A Study to evaluate the Safety and Efficacy of OPOA™ in patients with Osteoarthritis and Osteoporosis.

Contents

TITLE PAGE

A Study to evaluate the Safety and Efficacy of OPOA™ in patients with Osteoarthritis and Osteoporosis.

Protocol No.:	TCR/REE/17/007
Version No.:	Version No.: 1.0 Date:01.08.2017
Investigational Product:	OPOA™
Indication:	• Osteoporosis • Osteoarthritis
Development Phase:	
Sponsor:	Ree Veda (A division of Ree Labs Pvt. Ltd.)
CRO:	Taiyo Clinical Research
Name of Investigator	Name of Site
Dr. Shashikant Nawale	Shalyak Hospital, Jogeshwari
Dr. Kishore Manek	L.C. Manek Nursing Home and Polyclinic, Chembur
Dr. Virat Chavan	Parvatibai Chavan Charitable Trust Hospital, Kandivali
Dr. Vijay Goni	PGIMER, Chandigarh
Compliance	The study, including the archiving of essential documents has been conducted as per the protocol, GCP, Declaration of Helsinki, Indian Council of Medical Research (ICMR), SOPs and applicable regulatory requirements. We accept the responsibility for the correctness of the project and validity of the data produced in this clinical study report.

A Study to evaluate the Safety and Efficacy of OPOA™ in patients with Osteoarthritis and Osteoporosis.

SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor/ Company: Ree Veda (A division of Ree Labs Pvt. Ltd.)</td></tr>
<tr><td>Name of Finished Product: OPOA™</td><td>Volume: 01</td></tr>
<tr><td>Name of Active Ingredient:</td><td></td></tr>
<tr><td colspan="2">Title of Study: A Study to evaluate the Safety and Efficacy of OPOA™ in patients with Osteoarthritis and Osteoporosis.</td></tr>
<tr><td>Treatment period (months/Days): 3 months</td><td>Phase of development:</td></tr>
<tr><td colspan="2">Objectives:
Primary Study Objective
• To evaluate the effect of OPOA™ in the following symptoms in patients with Osteoarthritis of the knee and/or hip.
o Reduced Joint Movement
o Joint Pain
• To evaluate the effect of OPOA™ in the following parameters in patients with Osteoporosis.
o Change in Bone Mineral Density
Secondary Study Objective
• To Evaluate Safety and Tolerability of OPOA™.
• To observe the change in patients' Serum Calcium levels.
• Assessment of use of Paracetamol or any other NSAIDs as rescue medication
• Global Assessment for overall improvement by the Subject.
• Global Assessment for overall improvement by the Investigator</td></tr>
<tr><td colspan="2">Methodology: This was an open label, non-randomized study in 70 subjects with confirmed Osteoarthritis or Osteoporosis with or without OA.</td></tr>
</table>

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Subjects were screened to determine suitability for enrolment. Following a screening visit, subjects who met all of the inclusion criteria and none of the exclusion criteria were enrolled in the study. The treatment phase started on Baseline day (Day 0). The subjects received a box containing OPOA™ sachets of which one sachet had to be taken once daily. Subjects had to stop all their current medication for Osteoarthritis. Follow up visits were scheduled on 45th and 90th day (final visit) of treatment to assess safety, efficacy and tolerability of study medications. At the time of Screening, subject's medical history, current medication, medically known allergies and sensitivities, family history were recorded. The data were collected on e-CRF. The data analysis was performed for predefined parameters to correspond with primary and secondary endpoint outcome measures.
Number of Patients: (Planned & analyzed) The sample size calculation was done based on the request of the sponsor. Estimating a 10% drop out rate, the total sample size required for the study was 77 patients to obtain data for 70 completed patients. **Total sample size required for the study = 70 patients** **Approximate number of patients with = 45 patients** **Osteoarthritis** **Approximate number of patients with = 25 patients** **Osteoporosis with or without OA**
Diagnosis and main criteria for inclusion: • **Osteoporosis** • **Osteoarthritis**
Test product, dose, mode of administration and batch number: One sachet of OPOA™ whose contents should be mixed with water and stirred thoroughly, taken once daily, preferably after breakfast for 90 days. **Manufacturer:** Ree Veda (A division of Ree Labs Pvt. Ltd.).
Duration of treatment: 3 months

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Criteria for evaluation:

Efficacy:

- Improvement in Joint Movement as determined via VAS
- Change in Bone Mineral Density as determined via DEXA
- Improvement in Serum Calcium levels tested via blood test
- Reduction of Joint Pain as determined via WOMAC
- Reduction in number of rescue medications (Paracetamol or any other NSAIDs) taken
- Incidences of any Adverse Events

Safety:

Safety and tolerability of the test product were assessed depending on the outcome from this clinical study.

At the final visit, overall response of clinical cure & overall global assessment (based on total score and laboratory values) were done by Subject and Investigator.

Statistical Methods: Statistical analysis was done using Microsoft Excel.

