 (0.37)	-5.58 (0.38)
	Diclofenac	-4.14†(0.31)	-4.31†(0.33)	-5.46 (0.36)	-6.46 (0.40)
Time for climbing up the stairs (s)	DJW	-2.02 (0.33)	-2.27 (0.31)	-2.76 (0.32)	-3.24 (0.31)
	Diclofenac	-2.27 (0.31)	-2.38 (0.35)	-2.89 (0.35)	-3.36 (0.33)

Data represent mean (SD). [a]Summation of VAS assessing walking pain, standing pain, pain during climbing up and down the stairs, night pain and resting pain, [b]summation of VAS assessing morning stiffness and stiffness after rest. $^{\dagger}p<0.05$ versus DJW group at the same duration of treatment.

A. Intent-to-treat analysis



B. Analysis on completers

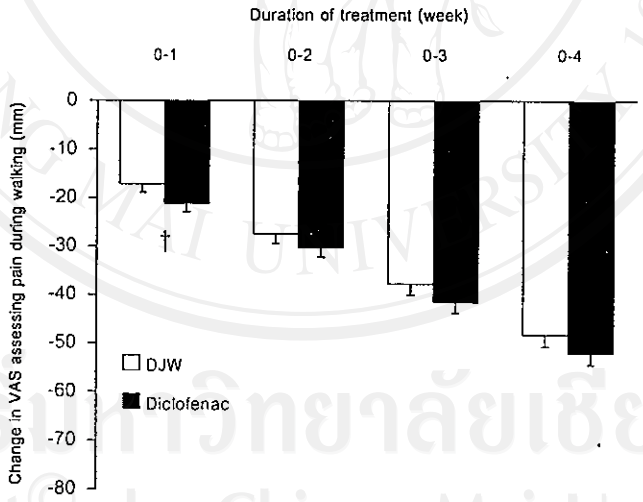
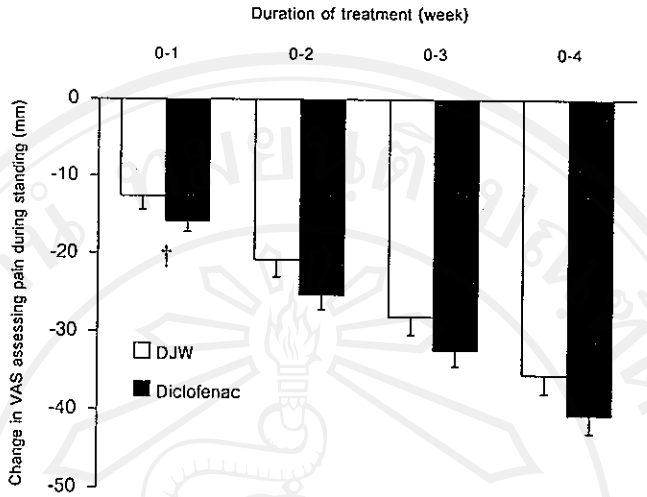


Figure 14. Changes in VAS assessing pain during walking compared to the base-line values. Data represent mean±SD. † $p < 0.05$ between group analysis.

A. Intent-to-treat analysis



B. Analysis on completers

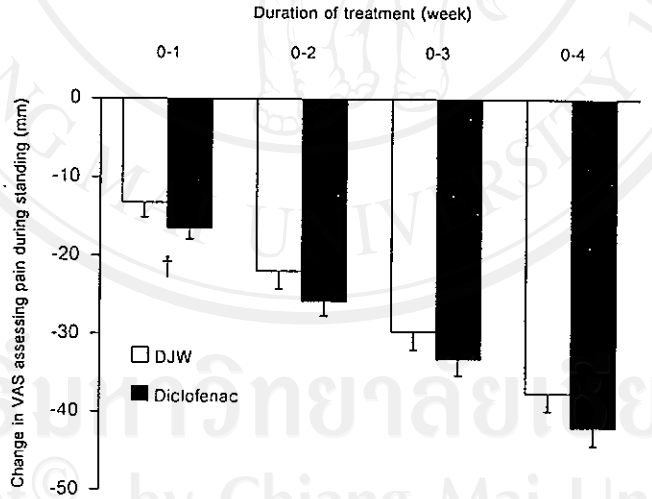
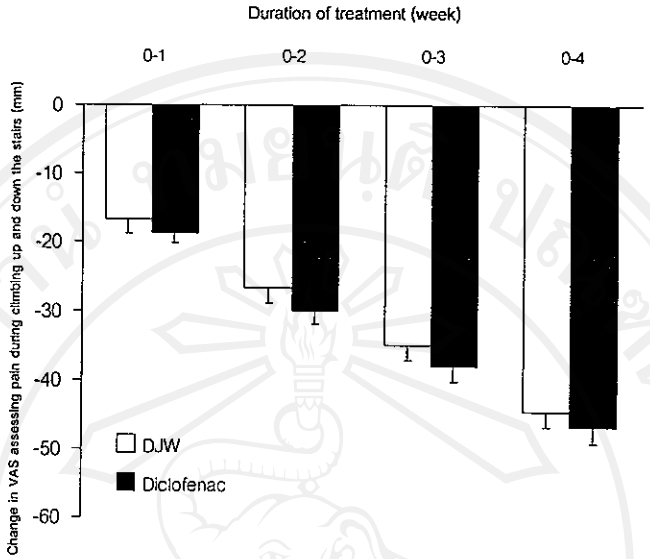


Figure 15. Changes in VAS assessing pain during standing compared to the base-line values. Data represent mean±SD. $^{\dagger}p$ <0.05 between group analysis.

