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Research Article

Efficacy and Safety of Acujoint™ in Joint Health: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study

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Abstract

Joint pain is a significant global health issue, prompting patients to seek alternatives to traditional nonsteroidal anti-inflammatory drugs and commercial supplements for joint pain and inflammation management. Efficacy and safety of Acujoint™, containing curcumin, boswellic acid, β-caryophyllene, and *Kaempferia galanga* extract, was evaluated in a randomized, double-blind, placebo-controlled trial with 132 physically active healthy subjects assigned to receive either Acujoint™ 250 mg, Acujoint™ 175 mg, or placebo. Key outcomes, including flexibility (range of motion), knee joint pain (measured by the Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC]), the Lequesne Functional Index, and the Visual Analogue Scale (VAS), showed significant improvements in both the Acujoint™ arms compared to the placebo ($p < 0.05$). These arms also exhibited better joint function, reduced osteoarthritis severity, and lower pain intensity. Only one adverse event was reported in the entire study which was mild in nature. These results indicate that Acujoint™ is effective in improving joint health and well-tolerated, suggesting it as a promising option for joint pain management.

Keywords: Acujoint™, boswellic acid, β-caryophyllene, curcumin, joint health, joint pain, Kaempferia galanga, osteroarthritis

Abbreviations: COMP (Cartilage Oligomeric Matrix Protein), CRP (C-Reactive Protein), CTX-II (C-Terminal cross-linking telopeptide of type II collagen), GCP (Good Clinical Practice, ICH (International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use), IEC (Independent Ethics Committee), IL-6 (Interleukin-6), KL (Kellgren-Lawrence score), OA (Osteoarthritis), PP (Per protocol), ROM (Range Of Motion), VAS (Visual Analog Scale) and WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index).

CTRI Registration: CTRI/2023/08/056099

Introduction

Joint pain, a common source of chronic discomfort, affects individuals of all ages but is particularly prevalent among older populations. It can stem from various causes such as arthritis, infections, autoimmune diseases, inflammation, and mechanical injuries, with knee pain being particularly frequent in adults [1] Besides arthritis, many otherwise healthy people experience pain

due to injuries, with knee injuries often resulting from sudden twisting or overuse from activities like walking, running, or cycling [2] Preventive measures include limiting joint overuse, encouraging healthy habits such as regular exercise, good nutrition, and keeping a healthy weight [3] The pathogenesis of joint pain involves inflammatory mediators sensitizing nociceptive receptors, which results in increased pain sensitivity and, potentially, chronic pain via central sensitization [1]

If acute symptoms are not treated in time, in the worst case, chronic conditions such as osteoarthritis can develop. The pathophysiology of OA involves a degenerative cascade leading to progressive cartilage loss and bone damage, characterized by subchondral cysts, osteophytes, and subchondral plate thickening. Inflammatory mediators, including interleukin-6, monokines, and macrophage chemotactic protein, induce the production of proteolytic enzymes such as matrix metalloproteinases, leading to joint collagen degradation [4] Two biochemical markers, cartilage oligomeric matrix protein (COMP) and C-terminal cross-linked telopeptides of type II collagen (CTX-II), are predictive of the development of knee OA and associated pain [5]

Current therapies for acute and chronic joint pain typically involve acetaminophen, nonsteroidal anti-inflammatory drugs, and opioids. However, continuous uses of these treatments are associated with unfavourable adverse effects as well as concerns about drug toxicity and dependency potential [1] NSAIDs primarily target pain through prostaglandin inhibition but do not address other inflammatory pathways, necessitating alternative treatments [6] In addition, NSAID therapy can lead to various side effects, such as gastrointestinal tract disorders, cardiovascular issues, liver damage, and decreased renal function. There is growing interest in natural supplements due to their potential for better tolerance and efficacy [7] Acujoint™ is a health supplement combining extracts from curcumin, boswellic acid, **β**-caryophyllene, and flavonoids obtained from *Curcuma longa, Boswellia serrata*, *Piper nigrum* and *Kaempferia galangal* respectively. These components are known for their anti-inflammatory and analgesic properties. Curcumin, a polyphenolic compound from turmeric (*Curcuma longa*) has been extensively used to treat knee OA. The active components responsible for the health benefits of turmeric are mainly curcuminoids, viz, Curcumin, Demethoxy curcumin and Bis Demethoxy curcumin. There are many mechanisms responsible for the anti-inflammatory activity of curcuminoids which include Downregulation of COX-2 and iNOS enzymes, Suppression of NF-kB activation, Inhibition of arachidonic acid metabolism via lipoxygenase and scavenging of free radicals generated in this pathway, Inhibition of production of inflammatory cytokines, TNF-α, IL-1, IL-2, IL-6, IL-8, IL-12.etc [7]. Traditionally *Boswellia serrata* extract is used in the Indian Ayurvedic medicine for the treatment of inflammatory diseases. The extract is rich in boswellic acids, especially 3-O-acetyl-11- keto-β-boswellic acid (AKBA), which can inhibit 5-lipoxigenase enzyme as well as NF-κB (nuclear factor kappa B) and TNF-α (tumour necrosis factor α) in many inflammatory pathways Boswellia extract can reduce pain, swelling, and stiffness of joint in OA compared to standard treatment [8] **β**-caryophyllene (BCP), a natural sesquiterpene present in *Piper nigrum or clove*, is a selective agonist of cannabinoid receptor type-2 (CB2) of the endocannabinoid system [9] BCP showed tissue protective properties and favorably modulates numerous signalling pathways and inhibits inflammatory mediators, including cytokines, chemokines, adhesion molecules, prostanoids, and eicosanoids. [10]. The *Kaempferia galangal* rhizome extract is used traditionally for inflammatory disorders. *K. galangal* extracts are used for the treatment of swelling, cytotoxic, antihypertensive, hypolipidemic effect. *K galanga* L. contains essential oils that can provide analgesic and anti-inflammatory effects, especially in arthritis disease. [11]. This study aims to evaluate the efficacy and safety of Acujoint™ 250 mg and 175 mg compared to a placebo in managing joint pain in Subjects with confirmed diagnosis of mild to moderate join pain over a 180-day period.

Materials and Methods

Test Products

Acujoint™ is a commercially available dietary supplement formulated with a combination of four components: turmeric extracts (Curcumin and turmeric water extract) comprising 32–36%, 3-O-acetyl-11-keto-β-boswellic acid (AKBA) at 18–22%, β-caryophyllene at 18–22%, and flavonoids from *Kaempferia galanga* extract at 22–26%. Acujoint™ 250 mg and Acujoint™ 175 mg are a yellow-coloured soft capsules. The placebo was an identically appearing soft capsule matching the appearance of the active capsules. Subjects were instructed to take one capsule daily for 180 days after food. They were also advised to maintain their usual diet and physical activity levels throughout the study period. At the end of the study, compliance was calculated as the number of capsules taken divided by the number of capsules dispensed, multiplied by 100. Treatment compliance is defined as administration of at least 80% but no more than 120% of the expected administration while enrolled in the study.

Ethics

The study was conducted at two clinical sites across India in city of Ahmedabad, adhering to regulatory and ethical guidelines including the Declaration of Helsinki, ICH GCP, and the New Drug and Clinical Trial Rules 2019, CDSCO, INDIA. The study protocol and related documents received approval from the institutional ethics committee prior to the initiation of trial activities. Written informed consent was obtained from all subjects before any screening assessments were conducted. The study was registered with the Clinical Trials Registry of India on Aug 3, 2023 (CTRI/2023/08/056099).