Summary: **Conclusion** **Efficacy Results**	Primary Efficacy Parameters	• Improvement of Joint Pain tested via WOMAC from baseline to the end of the study • Improvement in Joint Movement tested Via VAS from baseline to the end of the study • Change in Bone Mineral Density tested via DEXA from baseline to the end of the study
	Secondary Efficacy Parameters	• Improvement in serum Calcium levels tested via blood test from baseline to the end of the study

		• Tolerability of OPOA™ as observed by any Adverse Events • Reduction in number of rescue medications (Paracetamol or any other NSAIDs) taken • Global Assessment by Investigator and Subjects
Safety Results	There were no AE's or SAE's observed or reported during the study. Also, there was no use of any NSAID's / Painkillers as emergency during the course of the study.	
Conclusion	OPOA™ is effective and safe in overall maintaining bone and joint health	
Publications	Ongoing	
Date of Report	15th June 2018	

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LIST OF ABBREVIATIONS

AE	Adverse Event
ADR	Adverse Drug Reaction
ALP	Alkaline Phosphatase
BMD	Bone Mineral Density
BP	Blood Pressure
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CDSCO	Central Drugs Standard Control Organization
CRF	Case Report Form
CBC	Complete Blood Count
CRA	Clinical Research Associate
CRO	Contract Research Organization
DEXA	Dual Energy X Ray Absorptiometry
DLC	Differential Leukocyte count
EC	Ethics Committee
ESR	Erythrocyte Sedimentation Rate
HR	Heart Rate
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HBsAg	Hepatitis B Surface Antigen
Hb	Hemoglobin
ICF	Informed Consent Form
IEC	Institutional/ Independent Ethics Committee
IRB	Institutional/ Independent Review Board
ICH GCP	International Conference on Harmonization – Good Clinical Practices
ICMR	Indian Council of Medical Research
IP	Investigational Product
LAR	Legally Acceptable Representative
LFT	Liver Function Test

MSM	Methylsulfonylmethane
NSAID	Non-Steroidal Anti-Inflammatory Drug
OA	Osteoarthritis
PI	Principal Investigator
RBC	Red Blood Count
RR	Resting Rate
RFT	Renal Function Test
SGPT	Serum Glutamic Pyruvic Transaminase
SGOT	Serum Glutamic Oxaloacetic Transaminase
SAE	Serious Adverse Event
TCR	Taiyo Clinical Research
TLC	Total Leukocyte Count
UPT	Urine Pregnancy Test
VAS	Visual Analog Scale
VDRL	Venereal Disease Research Laboratory
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

A Study to evaluate the Safety and Efficacy of OPOA™ in patients with Osteoarthritis and Osteoporosis.

ETHICS

This was an open label, non-randomized study requiring Ethics Committee approval.

Ethics Committee (IEC)

Sites Name	**Ethics Committee**	**EC Registration Number**
Shalayak Hospital, Jogeshwari	Royal Pune Ethics Committee	ECR/45/Indt/MH/2013/RR-16
L. C. Manek Nursing Home and Polyclinic, Chembur		
Parvatibai Chavan Charitable Trust Hospital, Kandivali		
PGIMER, Chandigarh	Institutional Ethics Committee, PGIMER Chandigarh	ECR/25/Inst/CH/2013/RR-16

A Study to evaluate the Safety and Efficacy of OPOA™ in patients with Osteoarthritis and Osteoporosis.

List of Administrative Personnel

Sr. No.	Role and Name	Signature
1	**Sponsor: Dr. Rohit K.**	
2	**Clinical Operations: Dr. Kaushal K.**	
3	**Documentation Writer: Dr. Christina N.**	
4	**Reviewed and Quality Check: Kunal B. & Chrisann S.**	

A Study to evaluate the Safety and Efficacy of OPOA™ in patients with Osteoarthritis and Osteoporosis.

INTRODUCTION & RATIONALE

Osteoarthritis

Osteoarthritis (OA) is a common, age-related, chronic and slowly progressive joint disorder which ultimately leads to joint failure. It affects about 4-6% of adult population and is mentioned as one of the top 5 chronic diseases in India. The most common joints involved in osteoarthritic process are those which overwork during one's entire life viz. knees, neck, lower back and small hand joints of the finger-tips.

Osteoarthritis is a disease of cartilage – a smooth rubbery cushion which covers the surfaces of bones of the joint. It contains few cells which secrete a complex matrix made up of proteoglycans and hyaluronic acid. Worn out matrix components are regularly replaced during life although cartilage has very limited ability to repair and adapt. Cartilage break down in OA is associated with damage to menisci and other joint components as well as with remodeling of bone.

Osteoarthritis is not a disease of aging because about 45% people above 100 years do not have any pain due to OA. Half of elderly patients with knee pain have normal knee X-rays. OA is currently considered as a disease caused by dynamic reaction of joint to a variety of biomechanical and biochemical factors. It occurs when degradation of cartilage exceeds repair. The ligaments surrounding the joint become lax, joint capsule thickens, joint fluid becomes less viscous, muscle undergo wasting and become weak. These changes ultimately lead to joint failure - a condition akin to heart failure or kidney failure. Cartilage has no pain sensation. Pain in OA arises from bone and other structures within and around the joint. Crystals and swelling inside the joint are important causes of pain in OA.

