Evaluation of efficacy and safety of a novel lipogel containing diclofenac: A randomized, placebo controlled, double-blind clinical trial in patients with signs and symptoms of osteoarthritis

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ABSTRACT

Background: Effectiveness and safety of pharmaceuticals is the prime concern of every osteoarthritis (OA) treatment. Chronic administration of NSAIDs, especially in case of geriatrics, through oral route tend to compromise the patient's safety, whereas topical treatments are not found to be effective owing their poor ability to deliver drug molecules.
Thus, the present study deals with a randomized, double-blind, controlled trial conducted on patients with knee osteoarthritis (OA) for comparing the performance of a novel topical gel (liposomal gel) of diclofenac with a placebo and a marketed gel.
Methods: The patients were treated and evaluated for 6 weeks as per the Western Ontario McMaster Universities (WOMAC) Index for OA. Patients were also observed for any adverse events. All the results were analyzed statistically using Kruskal-Wallis test, followed by Student's t-test at $p \leq 0.05$.
Results: Patients treated with liposomal gel showed statistically significantly improvements in treatment in comparison to the other tested formulations. All the treatments were found to be well tolerated with no report of adverse event. The results unequivocally demonstrated the superiority of the diclofenac liposomal gel, in the relieving the symptoms of OA of the knee, in comparison to placebo and marketed gel.
Conclusion: From above results it was revealed that the drug in liposome have higher therapeutic potential. Thus, this can be a safe and effective option for the management of chronic OA especially for geriatric patients.

1. Introduction

Osteoarthritis (OA) is the commonest chronic musculoskeletal disease in which the cartilages of the joints become thin. This results in the rubbing of the joint bones leading to compromised locomotion with varied degree of pain and stiffness [1]. OA is generally an age related disorder and the major risk factors for the disease include sedentary life style, genetic factors, obesity, bone mineral density, injury and gender. As per World Health Organization (WHO), around 10%–15% of the elderly patients (age above 60 years) are associated with one or other problems due to OA [2,3]. This disease mostly affects the joints of hip, knee, shoulder, hands, feet and spine. This disease severely affects the quality of life of the affected population and is regarded as the "highest-burden condition" within musculoskeletal group of diseases. Radiographic evidences of the knee give the inference that around 30% of men and women over the age of 65 are affected with OA, with almost doubles the occurrence at age group of 60. The disease has a bit of gender biasness affecting women around twice more than the men

worldwide. As per the WHO reports, 80% of OA affected population has compromised locomotion, out of which, 25% cannot even perform the routine activities of the day. On economic fronts too the diseases poses a huge burden on the patients. About 82.9% of OA patients need at least one investigative test semi-annually, and around 7.9% of OA patients need to purchase various devices over the same period, as per WHO reports. As per the estimation, the approximate six-month costs arising due to OA rotates around US$ 2456, which is too huge. The economic factor is solely related to the drop outs from routine medication for OA and further severing of the disease [1–5].

Treatment options for OA are symptomatic and can be classified broadly into three categories: a) Non-pharmacological therapeutic interventions; b) Pharmacological therapeutic interventions and c) Pharmacologic operative interventions. Non-pharmacological therapeutic options refers to interventions that do not involve the use of medications to treat pain which include education programmes and social support; a host of physical treatments (aerobic exercises, muscle strengthening exercises, and patella strapping); the provision of aids and appliances through occupational therapists; and advice on weight loss [6–9].

Operative interventions include surgical interventions like joint replacement, etc. These are applicable in case of critical and emergency cases. Much of the efforts has been spent on developing non-surgical interventions to alleviate the pain and disability in patients with OA, once the disease has become established [8,9,12,13]. Pharmacological modalities that have a place in the management of patients with osteoarthritis include simple analgesics such as paracetamol, non-steroidal anti-inflammatory agents (NSAIDs), rubifacients, and intra-articular therapy with glucocorticoids, hyaluronic acid and finally surgical interventions like knee replacements [10,11]. Though the disease is incurable, but its progression and symptoms can be minimized in early stages. Under this oral NSAIDs are frequently prescribed for chronic use, which are reported to be associated with various cardiovascular, renal and gastrointestinal (GI) adverse events [7,9,12–15]. For minimization of risk associated with NSAID therapy, use with cautious of oral NSAIDs is recommended, especially in geriatric population [16,17].

