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To assess the efficacy & safety of NILIN™ SR tablets in the management of osteoarthritis of knee

Shankaran Natarajan[1]* and Muhammed Majeed[2]

Advisor / Sr. Vice President - R & D, Sami Labs, Bangalore, Karnataka - India

Founder & Managing Director, Sami Labs, Bangalore, Karnataka - India

Abstract

To assess the efficacy & safety of Nilin™ SR tablets in the management of osteoarthritis of knee. 32 subjects from the age group 40-65 years having osteoarthritis of the knee, with no other rheumatologic condition were enrolled. Subjects were judged to have osteoarthritis with clinical diagnostic features; Knee pain for most days of the month, Morning stiffness of less than 30 minute duration, stiffness while resting the affected joint and age over 40 years. The primary outcome was self-reported pain, stiffness and physical function scores as measured with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), 6-minute walk distance and VAS scale measured at 0hr and 1, 2 and 4hrs respectively. Secondary outcomes included laboratory investigations and serological biomarker, i.e. Hs-CRP. A significant improvement in the clinical and biochemical endpoints along with excellent tolerability indicates that Nilin™ SR can be used for the long term management of Osteoarthritis. Of the 32 subjects 30 subjects completed the study. Wilcoxon paired sample test indicated WOMAC Score significantly reduced from baseline to final visit for all the three parameters; Pain ($P<0.0001$) Stiffness ($P<0.0001$) and Physical disability ($P<0.0001$).A significant reduction was also noted in the visual analogue scale over the course of 4 hours after ingestion of medication. A significant improvement in the 6-minute walk distance ($P < 0.05$) and decrease in Hs-CRP levels was observed. No adverse events were reported in the trial.

Key-Words: Nilin SR, Osteoarthritis, WOMAC, VAS scale

Introduction

Arthritis is a common condition affecting millions of people all over the world. Osteoarthritis is one of the conditions commonly encountered among people. Osteoarthritis (OA) or degenerative joint disease is one of the oldest and most common type of arthritis. It is characterized by the breakdown of the joint's cartilage. Cartilage is the part of the joint that cushions the ends of bones. Its breakdown causes bones to rub against each other, causing pain and loss of movement. Most commonly affecting middle-aged and older people, OA can range from very mild to very severe. It affects hands and weight- bearing joints such as knees, hips, feet and the back. There are many factors that can cause OA. Although age is a risk factor, research has shown that OA is not an inevitable part of aging. Obesity may lead to OA of the knees. In addition, people with joint injuries due to sports, work related activity or accidents may be at an increased risk of developing OA. Women are more commonly affected than men.

*** Corresponding Author**

E-Mail: natrajan@samilabs.com

Fax: +91 080 28373035

Telephone: +91 080 28397973-75/78

Genetics has a role in the development of OA, particularly in the hands. Some people may be born with defective cartilage or defects in the way that joints fit together. As a person ages, this can cause early cartilage breakdown in the joint and there may be some inflammation, with enzymes released and more cartilage damaged.

NILIN ™ SR is an original research with selected ingredients proven to restore joint health and revive joint mobility. NILIN ™ SR aims to regenerate cartilage, reduce inflammation, and exert an antioxidant action. It retards the progression of Osteoarthritis, alleviates the signs and symptoms of arthritis and significantly improves quality of life.

The formulation NILIN ™ SR contains the following components:

Boswellic acid (Boswellin®) is a well-tolerated, safe and effective anti inflammatory agent without any associated untoward side effects. Boswellin® inhibits leukotriene synthesis and the enzyme HLE (Human Leukocyte Elastase). Boswellin® reduces joint discomfort, morning joint stiffness, improves grip strength and joint performance. Studies in India showed ingestion of an alcoholic extract of Boswellia

decreased polymorphonuclear leukocyte infiltration and migration, decreased primary antibody synthesis, and caused almost total inhibition of the classical complement pathway. In an in vitro study of b-Boswellic acid on the complement system, demonstrated a marked inhibitory effect on both the classical and alternate complement systems.