Causes of Osteoarthritis

The common causes of OA are as follows:

i. Age (weakness, joint laxity, decreased sensory capacities)
ii. Female sex (Post menopause)
iii. Being overweight
iv. Joint Injury or joints that are not properly formed
v. Genetic defects in joint cartilage
vi. Stresses in the joint from certain jobs and playing sports

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There is a direct correlation between obesity and osteoarthritis due to certain chemicals (adipokines) secreted by cells of fatty tissues. OA is also known to run in some families. Although heredity plays a very small role in OA, involvements of small hand joints and onset at younger age are common features in such patients. Certain mechanical factors such as joint hypermobility, previous surgery or injury, repetitive joint use (occupational-farmers and porters) and joint deformities (congenital or disease-related) also lead to early OA. Indian habits of squatting, kneeling and sitting cross-legged probably accelerate OA process in knees due to mechanical factors. Secondary OA can develop in diseases such as diabetes and leprosy (neuropathic joint – Charcot's). Other congenital, metabolic and endocrine diseases can also lead to secondary OA.

Features of Osteoarthritis

Pain in the involved joint especially after activity is the main feature of OA. There may also be some stiffness in the joint. Morning stiffness usually does not last for more than half an hour and stiffness after rest (gelling) lasts for just a few minutes. Some OA patients experience increased pain in cold and damp weather.

Pain usually waxes and wanes in early stages of OA. There may be intermittent inflammatory flares with severe pain and swelling. Night pain and crepitus (creaking in the joint) are some of the later features. There may be difficulty in walking upstairs or downstairs, standing for long time, doing household tasks, getting in or out of an auto rikshaw or a car and getting up from sitting when knees are affected. Hand OA leads to difficulty in opening lid of a container, writing with a pen, holding or lifting a utensil and operating door handle or latch-keys.

Joints become unstable with progression of disease; movements get restricted along with wasting of muscles. Locking and buckling are other mechanical features. Hands become square shaped in hand OA whereas gait changes due to hip or knee OA. Knee OA can complicate with swellings around the joints (Baker's cyst, anserine bursitis).

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Investigations

No laboratory tests are required for diagnosis of OA. The diagnosis can be easily reached from patient history and clinical examination. X-Rays of the affected joints can be helpful in grading severity of joint involvement. Medical treatment can be planned based severity of OA. New laboratory tests are being developed as research tool for early diagnosis of cartilage degradation. OA disease scores (which measure pain, stiffness and physical function through a questionnaire) have been developed and are useful in following disease progression and response to therapy.

Therapy for OA

Non-drug therapy is important in OA management. Lifestyle changes (pacing of activities-intermittent rest), avoidance of squatting, kneeling or sitting cross-legged, exercise (both aerobic as well as joint strengthening – under guidance of a physiotherapist) and weight reduction are essential for control of OA pain. It is estimated that 10% weight loss reduces OA pain by about 50%. Exercise has been shown to reduce pain and improve joint function. Some patients may require assistive devices such as knee caps, walking sticks or walkers. Appropriate footwear should be used after assessment from an occupational therapist. Some patients benefit from heat, ice-packs and local ointments/liniments.

Pain management is usually done with paracetamol (up to 4 grams per day). A combination of tramadol with paracetamol offers better pain relief. Nonsteroidal anti-inflammatory drugs (ibuprofen, piroxicam, diclofenac, etc) are also used during inflammatory flares for short periods under medical supervision in lowest possible dose to avoid possible adverse effects. Severe pain nonresponsive to oral drugs responds well to steroid injection in joint. This simple, safe and effective procedure relieves pain for 3-4 or more months especially if extra joint-fluid is also removed simultaneously. Diacerine, glucosamine and chondroitin are disease modifying drugs (efficacy questionable) available for treatment in early OA. They should not be continued for more than 3-6 months if there is no apparent response.

Knowledge about disease, regular exercise, healthy diet and adequate sleep are essential elements of OA management. One must learn to protect joints by avoiding overuse while

remaining active. A positive approach towards life and support from family and friends help in coping with this disease.

Osteoporosis

Osteoporosis is characterized by low bone mass with micro architectural deterioration of bone tissue leading to enhance bone fragility, thus increasing the susceptibility to fracture. Although exact numbers are not available, based on available data and clinical experience, on estimated 25 million Indians may be affected. Osteoporotic fractures in India occur commonly in both sexes and may occur at a younger age than in the West. Data has demonstrated widespread vitamin D deficiency across India, at all ages and in both sexes, particularly in the urban areas. Poor sunlight exposure, skin pigmentation and a vitamin D-deficient diet are some obvious causes for this finding. Indians have low Bone Mineral Density (BMD) as compared to the western Caucasians. This could be attributed to differences in skeletal size; however, the high prevalence of vitamin D deficiency is a major factor in the low BMD and poor bone health of Indians. Healthy lifestyle (diet, exercise and sunlight exposure) can have a major positive impact on the bone metabolism and bone health of Indians.