Owing to the obvious side-effects of oral NSAIDs in the chronic management of OA, patents and clinicians are exploring other options including topical administration of NSAIDs for the management of pain in the early to moderate stages of OA [18,19]. A numerous clinical trials have established the efficacy of topical NSAIDs, esp. diclofenac *vis-à-vis* the oral dosage forms [20–26]. However, there is immense need to deliver the drug to the desired site, in substantial amounts for desired duration for better therapeutic outcomes. In this regard, the novel drug delivery systems have established their potential to do so [27–31]. Henceforth, it was envisioned to explore the promises of novel topical liposomal gel (i.e., lipogel) of diclofenac in human subjects and compare the outcomes statistically to that from a market product (i.e., Emulgel®) and placebo.

2. Material and methods

2.1. Material

Diclofenac diethylamine and saturated phospholipid (soy phosphatidylcholine) were generous gifts from Biochem Pharmaceutical Industries (Mumbai, India) and Lipoid GmbH (Ludwigshafen, Germany), respectively. Triethanolamine (TEA) and sorbitan monooleate were procured from Sigma Chemicals Co. (St Louis, MO, U.S.A.). Carbopol 980 was obtained ex-gratis from Lubrizol Co. (Wickliffe, OH, U.S.A.). Diclofenac gel (Voveran® Emulgel®, Novartis India Limited, Bangalore) was procured from local pharmacy store. All other chemicals used in the study were of analytical grade.

2.2. Methods

The novel lipogel of diclofenac was optimized, developed, characterized and evaluated in-vitro and in-vivo using suitable animal model. This is based on the concept of advance drug delivery and contains nano-sized drug loaded vesicular systems composed of phospholipids [32]. For comparison a popular and highly recommended market product i.e. Voveran Emulgel was selected.

In order to test its clinical performance, the patients with signs and symptoms of OA of the knee were selected. The clinical study was initiated after obtaining the requisite approval for the study protocol by the Ethical Committee of the Post-Graduate Institute of Medical Education & Research (PGIMER), Chandigarh (Ref. No. Micro/2008/3614; NKG/545). The trial was conducted in accordance with the Indian Ethical Guidelines for Biomedical Research on Human Participants [33]. The study was carried out at PGIMER, a tertiary-level referral hospital located at Chandigarh, India. Patients were recruited from the out-patient clinics of the Department of Orthopaedic Surgery of the institute. The trial aimed to enroll a total of subjects/patients with signs and symptoms of OA. All the patients furnished their informed and written consent, after they were duly explained about the nature and details of the study. The clinical trial was registered at Clinical Trial Registry India.

2.2.1. Design of the trial

The efficacy and safety of the developed formulations was evaluated in a double blind randomized, placebo controlled, clinical trial in patients with signs and symptoms of OA of the knee [24,26,34].

2.2.2. Drug administration and treatment regimen

Patients were randomly provided with collapsible tubes (identified by a specific code number) containing DLF lipogel or Emulgel® or placebo gel, 20 g each. DLF lipogel and Emulgel® contains equivalent concentration/dose of diclofenac. Each patient was asked to apply the gel on the knees, twice a day. Treatment was continued for 6 weeks. One type of formulation was provided to the same patient throughout the study period regardless of the clinical improvement. Following completion of the treatment period and after all the definite results were obtained from all the participating patients, the formulation codes were opened [20].

Time period: 6 weeks (evaluation started 1st day [i.e. 0] and then at 1, 2, 4 & 6 weeks).