Subjects and Eligibility Criteria

Male and female subjects who were physically active, experienced knee joint pain after physical activity and were otherwise healthy were contacted for the study. All subjects provided voluntary written informed consent prior to screening. Subjects were screened according to predefined inclusion and exclusion criteria. They were included in the trial if they were aged 30 to 65 years, engaged in knee joint movement exercises (such as walking, jogging, cycling) at least three times a week, had a history of knee joint pain exacerbated by physical stress for 4 to 9 months with a Kellgren-Lawrence (KL) score of 0 to 2, and had a body mass index (BMI) between 20 and 35 kg/m^2. They needed to self-report knee joint pain of ≥ 70 mm on a 100-point Visual Analogue Scale (VAS) during extreme knee movement and pain ≤ 30 mm at rest on the Pain VAS. They should not have been diagnosed with osteoarthritis

(OA) or rheumatoid arthritis (RA) based on the American College of Rheumatology (ACR) criteria. Subjects also had to be willing to complete all study procedures, including questionnaires, comply with study requirements, report any use of other analgesics or pain relief drugs, and provide written, signed, and dated informed consent. Subjects were excluded from the study if they were obese with a BMI greater than 35 kg/m^2, unable to complete the exercise protocol of 10±2 minutes during screening, or had a clinical diagnosis of joint diseases such as osteoarthritis or autoimmune disorders like rheumatoid arthritis. Additionally, those suffering from insomnia or restless leg syndrome, uncontrolled hypertension (with systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg despite antihypertensive medication), or a history of asthma or diabetes were excluded. Other exclusion criteria included recent knee joint injury within the past six months, a history of knee surgery or other non-knee surgical procedures that could impact study outcomes, use of intra-articular injections or steroids for joint health in the last six months, significant cardiovascular events in the past six months, or clinically significant renal, hepatic, endocrine, biliary, gastrointestinal, pancreatic, or neurological disorders that might interfere with the study. Subjects with chronic or inflammatory diseases or those using medications, dietary supplements, Ayurveda treatments, or topical ointments for joint health that could pose unacceptable risks were also excluded. Furthermore, pregnant, planning to become pregnant, lactating females, or those taking oral contraceptives, individuals with a history of heavy alcohol consumption, and smokers or those using joint health supplements for pain or inflammation were not eligible for the study.

Experimental Design

This study was a randomized, double-blind, placebo-controlled, parallel-group clinical trial involving 132 subjects. Eligible subjects were randomized in a 1:1:1 ratio to receive either Acujoint™ 250 mg, Acujoint™ 175 mg (test arms) or a placebo once daily for 180 days. The randomization schedule was generated using a computerised random number generator with fixed block sizes to protect the identity of treatment assignment. Subjects were withdrawn from the study if they withdrew consent, were non-adherent to the study procedures, or experienced adverse events that significantly impacted their safety or the study results-were withdrawn from the study following the investigator's decision.

Study visits

Subjects visit the study centre eight times for evaluation of study parameters: during the screening and randomization visit days -5 to 1 and subsequent follow-up visits on days 4, 15, 30, 60, 90, 120 and the end-of-treatment (EOT) visit day 180. There was a telephonic follow-up post-study one month after day 180.

Minimum Core Set

Osteoarthritis Research Society International (OARSI) recommended set and minimal core set of performance-based tests to assess physical function in people diagnosed with hip and knee OA. [12] Subjects had to perform three minimum core sets which included a 30-second chair stand test, stair climb test and fast paced walk test on days 1, 4, 15, 30, 90, 120, and 180 (EOT) before evaluating any study endpoints.

Primary Efficacy Assessment

Flexibility

It was evaluated by range of motion (ROM) goniometry to determine changes from baseline to the end of treatment [13].

Knee Joint Pain

Knee joint pain was assessed by WOMAC Osteoarthritis Index, which includes 24 questions across three subscales: pain, stiffness, and difficulty with daily activities. Scores range from 0 to 4, with lower scores indicating less pain and better function. Measurements were taken from baseline to the end of the treatment. [14].

Lequesne Algo functional Index (LAI)

LAI was used to evaluate therapeutic effectiveness, covering pain, walking distance, and daily activities from baseline to the end of the treatment [15]

Change in VAS score

Pain was assessed using a 100-mm VAS during joint movement and joint rest. The scale ranges from 0 (no pain) to 100 (unbearable pain). Subjects recorded their pain intensity at each visit [7].

Secondary Efficacy Assessments

Inflammation assessment by change in CRP levels

CRP is one of the plasma proteins that significantly increases in persons with inflammatory diseases or in the event of body tissue necrosis and is an acute phase protein. It was measured from baseline to day 4, day 30, day 90 and day 180.

Inflammation as assessed by the change in the IL-6 levels

Interleukin-6 (IL-6) Levels: Immune response and inflammation was assessed by change in IL-6 levels from baseline to day 30, day 90 and day 180.

Change in exercise-induced cartilage turnover

Serum Cartilage Oligomeric Matrix Protein (COMP): COMP was monitored for changes in cartilage turnover from baseline IL-6 levels from baseline to day 30, day 90 and day 180.

Urinary CTX-II Levels: It was assessed to evaluate cartilage degradation from baseline to day 30, day 90 and day 180.

Improvement Assessment

Patient and Physician ratings were evaluated using the Patient's Global Impression of Change Scale (PGIC) and Physician's Global Assessment (PGA), respectively at baseline and the end of the treatment.

Safety Evaluations

The safety analysis assessed the type and incidence of adverse events (AEs), their severity, and their association with the test products. Additionally, clinical pathology tests (hematologic, biochemistry and blood lipids), vital signs (pulse, blood pressure, respiratory rate and body temperature) and physical measurements results were summarized descriptively. Adverse events were classified according to the Medical Dictionary for Regulatory Activities (MedDRA).

Statistics

Sample Size

Considering a common standard deviation of 4.50 for joint health assessment tools at the end of treatment, a total of 120 subjects was considered sufficient to detect a mean difference of 3.00 between any two treatments with power of 90% and a 0.05 two-sided level of significance. A sample size of total of 132 subjects were enrolled assuming 15% drop out at the end of the study.

Statistical analysis

Mean change in efficacy parameters from baseline to end of the study were analyzed using unpaired "t" test depending upon the distribution of data (For between group comparison). For Within group comparison, mean change in efficacy parameters from baseline to end of the study were analyzed using paired "t" test or depending upon the distribution of data. Normality test (Shapiro-Wilks test) was used to check the distribution of data. All tests were 2 sided. P values of less than 0.05 were considered as a statistically significant difference between treatment groups. The data presented as mean (±Standard deviation).