Osteoporosis occurs in almost 50% of people aged above 50 in India. Diagnosis of Osteoporosis can be done by a simple X ray or by measuring the Bone Mineral Density (BMD) through a DEXA scan (Dual Energy X ray Absorptiometry)

Risk Factors for Osteoporosis

i. Weight in infancy is determinant of bone mass in adulthood.
ii. Smoking can lead to lower bone density and higher risk of fractures. This risk increases with age
iii. Physical inactivity and a sedentary lifestyle as well as impaired neuromuscular function (eg: reduced muscle strength, impaired gait and balance)
iv. High intake of alcohol
v. Prolonged use of corticosteroids
vi. Long term use of Proton Pump inhibiting drugs
vii. Low body weight and weight loss is associated with greater bone loss

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Treatment for Osteoporosis

i. Medication and Pharmacotherapy: In osteopenia and early-stage osteoporosis, oral medicines are the most common treatment to control the problem. These medicines fall under the category of bisphosphonates. Examples of these medicines include Alendronate, Risedronate and Ibandronate

ii. Intravenous infusions of Zoledronic Acid: In more severe cases of osteoporosis, it becomes important to take more urgent action through intravenous infusions of medicines, like Zoledronic Acid.

iii. Calcium and Vitamin Supplementation

iv. Following a healthy diet and regular exercise

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Potential Benefits:

The following are the benefits of using OPOA™ in patients with OA and Osteoporosis:

i Helps restore joint movement.

ii Promotes cartilage repair.

iii Helps prevent cartilage damage & loss.

iv Helps keep bones healthy and strong.

v Reduces joint pain.

vi Helps in preventing progress of osteoarthritis.

A Study to evaluate the Safety and Efficacy of OPOA™ in patients with Osteoarthritis and Osteoporosis.

STUDY OBJECTIVES

Objectives

Primary Study Objective

- To evaluate the effect of OPOA™ in the following symptoms in patients with Osteoarthritis of the knee and/or hip
  - o Reduced Joint Movement
  - o Joint Pain
- To evaluate the effect of OPOA™ in the following parameters in patients with Osteoporosis.
- Change in Bone Mineral Density

Secondary Study Objective

- To Evaluate Safety and Tolerability of OPOA™.
- To observe the change in patients' Serum Calcium levels.
- Assessment of use of Paracetamol or any other NSAIDs as rescue medication
- Global Assessment for overall improvement by the Subject.
- Global Assessment for overall improvement by the Investigator.

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Study Outcome Measures

Primary Efficacy Parameter

- Improvement of Joint Pain tested via WOMAC from baseline to the end of the study
- Improvement in Joint Movement tested Via VAS from baseline to the end of the study
- Change in Bone Mineral Density tested via DEXA from baseline to the end of the study

Secondary Efficacy Parameters

- Improvement in serum Calcium levels tested via blood test from baseline to the end of the study
- Tolerability of OPOA™ as observed by any Adverse Events
- Reduction in number of rescue medications (Paracetamol or any other NSAIDs) taken
- Global Assessment by Investigator and Subjects

INVESTIGATIONAL PLAN

Overall Study Design and Plan Description

This was an open label, non-randomized study in 70 subjects with confirmed Osteoarthritis or Osteoporosis with or without OA. OPOA^{TM} were prescribed to these subjects as per recommended dose. Duration of patient participation of each patient was planned to be not more than 3 months