Groups & treatments: Each patient received one of the following formulations (which were assigned randomly) for the complete period of study. The scheme has been shown in consort flow chart:

Group 1: Diclofenac lipogel
Group 2: Market Product (i.e., Voveran® Emulgel®)
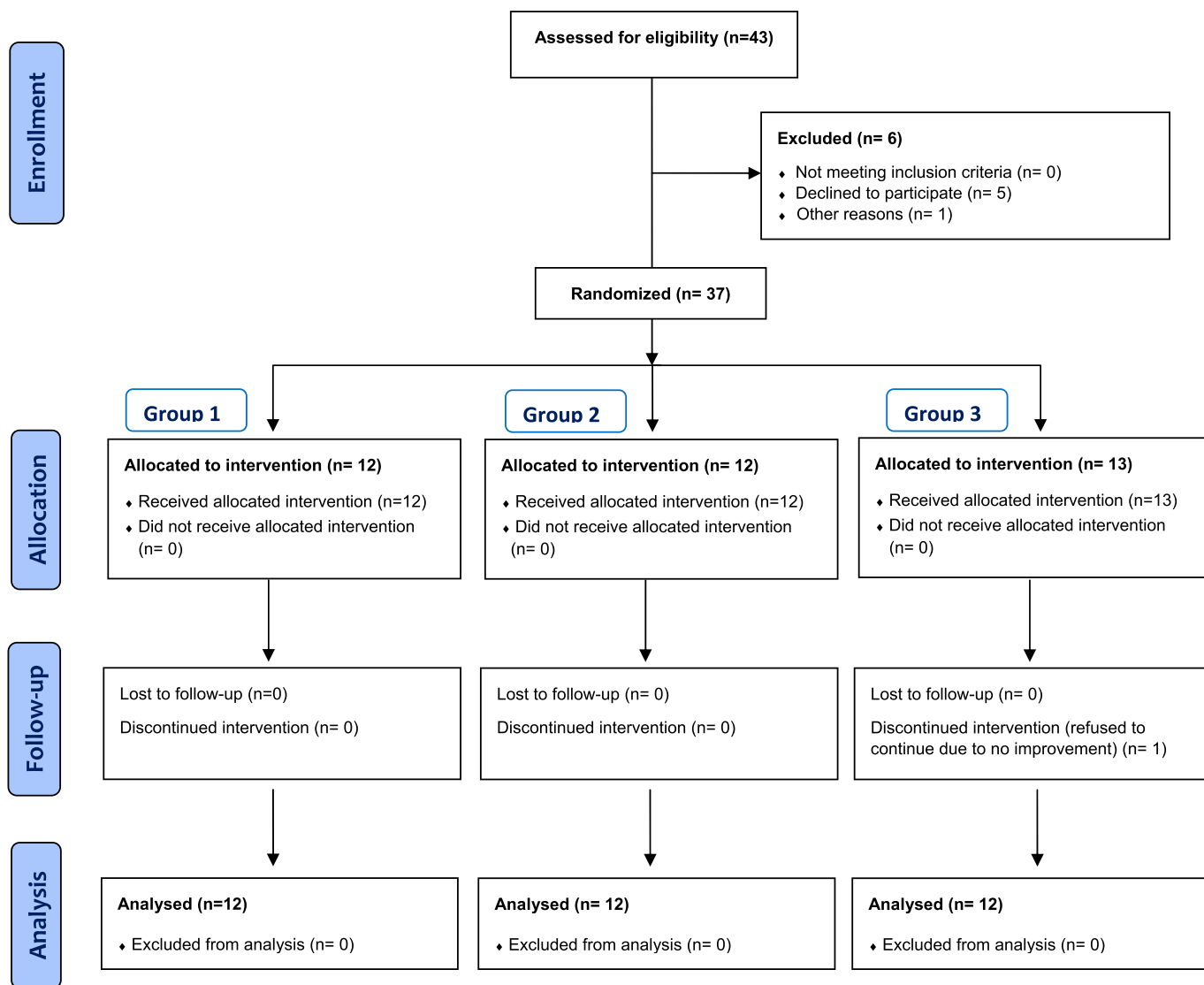Group 3: Placebo lipogel (i.e., lipogel without drug)

Sample size: In this study, three different treatments are attributed to three different groups of patients. The study aims to compare/find significant difference amongst the treatments. For this purpose, statistical tests were applied for comparing the outcomes of groups (i.e., scores). The required sample size in each group was calculated by following Eqn. (1):

$$\text{Minimum sample size} = [\text{power of test}] / [p \times (\text{absolute difference})^2] \quad (1)$$

At $p \leq 0.05$ with absolute difference of 19 and power of the test 80%, the minimum required sample size was found to be 4 patients for each group, i.e., a total of 12 patients. A higher number of patients were enrolled for the trial following inclusion and exclusion criteria of WOMAC for Osteoarthritis. Finally, 36 patients completed the study of 6 weeks (See CONSORT flow chart).