Results

Disposition of subjects

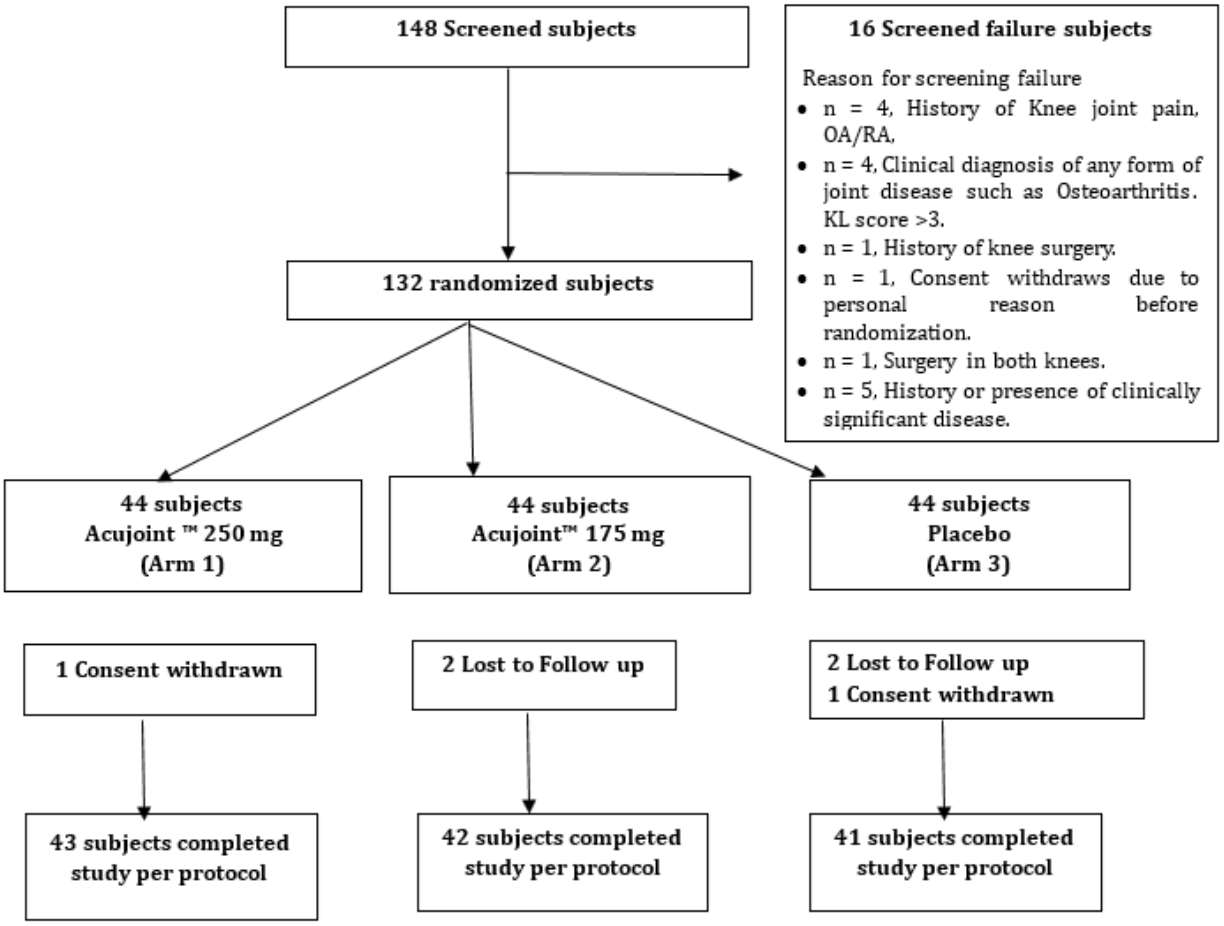

Figure 1: Subject disposition diagram
n= number of subjects

The study was conducted from Aug 17, 2023, to May 24, 2024. 132 subjects were randomized into three arms: Acujoint™ 250 mg (Arm 1, n = 44), Acujoint™ 175 mg (Arm 2, n = 44), or placebo (Arm 3, n = 44). In the Acujoint™ 250 mg arm, one subject withdrew consent. In the Acujoint™ 175 mg arm, two subjects were lost to follow-up. In the placebo arm, one subject withdrew consent and two were lost to follow-up. This resulted in 126 subjects completing the study. Figure 1 illustrates the disposition of subjects.

Subject Characteristics

A comparison of the demographic characteristics (age, gender, height, weight and BMI) across treatment arms is summarized in

the (Table 1) below. In the Acujoint™ 250 mg (Arm 1), there were 23 men and 21 women, with an average age of 41.64 years (SD = 7.80), height of 160.97 cm (SD = 7.50), weight of 64.68 kg (SD = 7.00), and BMI of 25.02 (SD = 2.68). The Acujoint™ 175 mg (Arm 2) had 20 men and 24 women, with an average age of 42.89 years (SD = 7.56), height of 160.72 cm (SD = 8.57), weight of 64.28 kg (SD = 7.47), and BMI of 24.92 (SD = 2.52). The placebo arm was comprised of 22 men and 22 women, with an average age of 43.95 years (SD = 7.62), height of 161.93 cm (SD = 7.50), weight of 64.74 kg (SD = 6.95), and BMI of 24.74 (SD = 2.66). There were no significant differences in baseline characteristics between the arms, indicating that the arms were comparable for evaluating differences in efficacy and safety.

Table 1: Participants demographic characteristics

Characteristics		Acujoint™ 250 mg (Arm 1) (N= 44)	Acujoint™ 175 mg (Arm 2) (N= 44)	Placebo (Arm 3) (N= 44)	Overall (N= 44)
Age (in years)	Mean ±SD	41.64 ±7.80	42.89 ±7.56	43.95 ±7.62	42.83 ±7.66
	Min, Max	30, 63	31, 61	31, 60	30,63
Gender, n (%)	Male	23 (35.38)	20 (30.77)	22 (33.85)	65
	Female	21 (31.34)	24 (35.82)	22 (32.84)	67
Height (cm)	Mean ±SD	160.97 ±7.50	160.72 ±8.57	161.93 ±7.50	161.21 ±7.83
	Min, Max	146.5, 183	146, 178	146, 179	146, 183
Weight (kg)	Mean ±SD	64.68 ±7.00	64.28 ±7.47	64.74 ±6.95	64.57 ±7.09
	Min, Max	53, 87	48.9, 86	50.9, 85	48.9, 87
BMI (kg/m^2)	Mean ±SD	25.02 ±2.68	24.92 ±2.52	24.74 ±2.66	24.89 ±2.61
	Min, Max	20.45, 31.29	20.62, 29.76	20.13, 30.8	20.13, 31.29

mITT= modified intended to treat; Values are expressed as Mean ± SD for numerical data; For gender, data presented as absolute number; N= number of subjects in specified treatment arm; n = number of subjects in specified category

Measurements of flexibility

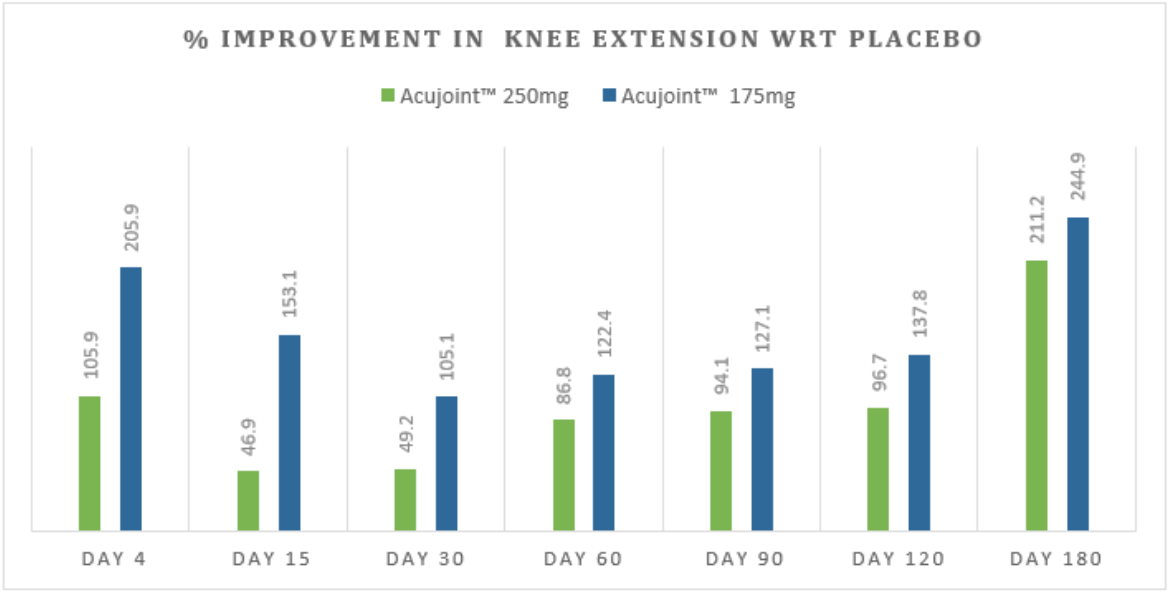

Figure 2: Percentage improvement in Knee extension of Acujoint™ 250 mg and Acujoint™ 175 mg against placebo up to day 180.