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STUDY FLOW CHART

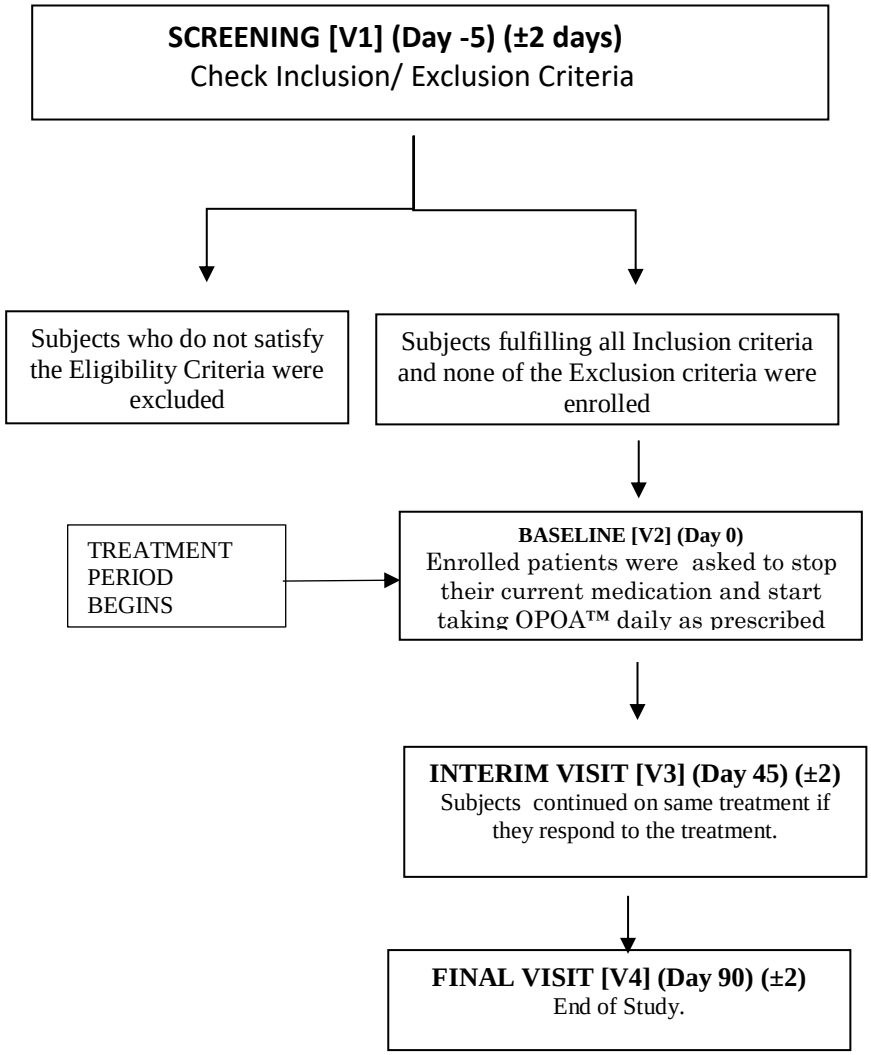

Figure 1: Study Activity Chart

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Discussion of Study Design

This study was a multi-centric, open label non – randomized **Study to evaluate the Safety and Efficacy of OPOA™ in patients with Osteoarthritis and Osteoporosis.**

The study was conducted at 04 centers in India.
Total 70 subjects were enrolled in the study. Data from all the sites were pooled and then used for statistical analysis.

Study Period

The observation period in the study was not more than 3 months.

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Selection of study population

Inclusion Criteria

Subjects meeting all of the following criteria were recruited for the study:

1. Male or Female adults aged between 45 and 60 years (both inclusive) having Osteoarthritis or Osteoporosis that was confirmed through previous medical records and prescription
2. Patients who have been on stable medication (conventional or complementary, including nutritional medicine) for the past 3 months or more, but are still getting symptoms (incomplete responders)
3. For study enrolment for OA, there had to be evidence of joint pain on movement scored by the patients at ≥ 35mm on a 100-mm Visual Analogue Scale (VAS)
4. Patients who record a WOMAC score of at least 20mm
5. For women of child bearing potential: negative pregnancy test. Such patients must accept to use contraceptive measures to prevent pregnancy during the study period.
6. Patients willing to give written consent for participation
7. Patients who were willing to comply with the study procedures.

Exclusion criteria

Subjects were excluded if ANY of the following conditions apply:

1. Pregnant women or women with potential for pregnancy and lactating patients
2. Patients with history of severe renal dysfunction
3. Patients with history of severe hepatic impairment
4. Patients with a history of hypersensitivity to the ingredients of the study drug.
5. Patients who are inappropriate for research participation for medical reasons (at discretion of treating physician).
6. Patients who have received any study medication or participated in any type of clinical study within 30 days prior to screening
7. Patients who are awaiting a knee or hip replacement.
8. Patients with other conditions that cause pain.
9. Patients who have had previous surgeries on their joints due to previous trauma within

the past year.

10. Patients with rheumatoid arthritis or gout.
11. Subjects suffering from malabsorption syndrome
12. Alcoholics or drug abusers

A Study to evaluate the Safety and Efficacy of OPOA™ in patients with Osteoarthritis and Osteoporosis.

Treatment

Treatments Administered

Each patient was prescribed OPOA™. One sachet of OPOA™(15g) whose contents should be mixed with water and stirred thoroughly, taken once daily, preferably after breakfast for 90 days.

STUDY PATIENTS

Disposition of Patients

The sample size calculation was done based on the request of the sponsor. Estimating a 10% drop out rate, the total sample size required for the study was 77 patients to obtain data for 70 completed patients.