A. Intent-to-treat analysis



B. Analysis on completers

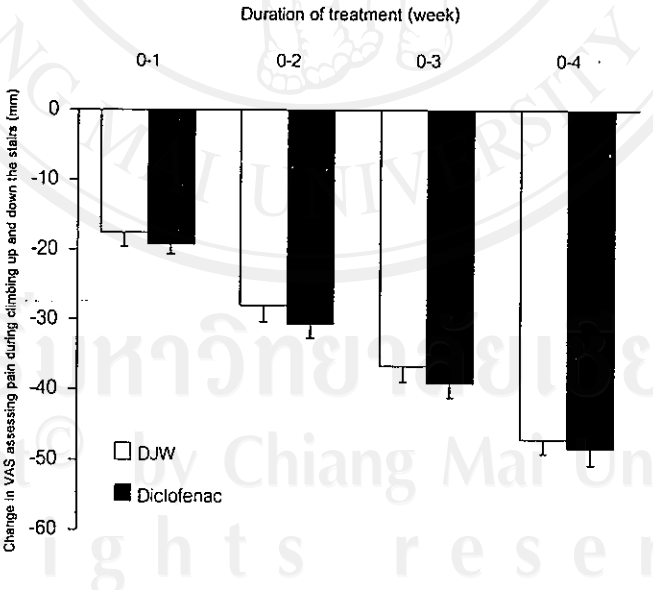
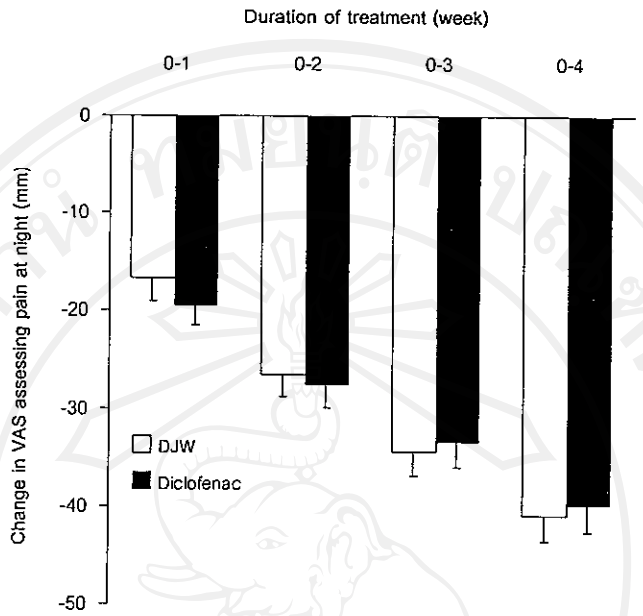


Figure 16. Changes in VAS assessing pain during climbing up and down the stairs compared to the base-line values. Data represent mean±SD.

A. Intent-to-treat analysis



B. Analysis on completers

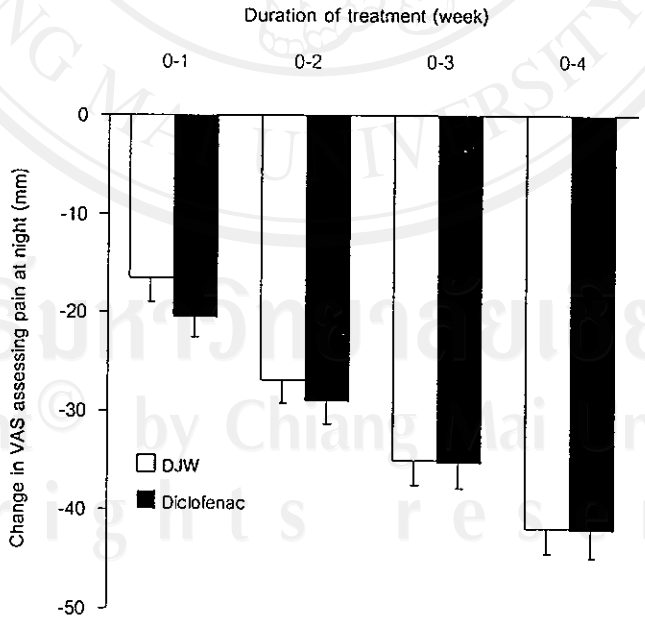
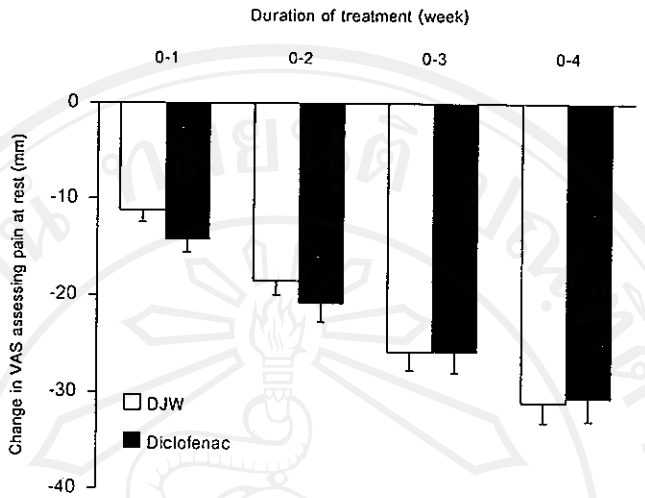