Curcumin C3 Complex® contains the three curcuminoids bisdemethoxy curcumin, demethoxy curcumin and curcumin. Curcumin C3 complex ® offers a unique mode of antioxidant action- it prevents the formation of free radicals and neutralizes free radicals. It has been found to positively influence osteoarthritis in animal studies. [2]

Gingerol- Ginger, the rhizome of Z.officinale is reported to possess antioxidant, anti-inflammatory, antiseptic and carminative properties.Studies have shown that ginger inhibits both cyclo-oxygenase and lipo-oxygenase pathways.The major constituents of ginger include volatile oils, oleoresin(gingerol), linoleic acid and trace elements such as magnesium, phosphorus and potassium. In vitro studies suggest that gingerol is a potent inhibitor of NO synthesis and also an effective protector against peroxynitrite mediated damage.[3]Another in-vitro study showed it to be effective in inhibiting production of PGE2 and TNF-a and COX-2 expression in human synoviocytes by regulating NF-KB activation and degradation of its inhibitor IKBa.[4]

This clinical trial was conducted with the aim of assessing the efficacy and safety of NILIN ™ SR in the management of Osteoarthritis of Knee, with regards to reduction of severity of pain, stiffness and improvement of joint function.

This study was aimed to assess the efficacy of NILIN™ SR in the management of Osteoarthritis of Knee.

- Reduction of severity of pain.
- Improvement of joint function in patients with Osteoarthritis.

To assess the safety of NILIN™ SR in patients with Osteoarthritis.

Outcome Measures

Primary Outcome Measures

Sum of the function, pain, and stiffness sub scores of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

Distance walked in 6 minutes to be measured

VAS Pain Scale at 0hr and 1, 2 and 4hrs respectively.

Secondary Outcome Measures

Laboratory Investigations

Material and methods

This was a single centered, open-labeled clinical trial .32 males or females suffering from osteoarthritis were enrolled in the study, of which 30 completed subjects were considered for further evaluation. The total study duration was 90 days ± 14 days, of which the patients study duration participation was for 56 ± 7 days.

All the enrolled subjects were given two tablets of NILIN™ SR twice a day for oral ingestion, for a period of 56 days.

Each sustained release bilayer tablet of NILIN™ SR contains:

Curcuminoids – 250mg

Boswellia serrata extract (40%AKBBA) – 272mg

Ginger extract (35% gingerol) – 100 mg

The age criterion for inclusion of patients was, 40-65 years. It was ensured that the patients only had osteoarthritis of the knee, with no other rheumatologic condition at the time of enrollment. They judged for osteoarthritis based on the following clinical diagnostic features; Knee pain for most days of the month, Morning stiffness of less than 30 minute duration, stiffness while resting the affected joint and age over 40 years. Incomplete responders were defined as patients who were on stable medication, which could be conventional or complementary, for the preceding three months, but still symptomatic, were also included in the trial. All subjects had to give informed consent and comply stringently with the requirements of the study.

Subjects with any previous clinical evidence or history of severe cardiac, pulmonary, gastrointestinal, renal, hepatic or neurological disorders were not included in the trial. Subjects with history of allergy to aspirin/NSAIDs or who had undergone total knee replacement in the contra lateral knee in preceding 6 months were excluded. Subjects who had received an intraarticular corticosteroid injection in a lower joint during the foregoing three months were not considered. Also not considered were patients with isolated lateral compartment disease defined by joint space loss in the lateral compartment only or who have received chondrocyte transplants in any lower extremity joint. Similarly, subjects with comorbid conditions restricting knee function or on treatment with corticosteroids or with infectious arthritis or gout were discarded.

The WOMAC (Western Ontario and McMaster Universities) index [5] was used to evaluate the therapeutic effects at baseline and at the subsequent weeks. The items on the WOMAC index included 3 dimensions—pain (5 questions), stiffness (2 questions) and physical function subscales (17 questions)—and were rated on an ordinal scale of 0

to 4, with the lower scores indicating lower levels of symptoms or physical disability. The validation study reported internal consistencies for the pain, stiffness and physical function subscales of 0.86, 0.86 and 0.95, respectively.[6] Reliability for the pain, stiffness and physical function subscales were 0.68, 0.48 and 0.68, respectively.[7]