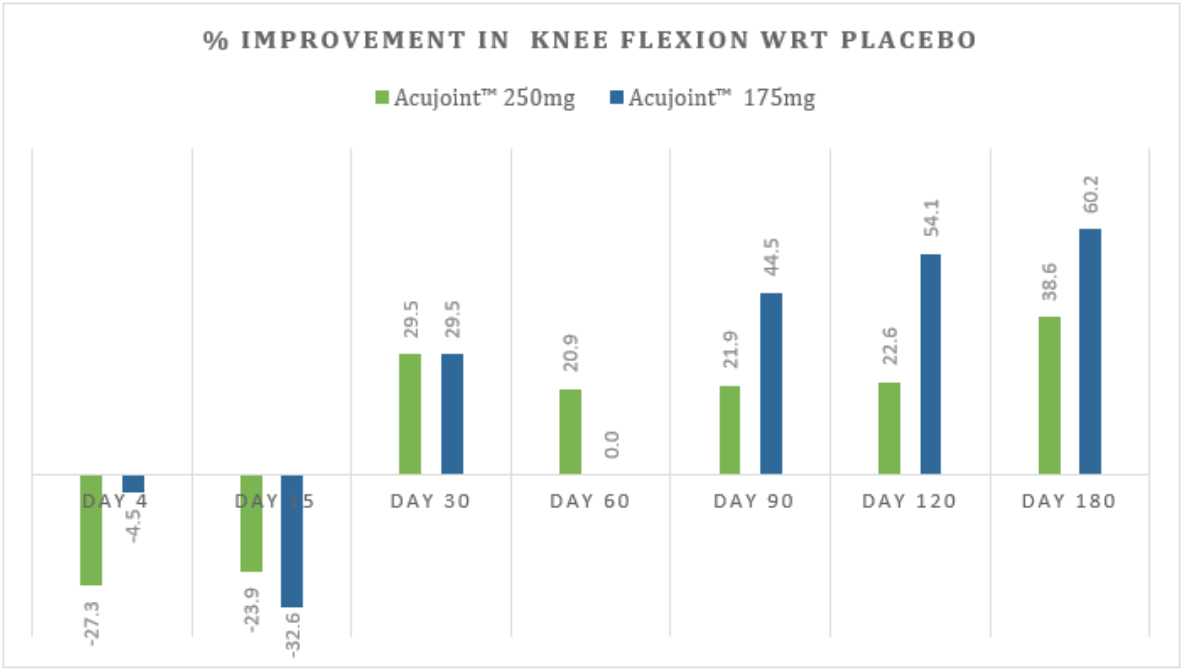

Figure 3: Percentage improvement in Knee flexion of Acujoint™ 250 mg and Acujoint™ 175 mg against placebo upto day 180.

Table 2: Changes in flexibility (Per protocol)

Variables	Acujoint™ 250 mg (Arm 1) (N= 43)	Acujoint™ 175 mg (Arm 2) (N= 42)	Placebo (Arm 3) (N= 41)
	Mean±SD	Mean±SD	Mean±SD
Knee Extension			
Baseline (Day 1)	12.63±2.06	13.17±2.05	12.12±2.16
Visit 2 (Day 4)	12.28*±1.93	12.64*±1.95	11.95±1.86
Change from baseline	0.35±1.00	0.52±1.09	0.17±0.95
Visit 3 (Day 15)	12.16*±1.70	12.36*±1.82	11.80±1.83
Change from baseline	0.47±1.01	0.81±1.27	0.32±1.15
Visit 4 (Day 30) Change from baseline	11.74*±1.69	11.95*±1.77	11.54*±1.87
	0.88±1.24	1.21±1.47	0.59±1.64
Visit 5 (Day 60)	11.21*±1.42	11.48*±1.61	11.37*±1.65
Change from baseline	1.42±1.68	1.69±1.83	0.76±1.39
Visit 6 (Day 90)	10.98*±1.28	11.24*±1.41	11.27*±1.43
Change from baseline	1.65±1.84	1.93±1.90	0.85*±1.78
Visit 7 (Day 120)	10.86*±1.13	11.02*±1.26	11.22*±1.39
Change from baseline	1.77±1.93	2.14±1.98	0.90±1.83
Visit 8 (Day 180)	9.58±2.72*$	9.79±2.66*#	11.15±1.35*$#
Change from baseline	3.05±3.28	3.38±2.79	0.98±1.52

*p-value <0.05 compared within arms based on t-test. $ p-value <0.05 based on t-test compared between Arm 1 and Arm 3. # p-value <0.05 based on t-test compared between Arm 2 and Arm 3.

For knee extension, no statistically significant differences were observed between Acujoint™ 175 mg and Acujoint™ 250 mg. However, statistically significant improvements were noted in both Acujoint™ arms compared to placebo at day 180 (Table 2) Within-group comparisons showed statistically significant improvements in knee extension from day 4 to day 180 for both the Acujoint™ arms. Specifically, Acujoint™ 175 mg arm experienced a 24.90% improvement from baseline while Acujoint™ 250 mg arm showed a 23.06% improvement. In contrast, the placebo group exhibited only a 6.58% change from baseline at day 180. The percentage improvement relative to placebo at day 180 was substantially greater in the treatment groups with the Acujoint™ 175 mg arm showing 244.90 and Acujoint™ 250 mg arm demonstrating a 211.22%, improvement. This indicates that the percentage improvement in both the test arms were much higher than in the placebo group (Figure 2). At baseline, knee flexion values were similar across the Acujoint™ 175 mg, Acujoint™ 250 mg and placebo arms. Between-group comparisons showed no statistically significant differences between Acujoint™ 175 mg and Acujoint™ 250 mg, and between both Acujoint™ arms and the placebo. Within-group analysis revealed statistically significant improvements in knee flexion from day 30 to day 180 in both Acujoint™ arms. Specifically, at 180 days the Acujoint™ 175 mg arm showed 2.74° change from a baseline while Acujoint™ 250 mg arm showed 2.37° change from baseline. In contrast, the placebo arm showed a mean change of 1.71° from baseline. As compared to placebo at day 180, the % improvement in Acujoint™ 175 mg was 60.23% and in Acujoint™ 250 mg was found to be 38.59% (Figure 3).

Knee Joint Pain

Baseline WOMAC total scores were similar across the Acujoint™ 175 mg, Acujoint™ 250 mg and placebo arms. Between-group analysis showed statistically significant reductions in the total WOMAC score for Acujoint™ 175 mg compared to placebo at day 120 and day 180 ($p<0.05$). Acujoint™ 250 mg also showed statistically significant improvement as compared to placebo at all visits from day 60 to day 180 ($p<0.05$) (Table 3). Specifically, at day 180, the Acujoint™ 175 mg showed 37.81% improvement from baseline while the improvement was 35.95% in the case of Acujoint™ 250 mg. In contrast, the placebo arm showed an improvement of 19.70%. As compared to placebo at day 180, the % improvement in Acujoint™ 175 mg was 104.64% and in Acujoint™ 250 mg was found to be 100.48% (Figure 4).

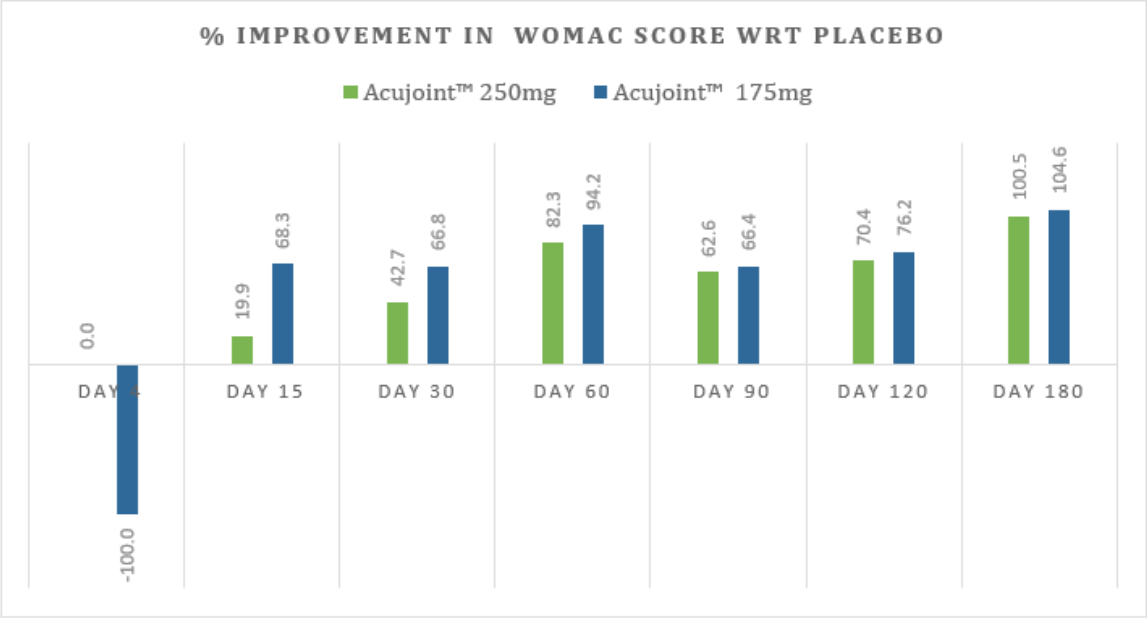

Figure 4: Percentage improvement in Total WOMAC score of Acujoint™ 250 mg and Acujoint™ 175 mg against placebo at different timepoints up to day 180.