Figure 17. Changes in VAS assessing pain at night compared to the base-line values.

Data represent mean±SD.

A. Intent-to-treat analysis



B. Analysis on completers

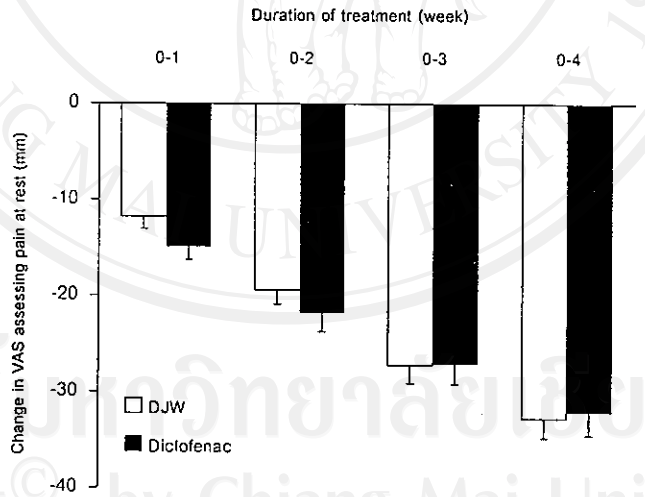
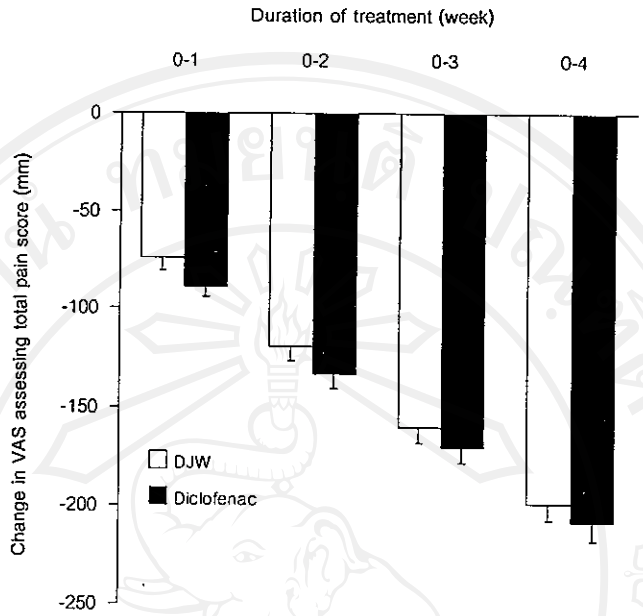


Figure 18. Changes in VAS assessing pain at rest compared to the base-line values.

Data represent mean±SD.