Total sample size required for the study = **70 patients**

Number of patients with Osteoarthritis = **45 patients**

Number of patients with Osteoporosis with or without OA = **25 patients**

Table: Overall Subject Disposition by Treatment Group - All Participants

	Total (N=100)
Total Patients Screened	75
Screening failure	05
Eligible for enrolment	70
Consent Withdrawn	00
Completed participants	70

EFFICACY EVALUATION

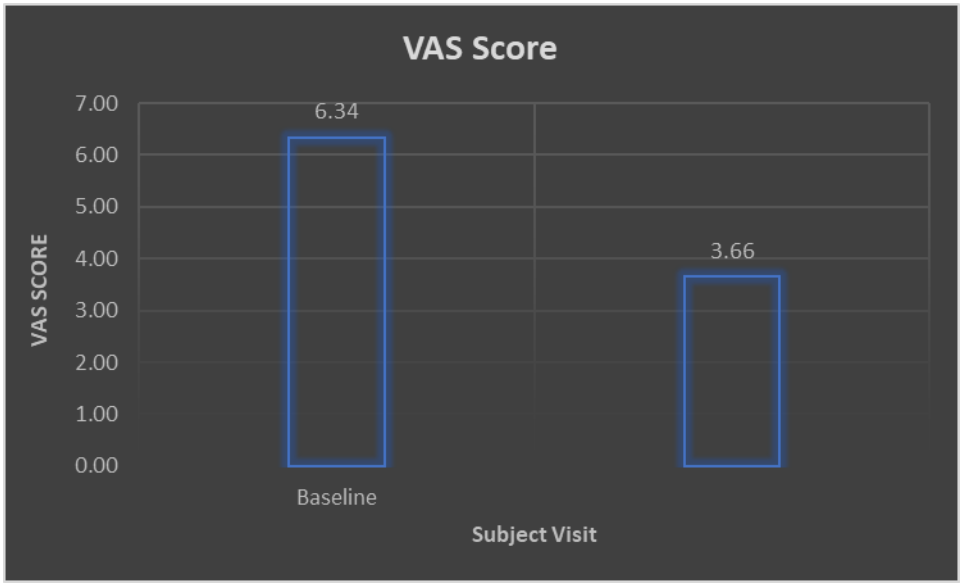
Efficacy Results and Tabulation of Individual Patient data

Analysis of Efficacy

The main symptoms of osteoporosis and osteoarthritis viz: Joint Pain, Difficulty in joint movements and change in bone mineral density were recorded and observed over a period of 3 months. It was observed that overall there was a decrease in the scores for all the efficacy parameters indicating an overall improvement in the condition of osteoporosis and osteoarthritis for all the patients. There was no difference in the improvements shown by men or women participants.

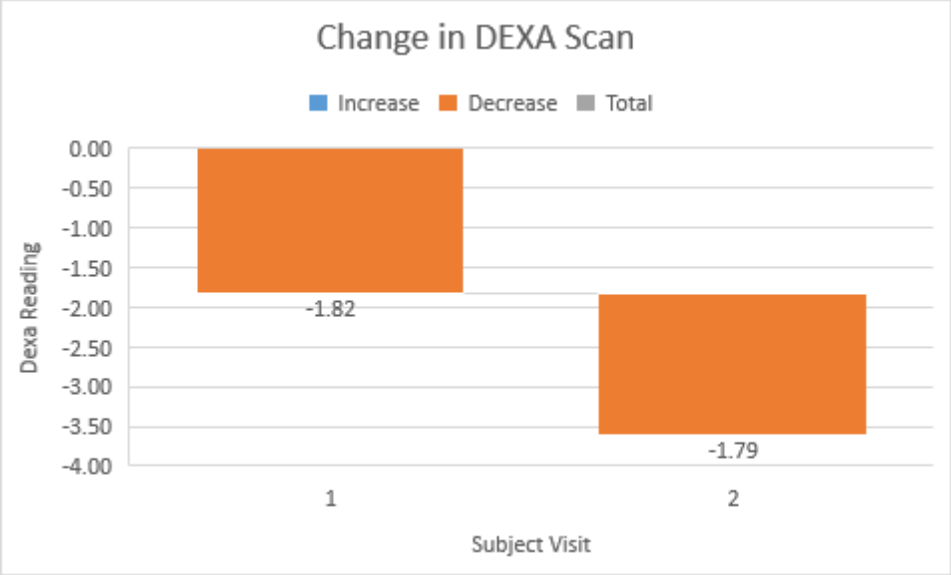
One of the other important objectives of the study was to observe any change in the blood serum calcium levels after taking the product continuously for 3 months form baseline to the end of the study. For this report only, the observations for 3 months were taken.

Improvement in Joint Movement as determined by VAS Score



Participants were asked to rate the joint pain on the scale of 0 to 10 where 0 = No Pain and 10 = Worst possible Pain. Average joint pain score at the start of the observation period was 6.34 (severe pain) which reduced to an average of 3.66 (moderate pain) at the end of the 3 months observation period. A total of 42.25% reduction was observed in the overall average joint pain at the end of the 3 months of observation period.

