Clinical Study Report

‘To Assess the Safety and Efficacy of Intra-articular Hyaluronic Acid (HA) in Patients with Knee Osteoarthritis (OA)’

‘Biovisc Ortho Single (Hyaluronic acid 30 mg/ml)’

‘A Non-interventional, Longitudinal, Retrospective, Phase-IV Study’

Document type:	Clinical Study Report
Development phase:	Phase-IV
Protocol Identification Code No.(s) :	BTVCPL/01/BIOVISC_ORTHOS
Study principal Investigator	Dr. Oguz Sukru Poyanli

Clinical Study Report Signature page				
Protocol Number:	To Assess the Safety and Efficacy of Intra-articular Hyaluronic Acid (HA)in Patients with Knee Osteoarthritis (OA)			
Sponsor Name:	Dr. Oguz Sukru Poyanli			
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1 Title page information

Study title: To assess the safety and efficacy of Intra-articular Hyaluronic Acid (HA) in Patients with Knee Osteoarthritis (OA).

Test Device/ investigational product: Biovisc Ortho Single (Hyaluronic acid 30 mg/ml) Intra-articular injection

Indication Studied: Osteoarthritis of knee

Study design: Non-interventional, longitudinal, retrospective.

Research supported by: Bio-Tech Vision Care Pvt. Ltd.

Protocol identification: BTVCPL/01/BIOVISC_ORTHOS

Development phase of study: Phase-IV

Principal or Coordinating Investigator(s): Dr. Oguz Sukru Poyanli

Statement: This study was conducted in compliance with principles of Declaration of Helsinki, ICH-GCP (International Conference on Harmonization of requirements for registration of pharmaceuticals for human use-Good Clinical Practice) guidelines, International Organization for Standardization (ISO) 14155:2011, and other regulatory authorities, including the archiving of essential documents.

Report date(s): 25-Jan-2016

Earlier reports from the same study: None

2 Synopsis

Name of Sponsor/Company: Not Applicable **Name of Finished Product:** Not Applicable **Name of Active Ingredient:** Cross Linked Sodium Hyaluronate - 30mg	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*(For National Authority Use only)*
Title of Study: To Assess the Safety and Efficacy of Intra-Articular Hyaluronic Acid (HA) in Patients with Knee Osteoarthritis (OA)		
Investigator: Dr. Oguz Sukru Poyanli		
Study Center: Single center study, Istanbul Medeniyet University Goztepe Research and Training Hospital		
Publication (reference): None		
Phase of development: Phase-IV		
Objective: To evaluate the efficacy and safety of intra-articular hyaluronic acid treatment in patients with osteoarthritis of the knee		
Methodology: This was a non-interventional, retrospective, longitudinal Phase-IV study. The study was planned to be performed on 30 male or female subjects with OA of knee. All patients' files were scanned. Those patients with OA of knee, who were given a single injection of intra articular HA at a dose of 30mg/ml (3ml), had attended 3 and 6 months routine follow up examinations and satisfied the inclusion and exclusion criteria, were enrolled in the study.		
Number of patients: **Planned:** 30 patients **Analysed:**35 patients		
Diagnosis and main criteria for inclusion: **Inclusion criteria:** Patients satisfying all of the following criteria were included in the study: 1. Patients of either gender, ≥ 40 years and ≤ 85 years of age 2. Documented diagnosis of Mild to moderate knee OA that fulfill the American College of Rheumatology (ACR) criteria 3. Radiographic diagnosis of osteoarthritis of the knee (Grade-II or III according to the Kellgren and Lawrence classification) 4. Patients with consistent symptoms (either joint pain, crepitus, swelling, effusion alone or combination of these symptoms) of knee OA for at least 3 months prior to screening. If bilateral knee pain was present, the Investigator selected the more painful knee 5. Minimum 3 months of unsuccessful non-surgical treatment, including (but not limited to) acetaminophen, anti-inflammatory medication, cortisone injection, physical therapy and bracing.		

Name of Sponsor/Company: Not Applicable	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*(For National Authority Use only)*
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6. The patients who had abstained from medication use 24 hours prior to any study visit and discontinued all non-steroidal anti-inflammatory drugs (NSAIDs) or other analgesic medication taken for any condition, including their knee pain.
7. Patients who gave written informed consent form regarding using their medical data with keeping their confidential information for scientific purposes

Exclusion criteria:

Patients satisfying none of the following criteria were included in the study:

1. Secondary OA of the knee according to ACR criteria
2. Radiographic diagnosis of osteoarthritis of the knee (Grade IV according to the Kellgren and Lawrence classification)
3. Having previously undergone surgery on target knee, including arthroscopy
4. Presence of any severe systemic disease(s)
5. Presence of significant OA symptoms in other joints apart from the target knee which would have required pharmacological treatment during the study.
6. History of receiving intra-articular HA within the previous 6 months and/or intra-articular steroids or articular lavage in the target knee within the previous 3 months prior to their inclusion in the study
7. Administration of glucosamine sulphate, chondroitin sulphate and diacerein within the 3 months prior to their inclusion in the study
8. History of allergy or hypersensitivity to HA
9. Participation in any clinical study in the last 3 months and any surgery scheduled in the next 8 months that could have affected directly the result of the present study.