A. Intent-to-treat analysis



B. Analysis on completers

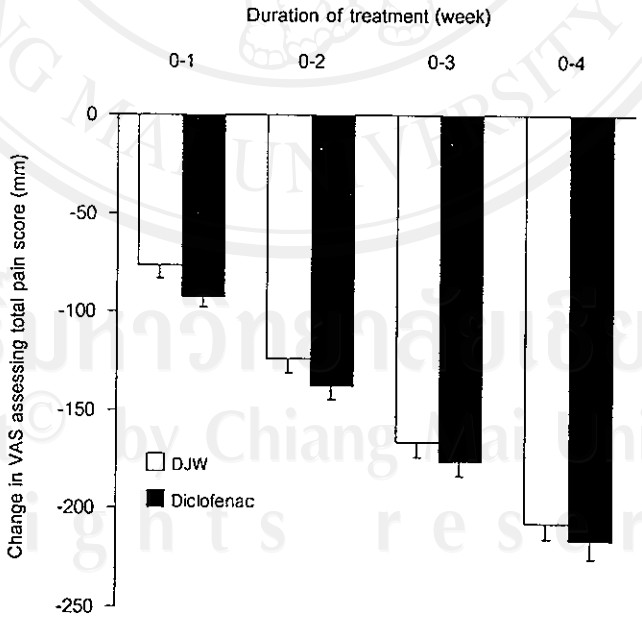
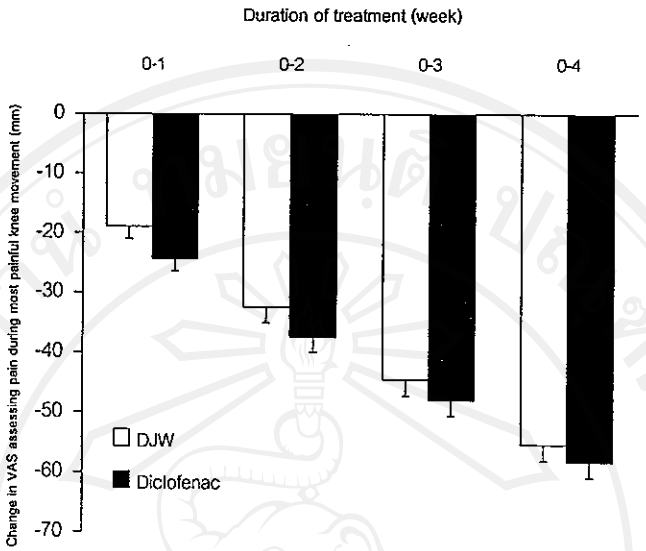


Figure 19. Changes in VAS assessing total pain score compared to the base-line values. Data represent mean±SD.

A. Intent-to-treat analysis



B. Analysis on completers

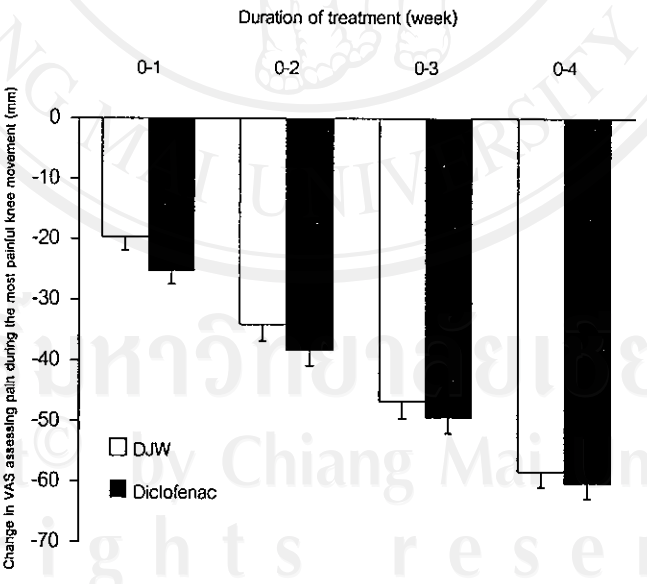
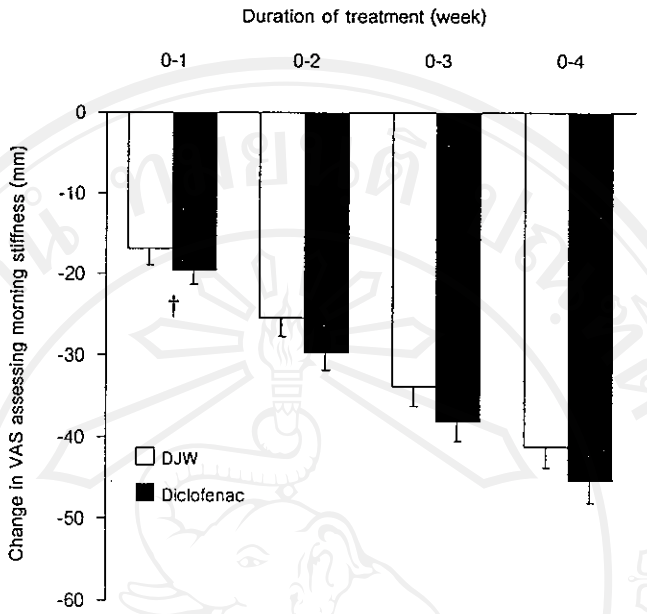


Figure 20. Changes in VAS assessing pain during the most painful knee movement compared to the base-line values. Data represent mean±SD. $^{\dagger}p < 0.05$ between group analysis.