The primary outcome measures were the sum of the function, pain, and stiffness sub scores of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the distance walked in 6 minutes and the visual analogue scale (VAS) for pain at 0hr and 1, 2 and 4hrs respectively. The secondary outcome measures were the laboratory investigations including the haematology investigations (haemoglobin, haematocrit, white blood count (WBC) (total and differential), red blood cell count (RBC), platelet count and erythrocyte sedimentation rate (ESR)), the biochemistry investigations (creatinine, urea, aspartate aminotransferase (SGOT/AST), alanine aminotransferase (SGPT/ALT), alkaline phosphatase, total bilirubin, sodium, potassium, uric acid, and Chloride), Urinanalysis (pH, protein, glucose, ketone bodies, leukocytes, nitrite, haemoglobin/erythrocytes, urobilinogen and bilirubin) and Special Procedures (Serological Biomarker: Hs-CRP).

At the screening visit, investigators confirmed the inclusion criteria and performed physical assessment of the involved knee. Subjects who fulfilled the enrollment criteria were given study information and a signed informed consent was obtained from them. Then a compilation of the demographic data, medical and medication history was obtained & vital signs were assessed. Subjects were asked to return for the baseline visit, after a washout period of 7 days if required.

At the baseline visit complete medical and physical examination was performed, BMI and fasting blood sample were measured, concomitant medications were noted and the WOMAC symptom assessment questionnaire was filled. VAS Pain Scale at 0hr and 1, 2 & 4hrs after dosing were recorded by the subject and Six-Minute Walk test for effectiveness was measured by the Investigator. Subjects were provided with patient diaries. 2000 mg of Acetaminophen for arthritis or other pain for not more than two days per week and only after each daily visit was the only concomitant medicine permitted.

The patients followed up at the site and similar evaluation was performed on days 3, 6, 9, 14, 28, 42 and 56. Empty medication containers were collected and patient diaries were reviewed. Any adverse events were noted. Additionally, laboratory test on day 28^{h} for HS-CRP was done.

At the final visit on day 56, all the lab tests were repeated and all the above mentioned procedure was carried out for the last time.

Patient withdrawals were noted with reasons and any adverse events or side effects in the course of trial were noted and classified as either mild, moderate, severe or life threatening based on the following scale:

- Mild: events require minimal or no treatment and did not interfere with the subject's daily activities.
- Moderate: events resulting in a low level of inconvenience or concern with the therapeutic measures, with some interference with functioning.
- Severe: events interrupting a subject's usual daily activity and requiring systemic drug therapy or other treatment, which are usually incapacitating.
- Life threatening: any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred.

They were also judged to be associated or not associated with the trial drug therapy.

Statistical analysis:

The Friedman test was used to evaluate the changes in the WOMAC index. If there was a significant difference ($p < 0.05$), the Wilcoxon signed rank test was used to identify which 2 periods were significantly different. Similarly VAS scores at 0, 1, 2 and 4 hours were analyzed using Friedman test and if significant difference obtained then a Wilcoxon signed rank test was used. The repeated measure ANOVA was applied to the whole group and if found to be significant, the student t test (two tailed, paired) was used to assess the treatment effect on the variables of the 6 minute walk test.

Results and discussion

Epidemiological Data

32 patients were enrolled for this trial, out which 2 patients dropped out during the course of the trial period. 30 completed patients were considered for analysis. The epidemiological data is presented in the attached table 1.

The Western Ontario and McMASTER Universities Osteoarthritis Index

The Friedman test showed significant difference between the different visits for all three parameters ($P<0.0001$) and hence the Wilcoxon paired sample was performed to compute the individual variation between

each visit and the baseline values.

As table 2 demonstrates, the WOMAC scores were significantly decreased from Day 3 onwards of treatment, for all the three parameters Pain ($P<0.002$), Stiffness ($P=0.0017$) and Physical disability ($P=0.003$). Over the trial period this difference got progressively more significant as the trial progressed from day 3 to the last day i.e. day 56. This observation led to the conclusion that the clinical efficacy of NILIN SR led to symptomatic relief for the patients on a long term basis and that the benefits were additive or accumulative over a longer course of time. Graph 1 shows the variation in the WOMAC scores over the course of the trial.