CONSORT
TRANSPARENT REPORTING of TRIALS

Clinical Study Flow Diagram

Enrollment

Assessed for eligibility (n=43)

Excluded (n= 6)

- Not meeting inclusion criteria (n= 0)
- Declined to participate (n= 5)
- Other reasons (n= 1)

Randomized (n= 37)

Allocation

Group 1

Allocated to intervention (n= 12)

- Received allocated intervention (n=12)
- Did not receive allocated intervention (n= 0)

Group 2

Allocated to intervention (n= 12)

- Received allocated intervention (n=12)
- Did not receive allocated intervention (n= 0)

Group 3

Allocated to intervention (n= 13)

- Received allocated intervention (n=13)
- Did not receive allocated intervention (n= 0)

Follow-up

Lost to follow-up (n=0)

Discontinued intervention (n= 0)

Lost to follow-up (n= 0)

Discontinued intervention (n= 0)

Lost to follow-up (n= 0)

Discontinued intervention (refused to continue due to no improvement) (n= 1)

Analysis

Analysed (n=12)

- Excluded from analysis (n= 0)

Analysed (n= 12)

- Excluded from analysis (n= 0)

Analysed (n= 12)

- Excluded from analysis (n= 0)

Prior to the treatment, the detailed history of all the patients was recorded. A minimum of four weeks of wash-over period was elapsed, during which no topical or systemic anti-arthritic therapy was administered to the patients.

Outcome measures: Primary efficacy outcome measure selected was the change from baseline to end of study on the WOMAC index of pain, stiffness and physical function having scores on 5-point Likert scale as shown in Table 1. And change from baseline and mean value per visit for WOMAC index [34,35].

Safety measures selected were, adverse effect, dermal-irritation scores, changes in vital signs of the patient obtained at each visit.

Statistical analysis: For WOMAC index of pain, stiffness and function subscales, calculation was done at, changes from baseline at each visit for each subject, available data at that visit. The changes were analyzed from baseline on the WOMAC subscales using analysis of covariance models with treatment as fixed effect and corresponding baseline value

Table 1

WOMAC OA index parameters – interpretations and scores.

WOMAC PARAMETERS	
PAIN (5)	
Walking, Stair Climbing; Nocturnal, Rest; Weight bearing	
STIFFNESS (2)	
Morning Stiffness; Stiffness occurring later in the day	
PHYSICAL FUNCTIONS (17)	
Descending stairs; Ascending stairs; Rising from sitting; Standing; Bending to floor; Walking on flat; Getting in or out of car; Going shopping; Putting on socks/stockings; Rising from the bed; Taking off socks/stockings; Lying in bed; Getting in/out of bath; Sitting; Getting on/off toilet; Heavy domestic duties; Light domestic duties	
Response	**Points/score**
None	0
Slight	1
Moderate	2
Severe	3
Extreme	4

Table 2

Baseline characteristics of patients randomized to lipogel, Emulgel®, or placebo.