A. Intent-to-treat analysis



B. Analysis on completers

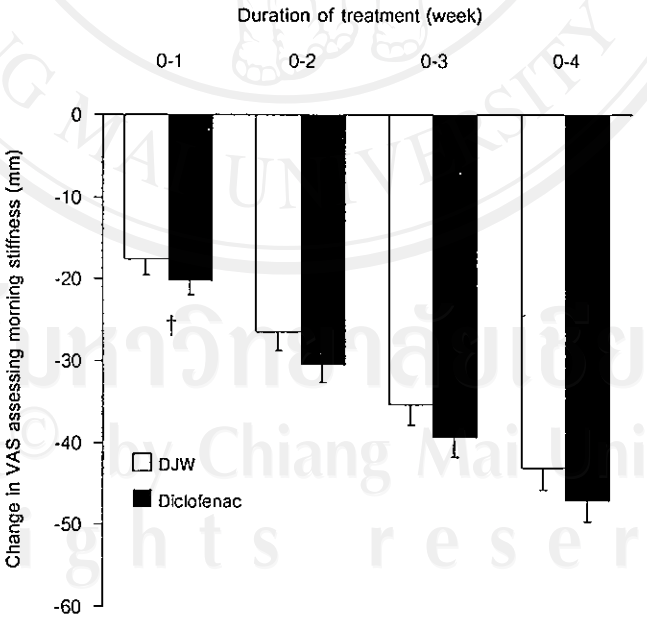
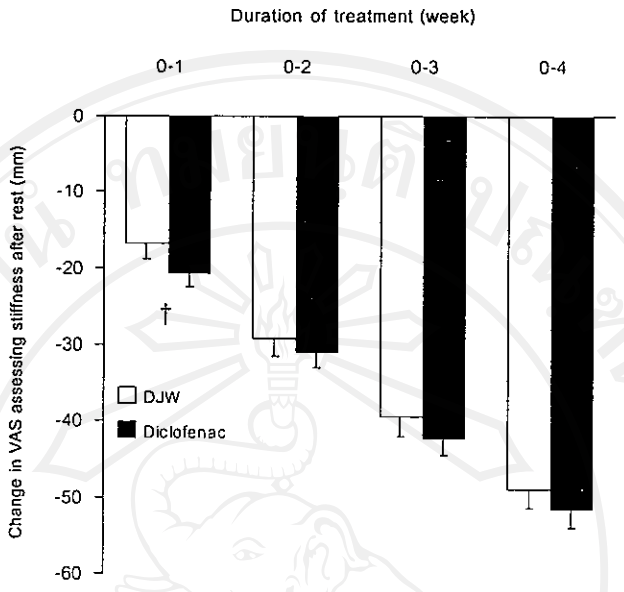


Figure 21. Changes in VAS assessing morning stiffness compared to the base-line values. Data represent mean±SD. $^{\dagger}p < 0.05$ between group analysis.

A. Intent-to-treat analysis



B. Analysis on completers

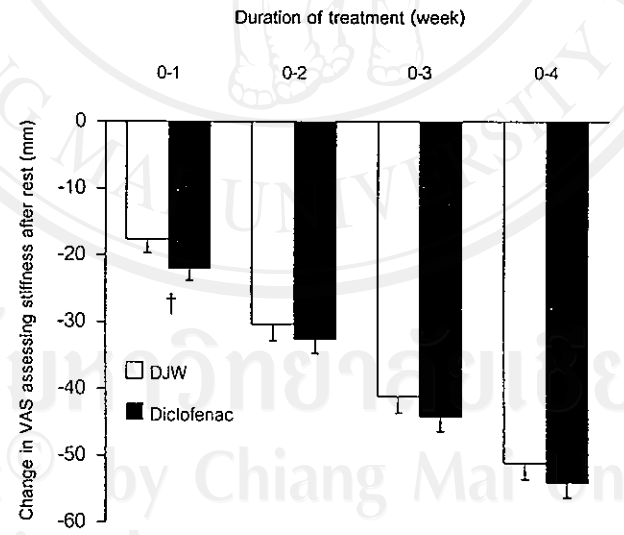
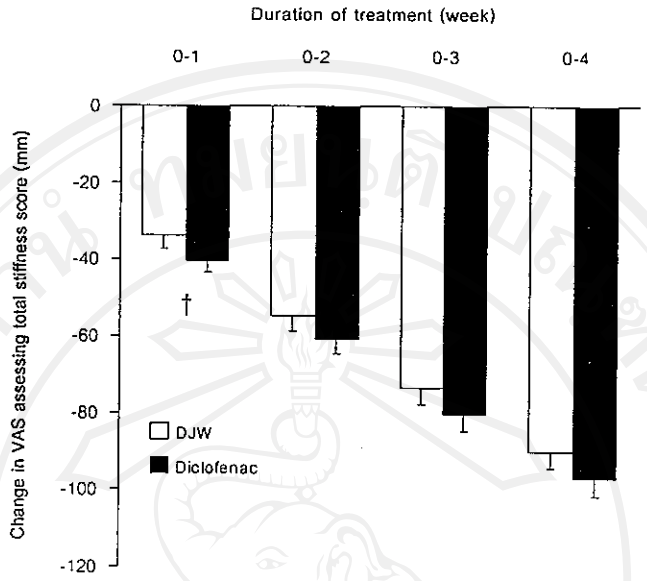


Figure 22. Changes in VAS assessing stiffness after rest compared to the base-line values. Data represent mean±SD. $^{\dagger}p$ <0.05 between group analysis.