Test product, dose and mode of administration:

Biovisc Ortho Single (Biotech Vision Care Pvt. Ltd., Ahmedabad, India) (Hyaluronic Acid 30 mg/ml)

Intra-articular mode of administration

Duration of treatment:

Single injection cycle and 2 follow-up visits (3 and 6 months) after treatment for evaluation of outcomes.

Reference therapy, dose and mode of administration, batch number: Not Applicable

Criteria for evaluation:

- Changes in Western Ontario McMaster Universities Arthritis Index (WOMAC) score between baseline visit and 3 and 6 month follow-up visit
- Demographic profile of Knee OA patients
- Evaluation of information regarding disease with medical history and treatment history
- Percentage of Treatment Emergent Adverse Events (TEAE)

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Name of Finished Product: Not Applicable		
Name of Active Ingredient: Cross Linked Sodium Hyaluronate - 30mg		

Statistical methods:

Descriptive statistical methods were used to summarize the demographic and disease characteristics. For continuous measurements such as age, the mean, median, standard deviation and range were tabulated and for categorical measurements such as gender, the frequencies were computed. All statistical analyses were conducted with the SAS System, version 9.2.

SUMMARY CONCLUSIONS

EFFICACY RESULTS:

Assessment of efficacy parameters revealed that percentage reduction in WOMAC index score from baseline at month 3 was 28.7% with a mean ± SD change of 21.4 ± 10.0. There was further reduction in percentage (39.7%) at month 6 from baseline with mean ± SD change of 29.6 ± 15.0. Similarly percentage reduction in WOMAC score for pain, stiffness and physical function from baseline to month 3 visit was 29.3%, 39.0%, and 27.4%, respectively with a mean ± SD change of 5.1 ± 2.8, 2.1 ± 1.7, and 14.2 ± 7.3, respectively. At month 6,the percentage reduction in WOMAC score for pain, stiffness and physical function was 36.9%, 48.9% and 39.7%, respectively with a mean ± SD change of 6.4 ± 3.8, 2.6 ± 2.1, and 20.6 ± 10.9, respectively.

The reduction in the overall WOMAC index score and individual WOMAC scores for pain, stiffness and physical function indicate that Biovisc Ortho Single device (Biotech Vision Care Pvt. Ltd, Ahmedabad, India) containing HA 3ml of 30mg/ml is efficacious in patients of OA of knee.

SAFETY RESULTS

Biovisc Ortho Single (Biotech Vision Care Pvt. Ltd, Ahmedabad, India) (with HA 3ml of 30mg/ml) is found to be safe and tolerable in patients with OA of knee.

CONCLUSION:

We found that Biovisc Ortho Single device (Biotech Vision Care Pvt. Ltd, Ahmedabad, India) intra-articular HA injection is safe and effective in patients with OA of knee. The findings of this study could be helpful for clinicians in developing strategies for treatment and management of OA of knee.

Date of the report: 25-JAN-2016

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4 List of abbreviations and definition of terms

ACR	American College of Rheumatology
AE	Adverse Event
CRF	Case Report / Record Form
CRO	Contract Research Organization
GCP	Good Clinical Practices
HA	Hyaluronic Acid
ICH	International Conference on Harmonization of requirements for registration of pharmaceuticals for human use
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
ISO 14155:2011	International Organization for Standardization 14155:2011
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OA	Osteoarthritis
SAE	Serious Adverse Events
TEAE	Treatment Emergent Adverse Event
WOMAC	Western Ontario McMaster Universities Arthritis Index

5 Ethics

5.1 Independent ethics committee or institutional review board

The study Investigators/designee obtained formal approval of study protocol from the Independent Ethics Committee (IEC) prior to start of the study. The details of IEC/IRB are listed in Appendix 16.1.3

5.2 Ethical conduct of the study

This study was conducted in compliance with the protocol, principles of Declaration of Helsinki, International council of Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines, and Good Clinical Practices (GCP), and International Organization for Standardization (ISO) 14155:2011. These regulatory standards provide assurance that the rights, safety, and well-being of patients participating in study were protected and that the study data were credible and responsibly reported.

5.3 Patient information and consent

Written informed consent was obtained from eligible patients for using their medical data for scientific purpose without disclosing their personal information. Samples of the written information given to each patient and the consent form are present in Appendix 16.1.

6 Investigators and study administrative structure

There was single investigative site to conduct the study.

Name of Investigator	**Address**
Dr. Oguz Sukru Poyanli	Docktor Erkin Cad. lstanbul Medeniyet Universitesi Goztepe Egitim Ve Arastirma Hastanesi.