| WOMAC OA index parameter	Average score at different time intervals (week)				
	1st	2nd	3rd	4th	6th
Group 1					
Pain	12.92 ± 3.5	12.00 ± 3.19	10.46 ± 3.33	9.31 ± 2.84	7.46 ± 2.73
Stiffness	6.08 ± 1.19	5.69 ± 1.49	4.92 ± 1.38	4.54 ± 1.26	3.92 ± 1.55
Physical function	50.54 ± 10.60	47.08 ± 11.01	44.46 ± 12.57	38.46 ± 11.36	32.85 ± 10.39
Group 2					
Pain	13.75 ± 5.22	13.08 ± 4.83	11.75 ± 4.37	10.64 ± 3.75	9.73 ± 3.72
Stiffness	6.50 ± 1.31	6.00 ± 1.65	5.75 ± 1.48	5.45 ± 1.13	4.91 ± 1.14
Physical function	51.25 ± 11.04	49.67 ± 10.26	47.82 ± 10.75	44.64 ± 8.83	40.45 ± 8.60
Group 3					
Pain	11.67 ± 4.72	11.67 ± 4.64	12.17 ± 4.88	12.50 ± 4.58	12.83 ± 4.67
Stiffness	5.67 ± 1.97	5.92 ± 1.93	6.08 ± 1.97	6.42 ± 1.62	6.5 ± 1.44
Physical function	47.25 ± 13.17	49.08 ± 13.63	49.75 ± 14.59	51.42 ± 14.21	53.67 ± 13.58
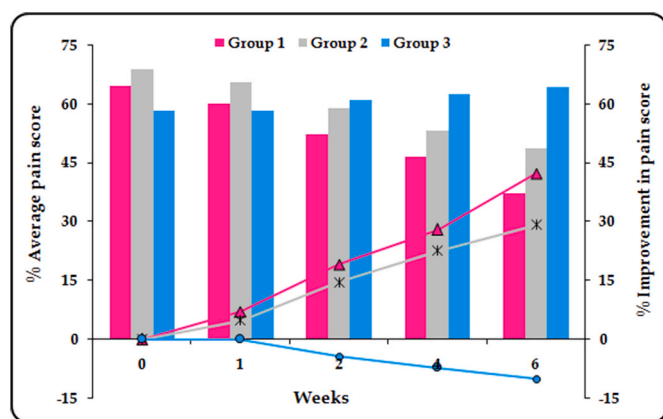
Fig. 1. Percent pain score and its improvement during six weeks of treatment with different formulations.

as covariate. Statistical analyses were performed with SPSS statistical software. Standard statistical methods were used for descriptive statistics. Kruskal-Wallis test, followed by Student's t-test (a parametric test), was used to determine the significance of differences in mean WOMAC score between groups at different time intervals. All the statistical tests were two-tailed [35–37]. First, the efficacy of the Emulgel® was
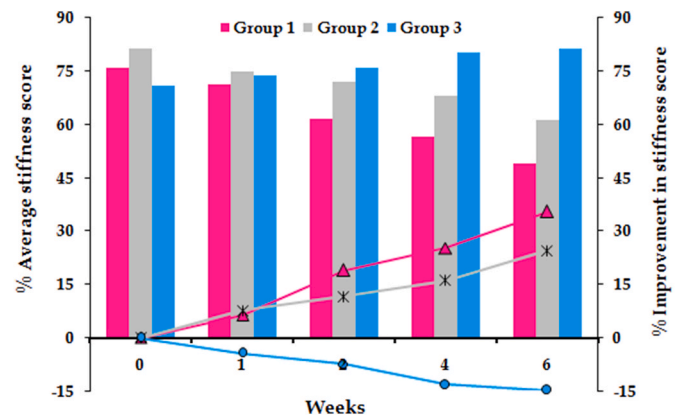

Fig. 2. Percent stiffness and its improvement during six weeks of treatment with different formulations.
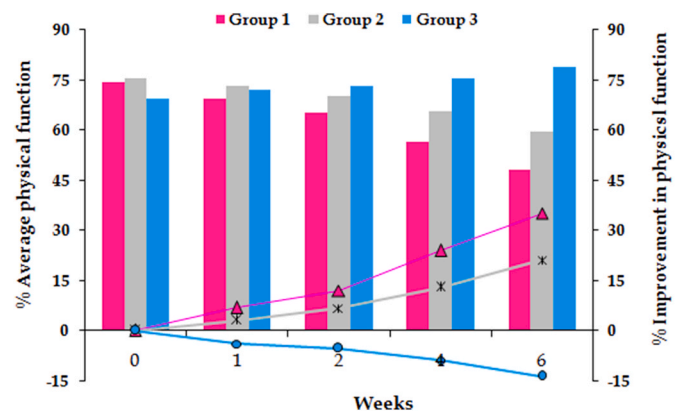

Fig. 3. Percent score of physical function and its improvement during six weeks of treatment with different formulations.

compared with placebo, when $p \leq 0.05$, lipogel was compared with placebo and with Emulgel®. Thus, no adjustment was required for type I error. A threshold value of $p \leq 0.05$ was considered as statistically significant.