A. Intent-to-treat analysis



B. Analysis on completers

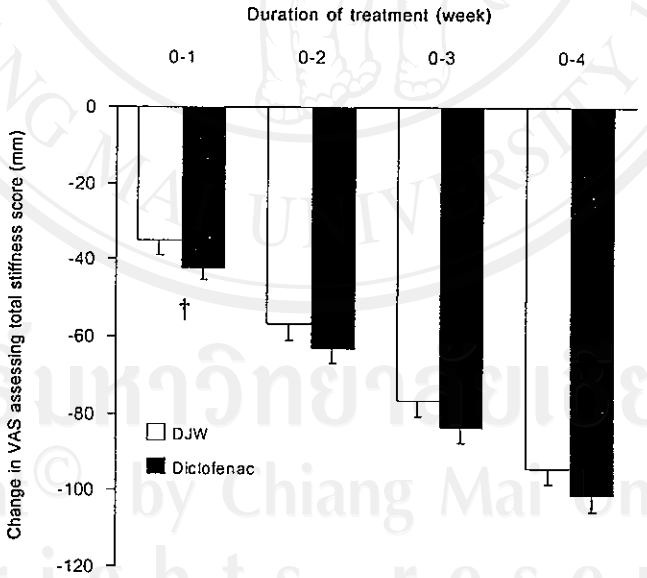
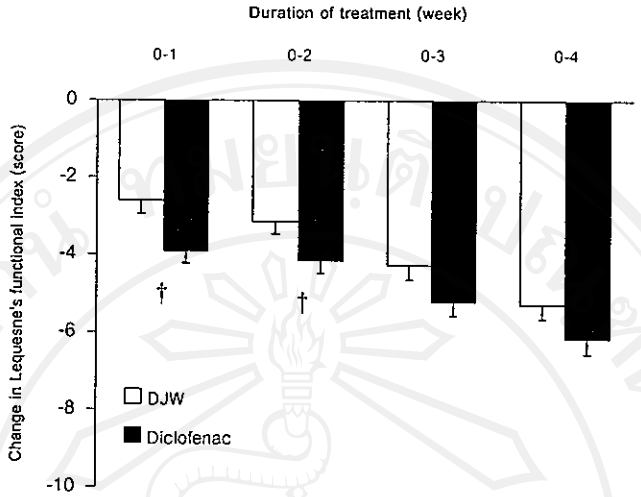


Figure 23. Changes in VAS assessing total stiffness score compared to the base-line values. Data represent mean±SD. $^{\dagger}p$ <0.05 between group analysis.

A. Intent-to-treat analysis



B. Analysis on completers

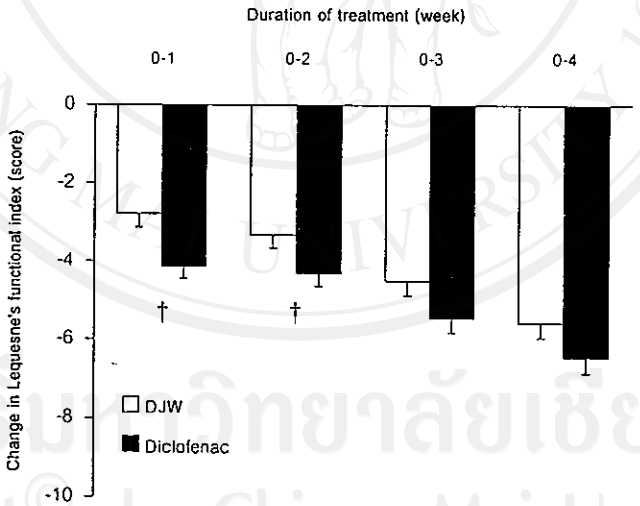
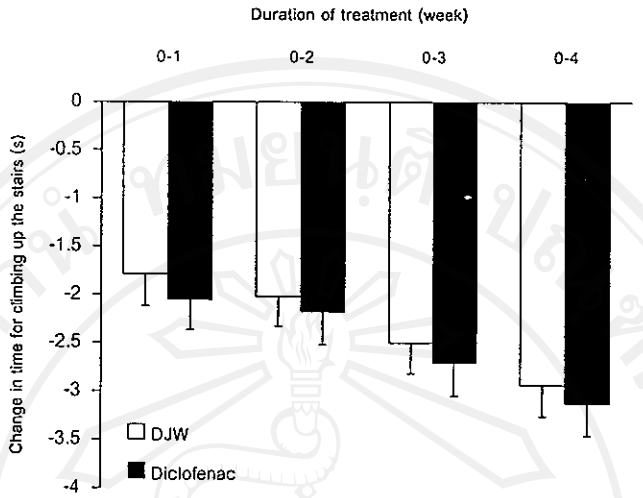


Figure 24. Changes in Lequesne's functional index compared to the base-line values. Data represent mean±SD. $^{\dagger}p$ <0.05 between group analysis.