Visual Analogue Scale

The Visual analogue test was performed to test for pain as a symptom. The Friedman test was applied to the complete data at each visit to test for significance. As illustrated in Table 2, the Friedman test was significant from Day 6 onwards up to day 56. For these days the Wilcoxon paired sample test was applied to evaluate individual variation from the baseline at each visit. The significant reduction in the VAS was seen directly from the first hour after intake of the active tablet, which continued till the last time of testing, at 4 hours post tablet. This clearly demonstrates the early onset action of the tablet on pain in knee osteoarthritis, which is the most debilitating symptom for the patients. Graph 2 shows the variation in the VAS scores

Distance walked in 6 minutes

The paired t Test was applied to measure the change in the vital parameters in both the groups. These vital parameters (heart rate, respiratory rate, Systolic and diastolic BP) were measured at the commencement and at the culmination of the trial. Significant increase was seen in all of them ($P<0.05$).This is consistent as after continuous exercise (continuous walking for 6 minutes) increase in the vital parameters is natural and physiological. (Table 4)

When the change in the total distance covered for 6 minutes at the visits was tested for significance by the repeated measures ANOVA, it was found to be statistically significant. ($P<0.001$) Therefore the paired t test was performed to evaluate the individual significance at each visit from the baseline.

As seen in Table 5 there is a significant increase in the distance covered at each visit from the baseline. This was additive in nature i.e. the distance lengthened at each visit over the preceding visit and at all times it is more than that at the baseline. This underscores the clinical improvement seen in the patients, as improved walking distance correlates with reduced morbidity and better quality of life for the patient.

Graph 3 demonstrates the abovementioned results in an illustrative format.

Laboratory Data

The significant finding in the laboratory investigations are tabulated in Table 6. Although significance was found by the paired t test, the values were still within the normal range for all the parameters. In addition, the trial was conducted over a relatively long course of time and hence some changes in the laboratory markers are to be expected.

A special assay of the C - reactive protein (Hs-CRP) was performed on day 28 and at the end of the trial and compared with the values obtained at the baseline. There was a significant difference at both time intervals from the baseline. (Table 6)

No adverse effects were reported in the trial.

The WOMAC scores demonstrate significant improvement in pain, stiffness and physical disability for patients with knee osteoarthritis. The scores were reduced significantly in all the parameters under consideration hence substantiating the efficacy of NILIN SR. Similarly on application of the visual analogue scale pain score, very dramatic improvement is seen over the course of 4 hours after ingestion of the tablet from Day 6 onwards, for the rest of the trial. The immediate onset pain relief which progressively improves in the trial is apparent. The mean distance covered in 6 minutes too increased noticeably and was consistently more than that seen at the baseline. Furthermore, no adverse effects were noted in the trial. A multitude of disadvantages are incurred with the standard line of treatment so far followed by clinicians worldwide for osteoarthritis, and hence safer and naturally active agents are a crying need of the hour. This clinical study brings forth NILIN SR as a new line of treatment, which is both safe and effective, for patients of Osteoarthritis. Further evaluation in larger study samples will affirm its utility in the management of osteoarthritis.

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Table 1: Epidemiological Data

Parameters	Values
No. of patients enrolled	32
No. of drop outs	2
No. of patients completed trial	30
Age (yrs) Range	49.12±5.27 years
Males	21 (70%)
Females	9(30%)
Weight (kgs)	65.84 ± 7.80
Height (cms)	160.78 ± 8.89
BMI (kg/m2)	25.69 ± 4.17
Knee involvement: Right Left Both	 13 (43.3%) 11 (36.7%) 6 (20%)