Table 3: Summary and change in WOMAC (Per protocol)

Variables	Acujoint™ 250 mg (Arm 1)(N= 43)	Acujoint™ 175 mg (Arm 2) (N= 42)	Placebo (Arm 3) (N= 41)
	Mean±SD	Mean±SD	Mean±SD
Baseline (Day 1)	36.40±15.24	38.24±15.52	37.80±14.64
Visit 2 (Day 4)	36.37±14.59	38.24±15.58	37.78±15.18
Change from baseline	0.02±2.67	0.00±3.04	0.02±4.28
Visit 3 (Day 15)	34.47*±13.16	35.52*±14.27	36.20*±14.35
Change from baseline	1.93±4.19	2.71±4.24	1.61±3.39
Visit 4 (Day 30)	31.58*±10.70	32.62*±11.80	34.44*±13.56
Change from baseline	4.81±6.24	5.62±5.45	3.37±3.85
Visit 5 (Day 60)	28.79*$±8.01	30.14*±9.60	33.63*$±12.65
Change from baseline	7.60±8.22	8.10±6.89	4.17±3.81
Visit 6 (Day 90) Change from baseline	26.60*$±7.23	28.21*±8.82	31.78*$±11.33
	9.79±9.09	10.02±7.95	6.02±4.67
Visit 7 (Day 120) Change from baseline	23.88*$±5.87	25.31*#±6.70	30.46*$#±10.51
	12.51±11.49	12.93±10.44	7.34±5.60
Visit 8 (Day 180)	19.53*$±4.15	21.02*#±4.70	29.39*$#±9.86
Change from baseline	16.86±15.70	17.21±14.09	8.41±6.02

*p-value <0.05 compared within arms based on t-test. $ p-value <0.05 based on t-test compared between Arm 1 and Arm 3. # p-value <0.05 based on t-test compared between Arm 2 and Arm 3.

Within-group analysis revealed statistically significant decreases in total WOMAC scores from day 15 to day 180 for both Acujoint™ arms. In Acujoint™ 250 mg arm the score was reduced from 36.40 ±15.24 at baseline to 19.53 ± 4.15 at visit 8. Similarly, in Acujoint™ 175 mg arm the score was decreased from 38.24 ±15.52 to 21.02 ± 4.70 (Table 3). In contrast, the placebo arm had a smaller change, from baseline to day 180, of 8.41 only.

Lequesne Algofunctional Index (LAI)

Table 4: Summary and change in Lequesne Algofunctional Index (Per protocol)

Variables	Acujoint™ 250 mg (Arm 1) (N= 43)	Acujoint™ 175 mg (Arm 2) (N= 42)	Placebo (Arm 3) (N= 41)
	Mean±SD	Mean±SD	Mean±SD
Baseline (Day 1)	9.55±3.21	9.85±4.29	9.61±2.84
Visit 2 (Day 4)	9.41±3.17	9.56±3.88	9.35*±3.02
Change from baseline	0.14±0.63	0.29±0.98	0.26±0.51
Visit 3 (Day 15)	8.73*±3.08	9.02*±3.51	8.96*±3.02
Change from baseline	0.81±0.92	0.82±1.29	0.65±0.68
Visit 4 (Day 30)	8.15*±2.47	8.26*±2.78	8.60*±2.73
Change from baseline	1.40±1.39	1.58±1.93	1.01±0.97
Visit 5 (Day 60)	7.40*±1.95	7.44*±2.05	8.23*±2.78
Change from baseline	2.15±1.72	2.40±2.55	1.38±1.12
Visit 6 (Day 90)	6.47*$±1.99	6.93*±2.04	7.90*$±2.67
Change from baseline	3.08±2.26	2.92±2.69	1.71±1.17
Visit 7 (Day 120)	6.03*$±1.72	6.40*#±1.61	7.68*$#±2.57
Change from baseline	3.51±2.70	3.44±3.11	1.93±1.40
Visit 8 (Day 180)	5.00*$±1.65	5.41*#±1.41	7.34*$#±2.23
Change from baseline	4.55±3.76	4.43±4.19	2.27±1.64

*p-value <0.05 compared within arms based on t-test. $ p-value <0.05 based on t-test compared between Arm 1 and Arm 3. # p-value <0.05 based on t-test compared between Arm 2 and Arm 3.

At baseline, LAI scores were similar for all treatment groups, reflecting a similar level of health status across all treatment arms at the start of the study. Between-group analysis revealed statistically significant improvement in the Acujoint™ 250 mg arm compared to placebo at day 90, and in the Acujoint™ 175 mg arm compared to placebo at day 120. No statistically significant difference was found between the Acujoint™ treatment arms (Table 4). The Acujoint™ 175 mg arm demonstrated a 35.49% improvement, Acujoint™ 250 mg arm showed a 41.10% improvement, compared to a 22.40% change in the placebo group in EOT visit. By day 180, the percentage improvements were 100.44% for the Acujoint™250 mg arm and 95.15% for the Acujoint™175 mg arm relative to placebo (Figure 5) Within-group analysis showed statistically significant reductions in LAI scores for both Acujoint™ arms from day 15 to day 180 ($p<0.05$) as compared to baseline (Table 4).

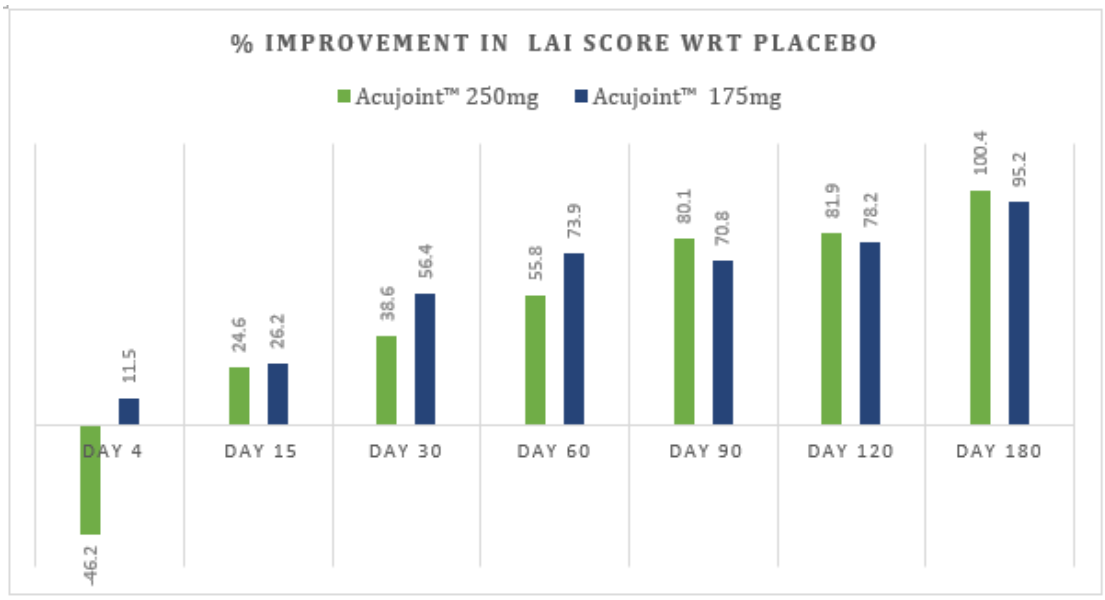

Figure 5: Percentage improvement in Lequesne Algo functional Index (LAI) of Acujoint™ 250 mg and Acujoint™ 175 mg against placebo at different timepoints up to day 180.