A. Intent-to-treat analysis



B. Analysis on completers

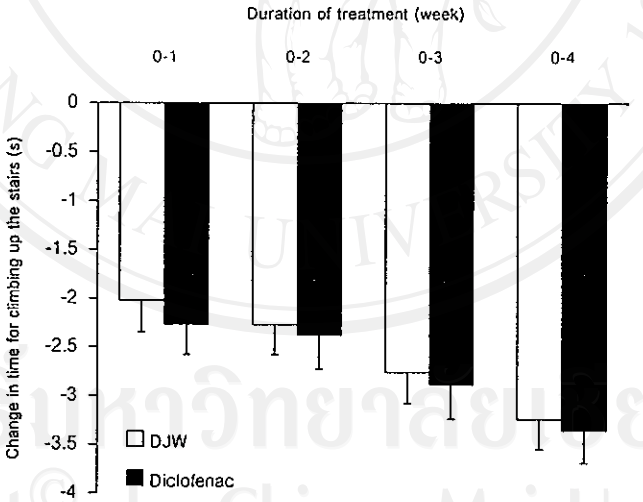


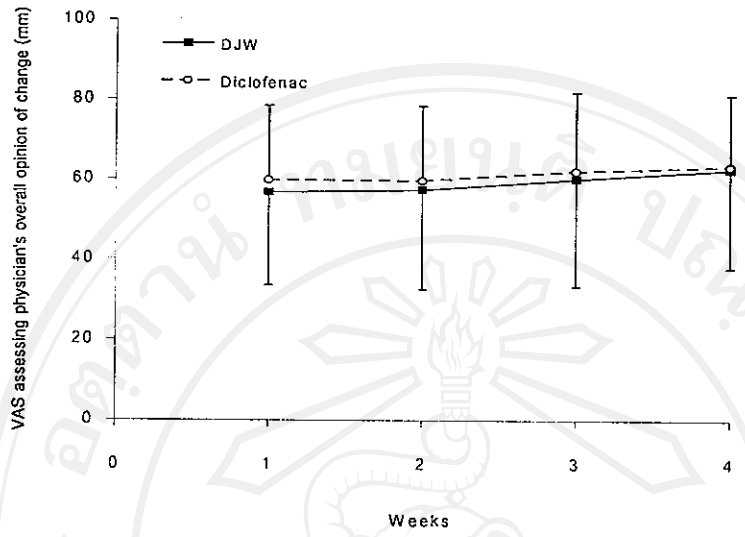
Figure 25. Changes in time for climbing up the stairs compared to the base-line values. Data represent mean±SD.

Table 20. Physician's and patients'overall opinions evaluated during treatment.

Variable	Treatment group	n	Week 1	Week 2	Week 3	Week 4
Intent-to-treat data set						
VAS assessing						
Physician's overall opinion	DJW	98[a]	56.69 (11.32)	57.30 (11.32)	60.06 (12.47)	62.55 (11.67)
	Diclofenac	97[a]	59.84 (7.53)	59.63 (7.74)	62.11 (7.57)	63.35 (7.90)
Patients' overall opinion	DJW	98[a]	32.58 (23.18)	45.53 (24.74)	58.10 (26.84)	71.13 (24.68)
	Diclofenac	97[a]	37.48* (18.59)	50.24 (18.79)	62.88 (19.75)	75.30 (17.95)
Completer data set						
VAS assessing						
Physician's overall opinion	DJW	94	57.34 (10.82)	57.88 (10.78)	60.70 (11.85)	63.29 (10.79)
	Diclofenac	94	59.96 (7.60)	59.76 (7.80)	62.23 (7.63)	63.51 (7.95)
Patients' overall opinion	DJW	94	32.84 (23.35)	46.00 (24.42)	58.96 (26.09)	72.55 (23.10)
	Diclofenac	94	37.55* (18.70)	50.24 (18.89)	62.96 (19.96)	75.77 (17.93)

Data represent mean (SD). [a]2 patients in DJW group and 3 patients in diclofenac group could not be assessed due to loss to follow up or withdrawn during week 0. *$p<0.05$ versus DJW group at week 1.