Table 2: The Western Ontario and McMaster Universities Osteoarthritis Index

	Day 1	Day 3	Day 6	Day 9	Day 14	Day 28	Day 42	Day 56
Pain								
Median (Interquartile range)	11 (10-13)	11 (9-12)	10 (8.25-11.75)	10 (9-11.75)	9.5 (9-11)	9.5 (8-10.75)	9 (7-10)	8 (6-10)
Freidman test	Significant difference in scores: P<0.0001							
Wilcoxon paired sample test (Day vs. Baseline)		P=0.00241 *Significant ↓	P<0.0002 *Significant ↓	P=0.0002 *Significant↓	P=0.0001 *Significant↓	P=0.0002 *Significant↓	P=0.0001 *Significant↓	P<0.0001 *Significant↓
Stiffness								
Median (Interquartile range)	5 (5-6)	5 (4-5)	5 (4-5)	5 (4-5)	4 (4-5)	4 (4-4.75)	4 (3-4)	3 (3-4)
Freidman test	Significant difference in scores: P<0.0001							
Wilcoxon paired sample test (Day vs. Baseline)		P=0.017 *Significant ↓	P=0.001 *Significant↓	P=0.001 *Significant ↓	P=0.0001 *Significant ↓	P=0.0001 *Significant ↓	P<0.0001 *Significant ↓	P<0.0001 *Significant ↓
Physical Disability								
Median (Interquartile range)	48 (41.25-51)	45 (42.25-49.75)	44 (40-48.5)	42 (37.25-7.75)	40 (34.5-46)	38 (34.25-2.75)	35 (32-39.75)	31 (26-37.5)
Freidman test	Significant difference in scores: P<0.0001							
Wilcoxon paired sample test (Day vs. Baseline)		P=0.003 *Significant ↓	P<0.001 *Significant ↓	P=0.0001 *Significant ↓	P=0.0001 *Significant ↓	P=0.0001 *Significant ↓	P<0.0001 *Significant ↓	P<0.0001 *Significant ↓

Table 3: Visual Analogue Score

Friedman test:		
Days	P value	Result
Day 1	0.270	Not significant
Day 3	0.290	Not significant
Day 6	<0.0001	Significant
Day 9	0.0001	Significant
Day 14	< 0.0001	Significant

Day 28		< 0.0001	Significant	
Day 42		< 0.0001	Significant	
Day 56		< 0.0001	Significant	
Wilcoxon test vs. baseline:				
Days		P value	Result	Median (Inter quartile Range)
Day 6	0 Hr			7(6-8)
	1 Hr	0.001	Significant reduction	6(5-7.5)
	2 Hr	<0.0001	Significant reduction	6(5-7)
	4 Hr	<0.0001	Significant reduction	6(5-7)
Day 9	0 Hr			7(6-8)
	1 Hr	0.001	Significant Reduction	6(5-7)
	2 Hr	0.0001	Significant Reduction	6(5-7)
	4 Hr	<0.0001	Significant Reduction	6(5-7)
Day 14	0 Hr			6(6-7)
	1 Hr	0.0001	Significant Reduction	5.5(5-6.75)
	2 Hr	0.0001	Significant Reduction	5.5(5-6)
	4 Hr	0.0005	Significant Reduction	6(5-7)
Day 28	0 Hr			6(5-7)
	1 Hr	0.0001	Significant Reduction	5(4-6)
	2 Hr	0.0001	Significant Reduction	5(4-6)
	4 Hr	0.0005	Significant Reduction	5(5-6)
Day 42	0 Hr			5(5-6)
	1 Hr	0.0001	Significant Reduction	4(4-5)
	2 Hr	0.0001	Significant Reduction	5(4-5.75)
	4 Hr	0.0007	Significant Reduction	5(4-6)
Day 56	0 Hr			5(4-5)
	1 Hr	<0.0001	Significant Reduction	4(3-4)
	2 Hr	<0.0001	Significant Reduction	4(3-4)
	4 Hr	<0.0001	Significant Reduction	4(3-5)