Change in VAS score

Table 5: Summary and change in VAS pain score on movement (Per protocol)

Variables	Acujoint™ 250 mg (Arm 1) (N= 43)	Acujoint™ 175 mg (Arm 2) (N= 42)	Placebo (Arm 3) (N= 41)
	Mean±SD	Mean±SD	Mean±SD
Baseline (Day 1)	80.79±4.32	80.50±4.06	80.61±3.98
Visit 2 (Day 4)	79.28*±3.72	79.83±3.99	79.51±3.96
Change from baseline	1.51±2.22	0.67±1.51	1.10±2.44
Visit 3 (Day 15)	77.58*±3.59	77.83*±4.09	77.90*±3.35
Change from baseline	3.21±3.24	2.67±2.04	2.71±3.18
Visit 4 (Day 30)	75.35*$±4.68	75.52*±4.61	76.98*$±3.85
Change from baseline	5.44±3.47	4.98±2.97	3.63±3.06
Visit 5 (Day 60)	71.12*$±9.30	72.55*#±6.24	75.98*$#±3.84
Change from baseline	9.67±7.42	7.95±4.92	4.63±3.06
Visit 6 (Day 90)	68.81*$±10.16	69.98*#±8.44	75.44*$#±4.35
Change from baseline	11.98±8.31	10.52±7.50	5.17±4.07
Visit 7 (Day 120)	64.67*$±14.05	66.83*#±11.81	73.76*$#±4.99
Change from baseline	16.12±12.24	13.67±10.61	6.85±4.56
Visit 8 (Day 180)	59.16*$±20.68	60.98*#±18.51	73.05*$#±6.30
Change from baseline	21.63±18.79	19.52±17.18	7.56±5.27

*p-value <0.05 compared within arms based on t-test. $ p-value <0.05 based on t-test compared between Arm 1 and Arm 3. # p-value <0.05 based on t-test compared between Arm 2 and Arm 3.

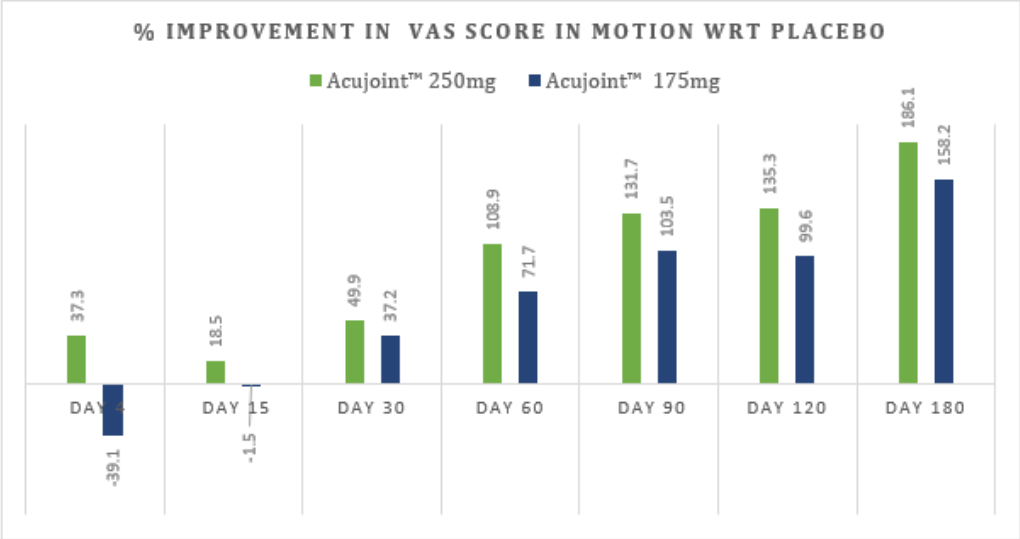

Figure 6: Percentage improvement in VAS score (at movement), of Acujoint™ 250 mg and Acujoint™ 175 mg against placebo at different timepoints up to day 180.

Joint Movement: Between-group comparisons showed statistically significant reductions in VAS scores for Acujoint™ 250 mg and Acujoint™ 175 mg compared to placebo. No statistically significant difference was observed between the two Acujoint™ arms. However, statistically significant improvements were noted from day 30 for Acujoint™ 250 mg and day 60 for Acujoint™ 175 mg when compared with placebo. The placebo arm showed minimal improvement (Table 5) Within group analysis revealed statistically significant decreases in VAS scores from day 4 to day 180 for Acujoint™ 250 mg arms while Acujoint™ 175 mg and placebo showed improvement from day 15 when compared with baseline. Overall, the test arms experienced a 24.56% (Acujoint™ 175 mg) and 27.28% (Acujoint™ 250 mg) improvement, whereas the placebo group showed only a 9.37% change as compared to baseline. However, the % improvement in Acujoint™ 250 mg was 186.11% and in Acujoint™ 175 mg was 158.20% as compared to placebo at day 180 (Figure 6).

Joint Rest: For pain at rest, statistically significant differences were observed between Acujoint™ 250 mg and Acujoint™ 175 mg compared to placebo from day 60 and day 90 respectively. No statistically significant difference was found between the two Acujoint™ arms. Both Acujoint™ arms demonstrated statistically significant improvement from day 4 (Table 6).

Table 6: Summary and change in VAS Pain score on rest (Per protocol)

Variables	Acujoint™ 250 mg (Arm 1) (N= 43)	Acujoint™ 175 mg (Arm 2) (N= 42)	Placebo (Arm 3) (N= 41)
	Mean±SD	Mean±SD	Mean±SD
Baseline (Day 1)	23.26±2.87	23.93±2.88	22.59±3.52
Visit 2 (Day 4)	22.49*±2.66	23.24*±3.37	22.41±2.64
Change from baseline	0.77±1.48	0.69±2.01	0.17±2.77
Visit 3 (Day 15)	21.60*±2.66	22.71*±2.77	21.61*±2.60
Change from baseline	1.65±1.78	1.21±1.62	0.98±2.35
Visit 4 (Day 30)	20.60*±2.25	21.00*±2.37	21.37*±2.69
Change from baseline	2.65±2.43	2.93±2.12	1.22±3.17
Visit 5 (Day 60)	19.84*$±2.87	20.38*±2.46	20.98*$±2.31
Change from baseline	3.42±3.32	3.55±2.52	1.61±3.32
Visit 6 (Day 90)	18.95*$±2.65	19.38*#±2.59	20.68*$#±2.22
Change from baseline	4.30±3.25	4.55±2.85	1.90±2.89
Visit 7 (Day 120)	17.98*$±3.70	18.79*#±2.84	20.76*$#±1.74
Change from baseline	5.28±4.45	5.14±3.45	1.83±3.40
Visit 8 (Day 180)	15.79*$±6.58	16.74*$#±5.73	20.41*$#±1.91
Change from baseline	7.47±7.32	7.19±6.45	2.17±3.83

*p-value <0.05 compared within arms based on t-test. $ p-value <0.05 based on t-test compared between Arm 1 and Arm 3. # p-value <0.05 based on t-test compared between Arm 2 and Arm 3.

The result from within group analysis showed statistically significant improvement from day 4 for both Acujoint™ arms as compared to baseline. The Acujoint™ 250 mg and Acujoint™ 175 mg achieved a 30.71% and 28.86% improvement, compared to a 6.44% change in the placebo group from baseline while % improvement was 244.24% and 231.34% for Acujoint™ 250 mg and Acujoint™ 175 mg, respectively when compared with placebo at day 180 (Figure 7).

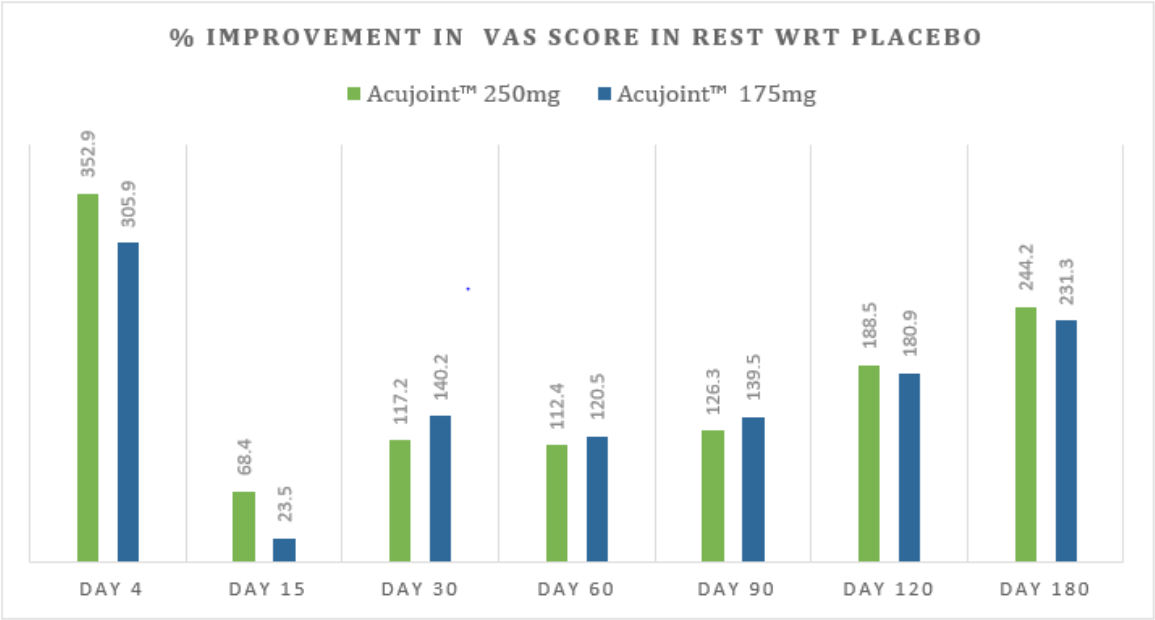

Figure 7: Percentage improvement in VAS score (at rest) of Acujoint™ 250 mg and Acujoint™ 175 mg against placebo at different timepoints up to day 180.