A. Intent-to-treat analysis



B. Analysis on completers

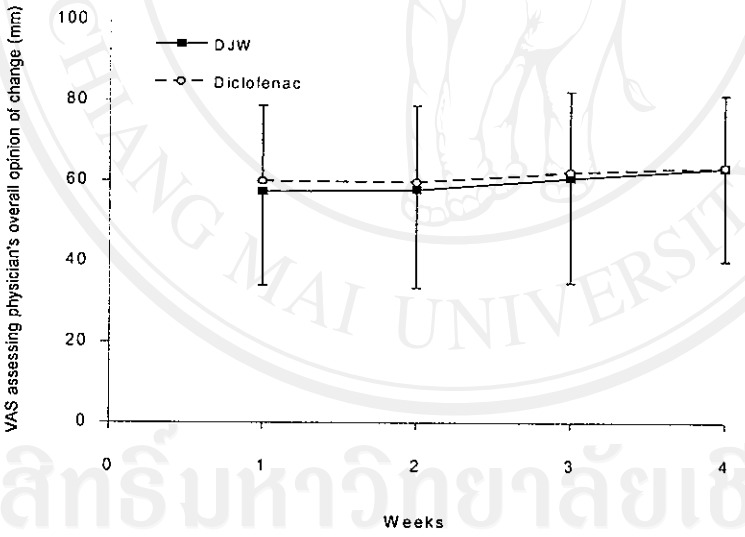
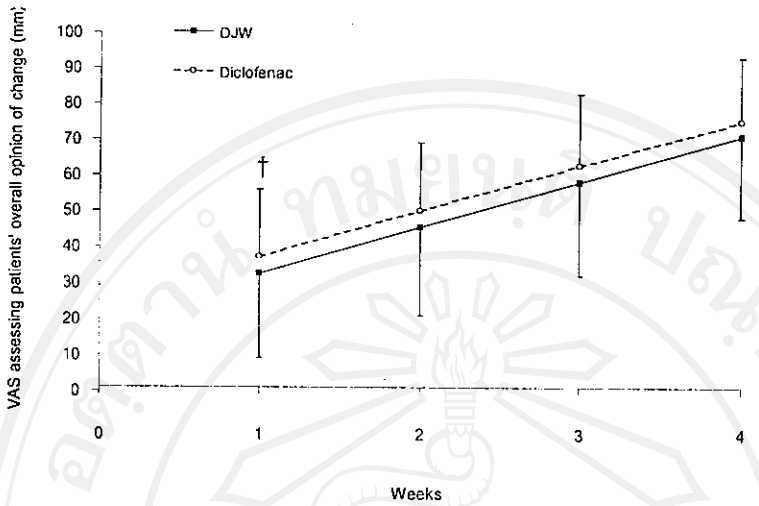


Figure 26. Mean VAS assessing physician's overall opinion of change in each treatment group evaluated during treatment. Data represent mean±SD.

A. Intent-to-treat analysis



B. Analysis on completer

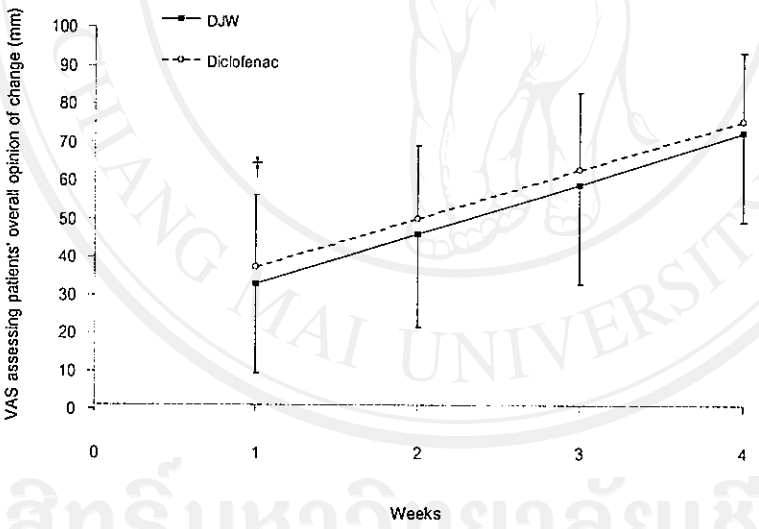


Figure 27. Mean VAS assessing patients' overall opinion of change in each treatment group evaluated during treatment. Data represent mean±SD. $^{\dagger}p < 0.05$ between group analysis.

Table 21. Percentage of patients experienced adverse events during treatment*.

Adverse events	Treatment groups: DJW (n = 100)	Treatment groups: Diclofenac (n = 100)	*p* value
No adverse events	72	73	NS
Raised blood pressure[a]	16	19	NS
Central nervous system symptoms (dizziness, somnolence, drowsiness)	16	11	NS
Gastrointestinal symptoms (dyspepsia, diarrhea, constipation, nausea/vomiting)	12	5	NS
Increased appetite	3	2	NS
Cramp	0	2	NS
Rash	0	1	NS
Flu	1	0	NS
Accident	1	3	NS

*More than one adverse events might be occurred in some patients. [a]Normotensive patient whose blood pressure was raised to 140/90 at least 2 consecutive weeks or hypertensive patient whose blood pressure was raised to more than base-line blood pressure at least 2 consecutive weeks (despite of concomitant antihypertensive drugs). NS: no statistical significance. Statistical analysis: Chi-square or Fisher's exact test.

Table 22. Number of responders at the end of the study (week 4) and at 1 and 2 month(s) after treatment*.

Treatment groups	Responders at week 4	1 month after treatment remaining responders/ evaluated responders**	2 months after treatment remaining responders/ evaluated responders**
DJW	73	33/66	20/64
Diclofenac	78	23/66	8/64
p value	0.41	0.046	0.01

*Only the responders at the end of the study were followed up to 2 months. **Some patients were unable to be evaluated due to loss to follow up or using NSAIDs for other purposes during follow-up period. Statistical analysis: Chi-square test.