Table 4: 6 Minute Walk Distance–Change in Vital Parameters

Paired t Test		P Value	Result	MEAN Baseline	Mean Final
Day 1	H.R	<0.001	Significant Increase	71.07	75.33
	R.R	<0.001	Significant Increase	19.33	21.47
	SYS B.P	<0.001	Significant Increase	126.47	130.53
	DYS B.P	0.0320	Significant Increase	67.40	68.90
Day 3	H.R	<0.080	Significant Increase	70.60	74.90
	R.R	<0.001	Significant Increase	21.80	24
	SYS B.P	<0.001	Significant Increase	126.53	131.67
	DYS B.P	0.0020	Significant Increase	65.90	67.40
Day 6	H.R	<0.001	Significant Increase	67.50	72
	R.R	<0.001	Significant Increase	21	23.40
	SYS B.P	<0.001	Significant Increase	126.53	132.13
	DYS B.P	0.002	Significant Increase	65.40	67.40
Day 9	H.R	<0.001	Significant Increase	68.67	72.47
	R.R	<0.001	Significant Increase	20.33	23.33
	SYS B.P	<0.001	Significant Increase	126.33	130.27
	DYS B.P	0.001	Significant Increase	64.27	66.93
Day 14	H.R	<0.001	Significant Increase	69	72.80
	R.R	<0.001	Significant Increase	20.47	26.80
	SYS B.P	<0.001	Significant Increase	126.73	123.80
	DYS B.P	0.001	Significant Increase	64.53	67.13
Day 28	H.R	<0.001	Significant Increase	68.13	71.13
	R.R	<0.001	Significant Increase	20.47	22.87
	SYS B.P	<0.001	Significant Increase	126.20	129.60
	DYS B.P	0.001	Significant Increase	64.13	66.53
Day 42	H.R	<0.001	Significants Increase	68.80	71.80
	R.R	<0.001	Significant Increase	21.07	21.13
	SYS B.P	<0.001	Significant Increase	126.07	129.60
	DYS B.P	0.001	Significant Increase	63.80	65.80
Day 56	H.R	<0.001	Significant Increase	68.80	71.87
	R.R	<0.001	Significant Increase	21.50	23.80
	SYS B.P	<0.001	Significant Increase	126.40	130.13
	DYS B.P	0.001	Significant Increase	64.20	66.47

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Table 5: 6 Minute Walk Distance–Change in total distance covered for NILIN SR

Repeated Measures ANOVA is Significant at P<0.0001			
Individual Comparison With Day 1			
Paired t Test:			
Day	Result	P value	MEAN ±S.D
DAY 1			269.03±48.66
DAY 3	Significant Increase	0.008	281.27±44.42
DAY 6	Significant Increase	0.0003	294.86±42.17
DAY 9	Significant Increase	0.0001	305.30±38.68
DAY 14	Significant Increase	0.0001	316.60±38.10
DAY 28	Significant Increase	0.0001	330.70±38.21
DAY 42	Significant Increase	<0.0001	342.10±40.05
DAY 56	Significant Increase	<0.0001	357.06±43.19

Table 6: Laboratory data for showing significant change from baseline

Variable	Visit	Mean	Std Dev.	P Value By t Test
MCH (pg)	Baseline	28.47	0.63	0.039
	Final	28.35	0.60	
SGOT(IU/L)	Baseline	22.13	2.9	0.001
	Final	24.7	2.5	
POTASSIUM(mEq/L)	Baseline	3.99	0.19	0.042
	Final	4.05	0.231	
URIC ACID (mg%)	Baseline	4.51	0.39	0.0003
	Final	4.17	0.370	
Hs-CRP(mg/dl)	Baseline	1.5	0.64	
	28th Day	1.13	0.47	0.0001
	Final	0.8	0.36	0.0001