Inflammation assessment by change in CRP levels

There was no statistically significant difference in CRP levels between the treatment arms at any visit.

Inflammation as assessed by the change in the IL-6 levels

No statistically significant differences were observed between the test arms or between the test and placebo arm. However, statistically significant changes were noted at days 90 and 180 compared to baseline within the Acujoint™ 250 mg arm while in Acujoint™ 175 mg and placebo, statistically significant change was noted at day 180.

Change in exercise-induced cartilage turnover

Within-group analysis revealed that subjects in the Test arms exhibited a statistically significant decrease in COMP levels at day 90 as compared to baseline ($p<0.05$), whereas the placebo arm showed no significant change. Both doses of Acujoint™ demonstrated a statistically significant reduction in COMP levels on day 180 compared to placebo ($p<0.05$), with no significant difference between the different doses (Table 7). The results of the urinary CTX-II level test showed that there was statistically non-significant difference reported between both Acujoint™ arms and Acujoint™ arms verses placebo, in between group comparison. Within group comparison showed a statistically significant reduction on days 90 and 180 from baseline in the Acujoint™ 250 mg arm while the Acujoint™ 175 mg arm exhibited an early statistically significant reduction from day 30. (Table 7).

Improvement assessment

Both the Physicians' Global Assessment and Participants' Global Impression of Change Scale revealed statistically significant improvements with Acujoint™ compared to placebo. Physicians' assessments showed a notable reduction in pain for Acujoint™ 250 mg from a baseline mean score of 79.50 to 60.21 at day 180, significantly differing from the placebo (mean score of 76.54) ($p < 0.05$) (Table 8, Figure 8). Similarly, subjects reported greater satisfaction with Acujoint™ 250 mg, with a mean score improvement from 7.84 at baseline to 5.65 at day 180, versus minimal change in the placebo arm (mean score of 7.32) ($p < 0.00001$) (Table 8, Figure 9). These results collectively demonstrated that Acujoint™ significantly enhanced both physician-assessed and self-reported satisfaction compared to placebo.

Safety Evaluation

Adverse events are summarized in Table 9. There was not any treatment related adverse event observed in the entire study.

Table 7: Summary of COMP (ng/mL) and Urinary CTX-II (pg/mL) levels (mITT population)

Variables	Acujoint™ 250 mg (Arm 1) (N= 44)	Acujoint™ 175 mg (Arm 2) (N= 44)	Placebo (Arm 3) (N= 44)
	Mean±SD	Mean±SD	Mean±SD
Baseline (Day 1)	45.61±16.21	46.35±17.76	44.79±16.46
Visit 4 (Day 30)	43.62±12.57	43.16±14.08	51.46±21.66
Change from baseline	4.18±19.98	4.18±26.30	-4.33±29.59
Visit 6 (Day 90)	39.72*±8.79	39.38*±11.23	42.46±12.45
Change from baseline	8.73±20.58	7.87±20.64	5.23±20.40
Visit 8 (Day 180)	37.18*$±11.10	36.55*#±8.78	44.49$#±14.23
Change from baseline	10.17±20.63	11.85±22.94	0.92±19.69
CTX-II			
Baseline (Day 1)	269.75±169.75	288.13±184.00	275.67±182.17
Visit 4 (Day 30)	213.95±208.63	188.38*±174.69	277.84±255.47
Change from baseline	56.86±239.80	101.26±231.09	4.34±351.29
Visit 6 (Day 90)	156.21*±201.36	193.44*±191.97	239.81±205.90
Change from baseline	112.89±254.65	75.14±227.35	27.14±265.11
Visit 8 (Day 180)	119.89*±188.00	137.61*±215.62	113.80*±167.87
Change from baseline	158.71±248.56	155.30±283.32	160.09±214.11

*p-value <0.05 compared within arms based on t-test. $ p-value <0.05 based on t-test compared between Arm 1 and Arm 3. # p-value <0.05 based on t-test compared between Arm 2 and Arm 3.

Table 8: Physicians' Global Assessment and Participants' Global Impression of change scale

Variables	Acujoint™ 250 mg (Arm 1) (N= 44)	Acujoint™ 175 mg (Arm 2) (N= 44)	Placebo (Arm 3) (N= 44)
	Mean±SD	Mean±SD	Mean±SD
Physicians' Global Assessment			
Baseline (Day 1)	79.50±5.20	78.89±4.84	79.43±5.43
Visit 8	60.21*$±20.72	62.69#±19.28	76.54$#±8.92
Change from baseline	20.66±20.88	19.05±23.07	8.11±21.83
Participants' Global Impression of change scale			
Baseline (Day 1)	7.84±0.61	7.77±0.65	7.84±0.48
Visit 8 (Day 180)	5.65*$±2.08	5.95#±1.67	7.32$#±0.76
Change from baseline	2.32±2.36	2.09±2.31	1.02±2.14

*p-value <0.05 compared within arms based on t-test. $ p-value <0.05 based on t-test compared between Arm 1 and Arm 3. # p-value <0.05 based on t-test compared between Arm 2 and Arm 3.

Table 9: Adverse Events by Severity grade (mITT population)

	Acujoint 250 mg (Arm 1) (N = 44)	Acujoint 175 mg (Arm 2) (N = 44)	Placebo (Arm 3) (N = 44)	Overall (N = 132)
Mild	00	01	00	01
Moderate	00	00	00	00
Severe	00	00	00	00

N=Number of subjects

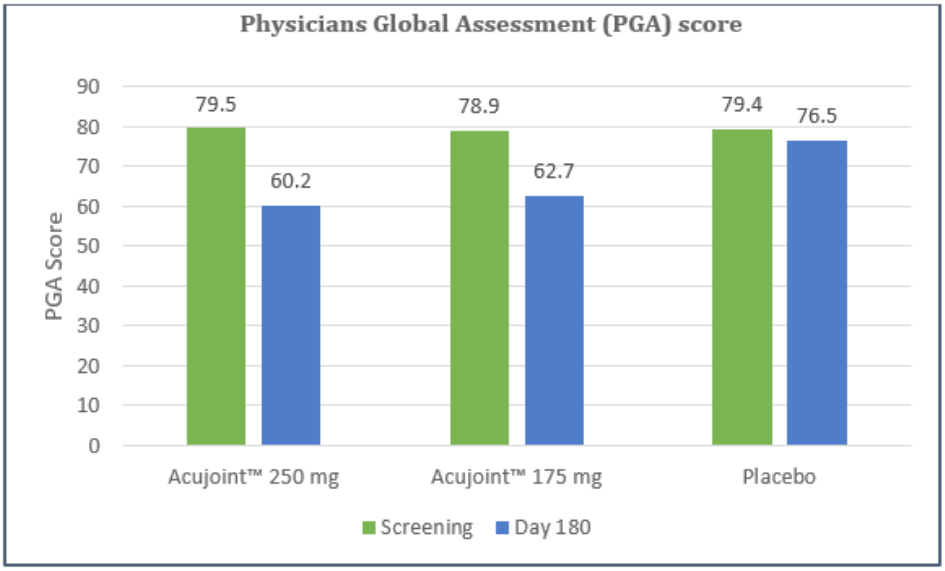

Figure 8: Changes in PGA Score between Acujoint™ 250 mg Acujoint™ 175 mg and Placebo at screeningand day 180.