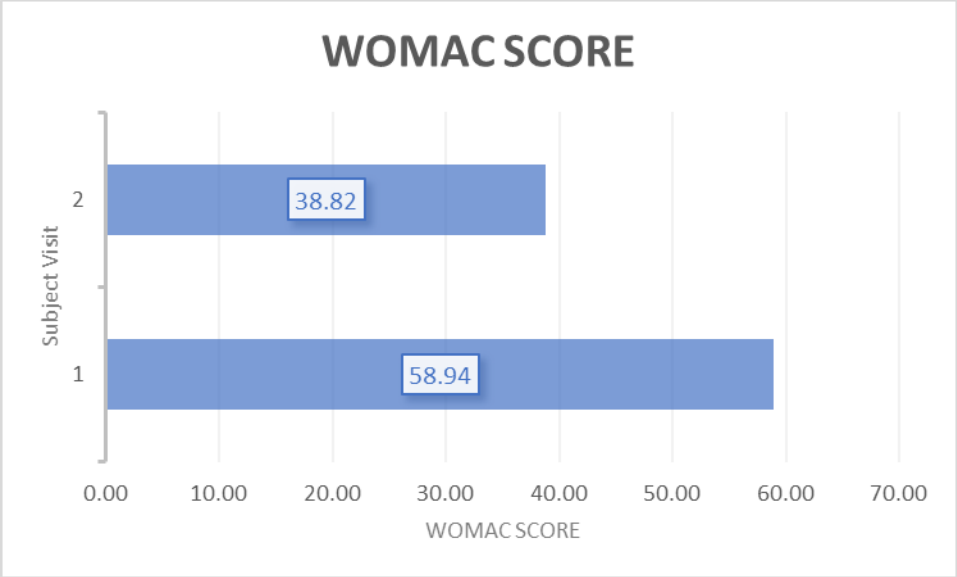
Change in Bone Mineral Density Via DEXA from baseline to the end of the study



To access change in bone mineral density DEXA scan was performed at the baseline and end of study visits, where the T score of -1 is considered normal, -1.1 and -2.4 =osteopenia, below -2.5=osteoporosis.

It was found that there is no significant change in the DEXA scans done at the baseline and at the end of 3 months.

Improvement in Joint Pain as determined by WOMAC score from baseline to the end of the study



In one of the key parameters where the improvement in joint movement was analysed it was observed that there was a reduction from an average score of 58.94 to 38.82. A total of 34.14% reduction seen over the period of 3 months. The participants were asked to rate the activities in the categories of pain, stiffness and physical function on a scale of 0-4, 0=none and 4=extreme. The WOMAC consists of 24 items divided into 3 subscales:

- Pain (5 items): during walking, using stairs, in bed, sitting or lying, and standing
- Stiffness (2 items): after first waking and later in the day
- Physical Function (17 items): stair use, rising from sitting, standing, bending, walking, getting in / out of a car, shopping, putting on / taking off socks, rising from bed, lying in bed, getting in / out of bath, sitting, getting on / off toilet, heavy household duties, light household duties

  The scores for each subscale are summed up, with a possible score range of 0-20 for Pain, 0-8 for Stiffness, and 0-68 for Physical Function.

  Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations.

SAFETY EVALUATION

OPOA™ has been safely given in patients suffering from complains of Joint Pain due to Osteoarthritis or Osteoporosis. There were no AE's or SAE's observed or reported during the study. Also, there was no use of any NSAID's / Painkillers as emergency during the course of the study.

DISCUSSION AND OVERALL CONCLUSIONS

Osteoarthritis (OA) is a common, age-related, chronic and slowly progressive joint disorder which ultimately leads to joint failure. It affects about 4-6% of adult population and is mentioned as one of the top 5 chronic diseases in India. The most common joints involved in osteoarthritic process are those which overwork during one's entire life viz. knees, neck, lower back and small hand joints of the finger-tips.

Osteoarthritis is a disease of cartilage – a smooth rubbery cushion which covers the surfaces of bones of the joint. It contains few cells which secrete a complex matrix made up of proteoglycans and hyaluronic acid. Worn out matrix components are regularly replaced during life although cartilage has very limited ability to repair and adapt. Cartilage break down in OA is associated with damage to menisci and other joint components as well as with remodeling of bone.

OA is currently considered as a disease caused by dynamic reaction of joint to a variety of biomechanical and biochemical factors. It occurs when degradation of cartilage exceeds repair. The ligaments surrounding the joint become lax, joint capsule thickens, joint fluid becomes less viscous, muscle undergo wasting and become weak. These changes ultimately lead to joint failure - a condition akin to heart failure or kidney failure. Cartilage has no pain sensation. Pain in OA arises from bone and other structures within and around the joint. Crystals and swelling inside the joint are important causes of pain in OA.

Causes of Osteoarthritis

The common causes of OA are as follows:

i. Age (weakness, joint laxity, decreased sensory capacities)
ii. Female sex (Post menopause)
iii. Being overweight
iv. Joint Injury or joints that are not properly formed
v. Genetic defects in joint cartilage
vi. Stresses in the joint from certain jobs and playing sports

There is a direct correlation between obesity and osteoarthritis due to certain chemicals (adipokines) secreted by cells of fatty tissues. OA is also known to run in some families. Although heredity plays a very small role in OA, involvements of small hand joints and onset at younger age are common features in such patients. Certain mechanical factors such as joint hypermobility, previous surgery or injury, repetitive joint

use (occupational-farmers and porters) and joint deformities (congenital or disease-related) also lead to earlyOA.