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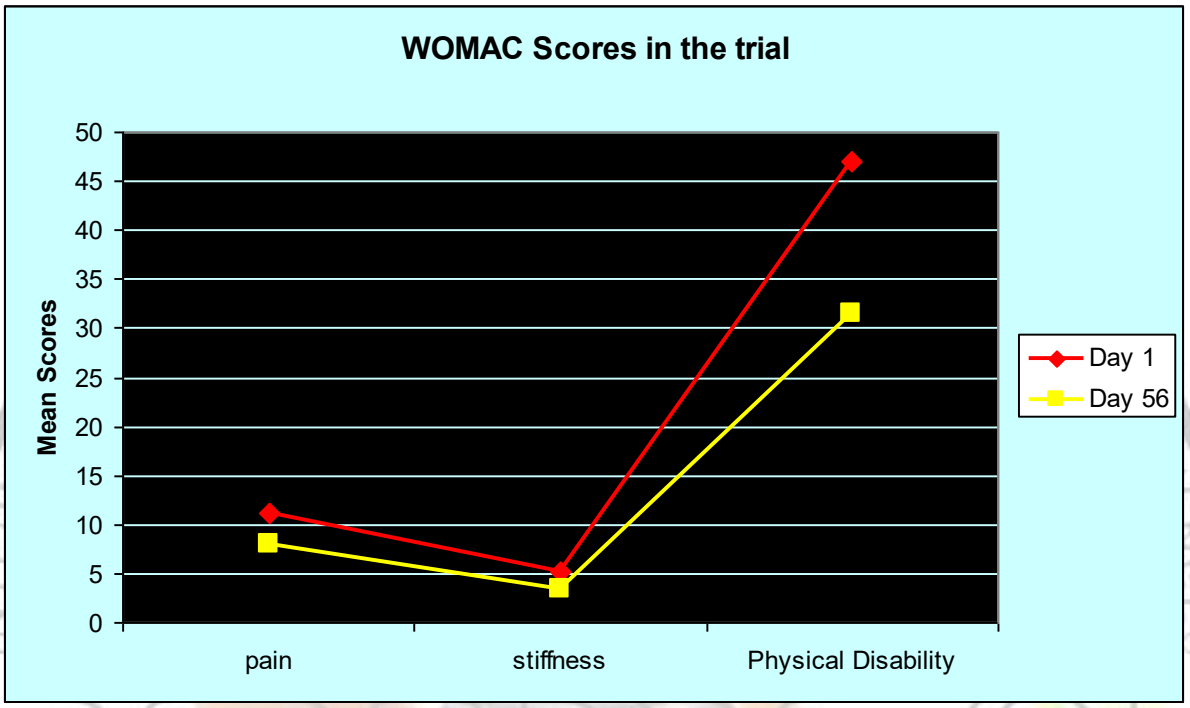
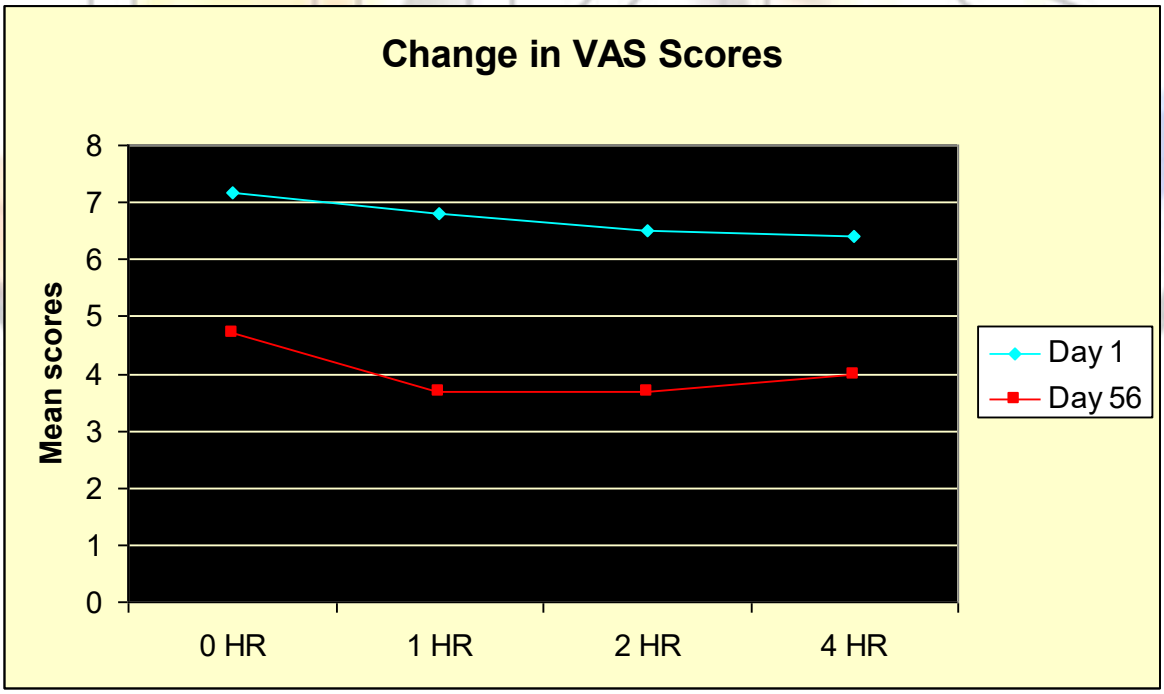
Graph 1: WOMAC Scores for NILIN SR



Graph 2: Visual Analogue Scale for NILIN SR.



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Graph 3: 6 Minute Walk Distance for NILIN SR