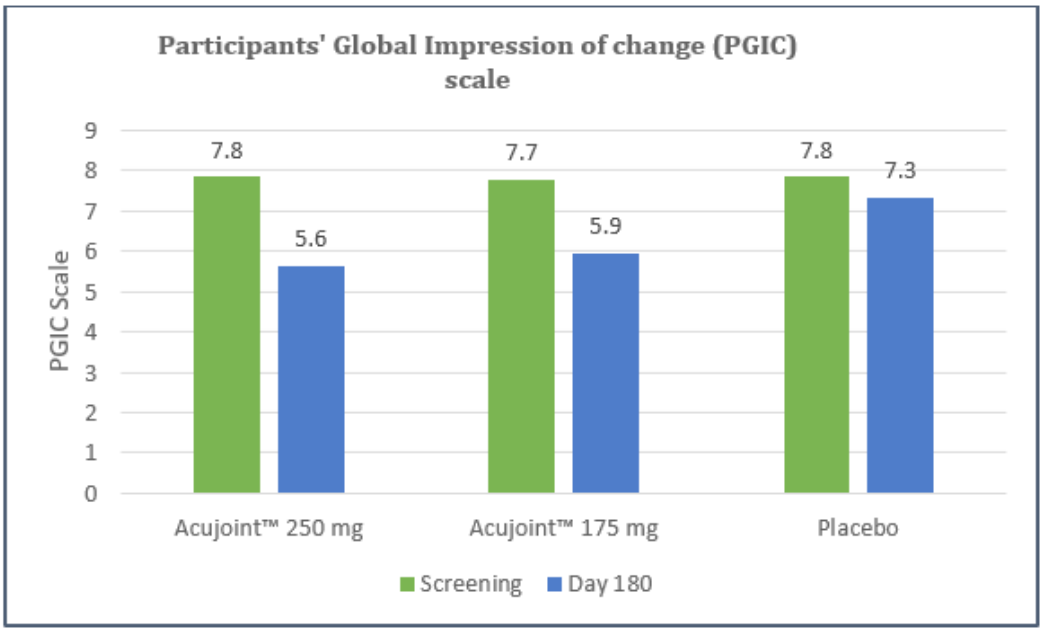

Figure 9: Change in PGIC scale between Acujoint™ 250 mg Acujoint™ 175 mg and Placebo at screening and day 180.

Discussion

Joint pain is a prevalent and often debilitating condition that affects millions of individuals worldwide. Acujoint™, containing natural ingredients, offers comparable efficacy to NSAIDs but with a potentially better safety profile. Unlike NSAIDs, which have risks such as gastrointestinal and cardiovascular issues, Acujoint™'s natural composition may present fewer side effects. This study evaluated the efficacy of Acujoint™ at dosages of 250 mg and 175 mg, focusing on its impact on joint health. The active compounds—*Curcuma longa, Boswellia serrata, Kaempferia galanga*, and β-caryophyllene—interact synergistically to enhance anti-inflammatory and analgesic effects. Curcumin in *Curcuma longa* inhibits key inflammatory enzymes, while β-caryophyllene, *Boswellia serrata* and *Kaempferia galanga* contribute to reducing inflammation through different pathways potentially boosting overall efficacy [16,17].

The Minimum Core Set tests recommended by the Osteoarthritis Research Society International (OARSI)—the 30-second Chair Stand Test, Stair Climb Test, and Fast Paced Walk Test—were implemented at multiple time points (day 1, day 4, day 15, day 30, day 60, day 90, day 120 and day 180 i.e EOT) to ensure that subjects experienced a consistent level of physical stress before evaluating study endpoints. These tests were conducted to create a standardized baseline of joint stress and function, which is crucial

for accurately assessing changes in pain and functional outcomes over time. Although these tests were not directly compared with the study endpoints, they served to establish a uniform level of physical exertion that helped in evaluating the effects of Acujoint™ on knee joint pain and function. The aim was to isolate and measure the impact of the intervention on pain and mobility by inducing a standardized degree of physical activity. This approach allowed to assess the effectiveness of Acujoint™ in a controlled manner, ensuring that any observed changes in endpoints could be attributed more reliably to the treatment rather than variations in baseline physical stress or activity levels.

In this study, we observed statistically significant improvements ($p<0.05$) in knee muscle strength, measured through knee extension after supplementation with Acujoint™ at both 250 mg and 175 mg. This aligns with prior research indicating that formulated curcumin can enhance muscle performance and reduce muscle soreness post-exercise [18].

In addition to the above, widely recognised WOMAC parameters were also used as the primary endpoint of efficacy followed by LAI and VAS scale for determination of relief from pain. We observed that Acujoint™ at 250 mg and Acujoint™ 175 mg showed statistically significant improvement in reducing pain, stiffness and physical function as compared to placebo and the LAI score was also statistically ($p<0.05$) improved indicating the therapeutic efficacy of Acujoint™ 250 mg and Acujoint™ 175 mg. Also, the Acujoint™ 250 mg and Acujoint™ 175 mg were found to be effective in statistically reducing the pain score as compared to placebo. Furthermore, WOMAC parameters, LAI and VAS pain showed significantly improvement, likely due to the anti-inflammatory effects of the various phytochemical extracts present in Acujoint™, as evidenced by reduced levels of serum inflammatory biomarkers such as COMP. The levels of C-reactive protein (CRP) and IL-6 remained stable throughout the study suggesting that the treatments anti-inflammatory properties were effective, however, reduction in COMP was particularly notable. Previously, "Acujoint" has been studied in osteoarthritis (OA). Study results showed that it was significantly effective in decreasing the total WOMAC score, pain score, functional ability score, VAS score and Lequesne Algofunctional Index index (LF) values at $P < 0.05$ level with no adverse events. It also showed reduction of hsCRP level. Acujoint™ contains components that manage joint health and reduce pain. *B. serrata* extracts inhibit 5-lipoxygenase, reducing inflammation and improving pain. [3] Curcumin lowers pain scores through anti-inflammatory properties. β-caryophyllene reduces NF-κB activation, diminishing joint inflammation and facilitating bone structure recalcification [7] *Kaempferia galanga L.* extracts inhibit COX enzyme, reducing inflammatory mediators and alleviating osteoarthritis symptoms, enhancing joint health. [11]. While prior studies on individual components indicate positive effects on joint health, our findings emphasize the importance of using Acujoint™ as a formulated product that leverages the synergistic effects of its components for enhanced joint health. in the present study no difference in safety parameters were observed between treatment and placebo arms. Only one subject reported an adverse event throughout the study which was unlikely related to the study drug. None of the subjects reported any adverse event after the completion of study treatment and none of them reported having taken any rescue medication.

The clinical benefits of Acujoint™, including pain relief and improved function, underline its potential as a cost-effective treatment for joint pain. The lack of significant difference between the 175 mg and 250 mg doses suggests that the lower dose may also be equally effective offering a more economical option. Future research should include larger sample sizes and longer follow-up periods to confirm these findings. Subgroup analyses could further elucidate which populations benefit most from Acujoint™.

Conclusion

This clinical trial comparing two strengths of Acujoint™ (175 mg and 250 mg) found no significant difference in efficacy between the doses, with both being superior to placebo. This result suggests that the lower strength may be equally effective, offering potential benefits in terms of cost-effectiveness. The combined effects of *Curcuma longa*, *Boswellia serrata*, *Kaempferia galanga*, and *Piper nigrum* Oil in Acujoint™ highlight the potential of multi-component herbal formulations in providing comprehensive relief from joint pain while maintaining a favourable safety profile. The absence of significant adverse events and the maintenance of baseline blood parameters further support the use of Acujoint™ as a safe and effective treatment option. The holistic approach in joint pain management, incorporating pharmacological, non-pharmacological, and lifestyle interventions, can optimize patient outcomes. The validation of traditional Ayurvedic medicine practices through rigorous scientific research enhances the credibility and acceptance of such formulations in modern healthcare.

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We are thankful to all the subjects who gave their consent to participate in this trial, without which this work was not possible.

We would like to thank Ethics committee for approval of this study.

Conflicts of interest

There are no conflicts of interest to declare.

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