3. Results and discussion

Patients included in the study was found to age range between 23 and 75 years, with 24 females and 12 males. It took around 1 year to complete the study on all selected patients.

The outcome data obtained were of ordinal and non-parametric nature. Hence, Kruskal-Wallis test was employed to find out the difference in treatments ($p \leq 0.05$). Comparison was made amongst all the groups simultaneously for pain, stiffness and physical function [35,37, 38]. Baseline characteristics for different treatments have been enlisted in Table 2.

For stiffness and physical function, the significant difference between all the groups was observed after 4 weeks of treatment, while for the pain, significant difference was ascertained later on the 6th week. Followed by application of Kruskal-Wallis test, the Student's t-test for statistical comparison was performed between the two active treatments (*viz.* lipogel and Emulgel®) and placebo. For pain score, a significant difference ($p \leq 0.05$) was observed between Group 1 and Group 3 for whole treatment period, whereas significant difference between Group 2 and Group 3 was recorded only after 4 weeks treatment (Fig. 1). For stiffness, Group 1 and Group 3 showed significant difference ($p \leq 0.01$) for throughout period of treatment. On the other hand, significant difference ($p \leq 0.05$) was observed between Group 2 and Group 3 only
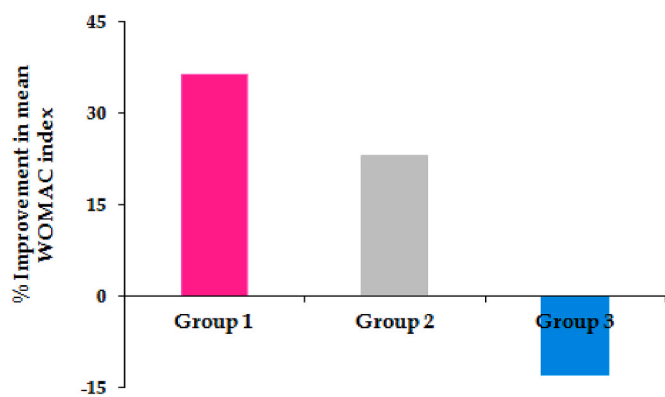
Fig. 4. Percent improvement in mean WOMAC OA index after six weeks treatment with different active and placebo formulations.

after 4 weeks of treatment (Fig. 2). Analogous results were obtained for physical function (Fig. 3). In a nutshell, it was found that both of the active treatments were superior to the placebo. Topically applied lipogel was significantly more effective than the placebo for all outcome measures i.e., pain ($p = 0.002$), physical function and stiffness ($p = 0.01$). The efficacy of the DLF lipogel was found to be significantly superior ($p \leq 0.05$) to the Emulgel® for improving stiffness and physical functions of treated patients 4 weeks onwards, whereas the pain relieving action was found to be comparable. Overall change in the WOMAC index after different treatments portrayed in Fig. 4.

As portrayed in Fig. 4 improvement in WOMAC index after 6 weeks was found be higher with diclofenac lipogel (i.e., 36.39% ± 4.76) as compared to Emulgel® (i.e., 22.94% ± 3.22). On the other hand it deceases with placebo gel (i.e., −13.03% ± 2.01), indicating no effect of this gel. With respect to safety evaluation, all the tested formulations were found to be safe, as no dermal as well as GI adverse event was recorded during complete period of study. The results once again affirm the potential of diclofenac lipogel, as topical drug delivery system, for the management of OA.

4. Conclusions

In conclusion, the data from this randomized trial demonstrated that the studied diclofenac lipogel offered better analgesic effect to that of the marketed product as well as placebo. Despite efficacy, the safety was substantially enhanced. As the product was better tolerated and offered significant improvement than the other test formulations, it can be concluded that the liposomal diclofenac based gel can be a better option for the treatment of symptoms of chronic osteoarthritis over the oral NASID therapy.

Registration of trial

The clinical trial was registered at Clinical Trial Registry India (reference). National Institute of Medical Statistics, Indian Council of Medical Research with reference number CTRI/2012/12/003263.

Author declaration

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Declaration of competing interest

The Author(s) declare(s) that there is no conflict of interest.

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