Indian habits of squatting, kneeling and sitting cross-legged probably accelerate OA process in knees due to mechanical factors. Secondary OA can develop in diseases such as diabetes and leprosy (neuropathic joint – Charcot's). Other congenital, metabolic and endocrine diseases can also lead to secondary OA.

Features of Osteoarthritis

Pain in the involved joint especially after activity is the main feature of OA. There may also be some stiffness in the joint. Morning stiffness usually does not last for more than half an hour and stiffness after rest (gelling) lasts for just a few minutes. Some OA patients experience increased pain in cold and damp weather.

Pain usually waxes and wanes in early stages of OA. There may be intermittent inflammatory flares with severe pain and swelling. Night pain and crepitus (creaking in the joint) are some of the later features. There may be difficulty in walking upstairs or downstairs, standing for long time, doing household tasks, getting in or out of an auto rikshaw or a car and getting up from sitting when knees are affected. Hand OA leads to difficulty in opening lid of a container, writing with a pen, holding or lifting a utensil and operating door handle or latch-keys.

Joints become unstable with progression of disease; movements get restricted along with wasting of muscles. Locking and buckling are other mechanical features. Hands become square shaped in hand OA whereas gait changes due to hip or knee OA. Knee OA can complicate with swellings around the joints (Baker's cyst, anserine bursitis).

Investigations

No laboratory tests are required for diagnosis of OA. The diagnosis can be easily reached from patient history and clinical examination. X-Rays of the affected joints can be helpful in grading severity of joint involvement. Medical treatment can be planned based severity of OA. New laboratory tests are being developed as research tool for early diagnosis of cartilage degradation. OA disease scores (which measure pain, stiffness and physical function through a questionnaire) have been developed and are useful in following disease progression and response to therapy.

Therapy for OA

Non-drug therapy is important in OA management. Lifestyle changes (pacing of activities-intermittent rest), avoidance of squatting, kneeling or sitting cross-legged, exercise (both aerobic as well as joint strengthening – under guidance of a physiotherapist) and weight reduction are essential for control of OA pain. It is estimated that 10% weight loss reduces OA pain by about 50%. Exercise has been shown to reduce pain and improve joint function. Some patients may require assistive devices such as knee caps, walking sticks or walkers. Appropriate footwear should be used after assessment from an occupational therapist. Some patients benefit from heat, ice-packs and local ointments/liniments.

Pain management is usually done with paracetamol (up to 4 grams per day). A combination of tramadol with paracetamol offers better pain relief. Nonsteroidal anti-inflammatory drugs (ibuprofen, piroxicam, diclofenac, etc) are also used during inflammatory flares for short periods under medical supervision in lowest possible dose to avoid possible adverse effects. Severe pain nonresponsive to oral drugs responds well to steroid injection in joint. This simple, safe and effective procedure relieves pain for 3-4 or more months especially if extra joint-fluid is also removed simultaneously. Diacerine, glucosamine and chondroitin are disease modifying drugs (efficacy questionable) available for treatment in early OA. They should not be continued for more than 3-6 months if there is no apparent response.

Knowledge about disease, regular exercise, healthy diet and adequate sleep are essential elements of OA management. One must learn to protect joints by avoiding overuse while remaining active. A positive approach towards life and support from family and friends help in coping with this disease.

In this report the primary objective of the study was to understand the use of OPOATM in patients with Osteoarthritis of the knee and/or hip. OPOATM is a unique Nutraceutical formulation of scientifically chosen ingredients derived from food which help in reducing joint pain, decrease swelling and improve mobility.

In this study the doctors were asked to capture and share data of their OPD patients who satisfied the eligibility criteria of the study. A total of 70 patients who satisfied the eligibility criteria were provided

with OPOATM for a period of 3 months and were assessed on Reduced Joint Movement, Joint Pain and use of Paracetamol or any other NSAIDs as rescue medication

It was observed that participants who were asked to rate the joint pain on the scale of 0 to 10 saw a total of 42.25% reduction from baseline to the end of the observation period.

In regard to the BMD, literature shows that usually patients who are taking any kind of supplements for joint pain show changes in the DEXA scans over a period of 6 months to 1 year. In the study it was found that there was no significant change in the DEXA scans done at the baseline and at the end of 3 months.

In this study the participants were asked to rate the activities in the categories of pain, stiffness and physical function on a scale of 0-4, 0=none and 4=extreme. This being one of the key parameters where the improvement in joint movement was analysed it was observed that there was a reduction of 34.14% in the WOMAC scores over the period of 3 months.

OPOA^{TM} can effectively and safely given to patients suffering from complains of Joint Pain due to Osteoarthritis or Osteoporosis. There were no AE's or SAE's observed or reported during the study period of 3 months and also, there was no use of any NSAID's / Painkillers as emergency / rescue medication during the course of the study.