7 Introduction

Osteoarthritis (OA) of knee is the most common progressive joint disorder in older adults, which causes joint pain, disability, and dysfunction, affecting quality of life of individual (1). The characteristics of OA include slow degradation of articular cartilage, sub-chondral bone damage, inflammation/synovitis, osteophyte formation, and joint space loss (1, 2). The etiology of OA of knee is not entirely clear, but its incidence increases with age, particularly in women (3). Obesity is considered as one of the main risk factor for the development and progression of OA along with other genetic or traumatic factors (4). Clinical manifestations of OA of knee are mainly characterized by gradually increasing joint pain, stiffness and joint enlargement with limited mobility (2). Due to the global trend of ageing population and increase in life expectancy, OA is becoming a greater cause of concern among healthcare professionals. Epidemiological studies have estimated that symptomatic and radiographic OA of knee affects 10% of adults over 55 years old (5). Worldwide burden of OA is increasing. According to a report of World Health Organization, OA of Knee is likely to become the 4th most important cause of disability in women and the 8th in men (6). OA of knee is more prevalent in India than in western countries (7).

According to the American College of Rheumatology (ACR) guidelines on treatment of OA of knee, analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) are considered as the first line treatment options (8). However, due to the known facts of NSAIDs causing potential systemic side effects, caution must be taken before prescribing NSAIDs to the elderly patients who consists the main population of OA (8). Intra-articular injection of HA is currently recommended by the main therapeutic guideline in the treatment of OA and is recommended to those patients who do not respond to non-pharmacological therapy, NSAIDs or analgesics (9).

In the setting of knee joint, synovial fluid acts as a joint lubricant and shock absorber during shear and compressive stress (10). Typically, synovial fluid mainly consists of HA that helps in maintaining high fluid viscosity and the normal integrity of the joint (10). In OA, viscoelastic properties of synovial fluid are decreased due to the degradation of endogenous HA (11). Intra-articular injection of exogenous HA stimulates production of endogenous HA which may relieve symptoms of OA of knee via multiple pathways (12). Besides structural benefits, HA has short-term efficacy due to analgesic effect and has long-term effect, which helps in pain and joint function (13).

Both long and short term therapeutic effects of HA in OA of knee patients were shown in various clinical trials in comparison to intra-articular injection of corticosteroids and placebo (13). The current study is designed to support the safety and efficacy profile of HA in patients with OA of knee thereby optimizing the HA treatment with the eventual aim of helping the physician in better managing the patients.

8 Study objective

To evaluate the efficacy and safety of intra-articular hyaluronic acid treatment in patients with osteoarthritis of the knee.

9 Investigational plan

9.1 Overall study design and plan

This was a retrospective, longitudinal, Phase-IV study, conducted at a single site. All patients' files were scanned. Those patients with OA who were given a single injection of intra articular HA at a dose of 30mg/ml (3ml) and who attended to 3 and 6 month routine follow up examinations and satisfied the inclusion and exclusion criteria, were enrolled in the study.

9.2 Investigator Selection Criteria

Physician with extensive experience in management of OA using the HA injections and having knowledge of ICH-GCP guidelines was selected for participation in the study.

9.3 Discussion of study design

This was a Phase-IV study, which was conducted in Turkey at a single center. In this study, the study population consisted of male or female OA of knee, aged ≥ 45 and 80 ≤ years.

In this retrospective, longitudinal study data of patients who received intra-articular injection of HA (3ml of 30mg/ml) as recommended treatment of OA was selected. Reasons for choosing this design are as follows:

Longitudinal: In this study, data was collected beyond a single moment of time. Therefore, to establish a sequence of events longitudinal design was chosen.

Phase-IV: This study was conducted on a marketed product in order to generate safety and effectiveness data; hence, the Phase-IV study was conducted.

9.4 Selection of study population

Male or female patients diagnosed with OA of knee, who satisfied all inclusion and none of the exclusion criteria and provided written informed consent to allow usage of their data were included in the study.

9.4.1 Inclusion criteria

Patients satisfying all of the following criteria were included in the study:

1. Patients of either gender, ≥ 40 years and ≤ 85 years of age
2. Documented diagnosis of mild to moderate knee OA that fulfill the American College of Rheumatology (ACR) criteria
3. Radiographic diagnosis of OA of the knee (Grade II or III according to the Kellgren and Lawrence classification)
4. Patients with consistent symptoms (either joint pain, crepitus, swelling, effusion alone or combination of these symptoms) of knee OA for at least 3 months prior to screening. If bilateral knee pain was present, the investigator selected the more painful knee.
5. Minimum 3 months of unsuccessful non-surgical treatment, including (but not limited to) acetaminophen, anti-inflammatory medication, cortisone injection, physical therapy and bracing.
6. The patients who had abstained from medication use 24 hours prior to any study visit and discontinued all non-steroidal anti-inflammatory drugs (NSAIDs) or other analgesic medication taken for any condition, including their knee pain.
7. Patients who gave written informed consent form regarding using their medical data with keeping their confidential information for scientific purposes

9.4.2 Exclusion criteria

Patients satisfying none of the following criteria were included in the study:

1. Secondary OA of the knee according to ACR criteria
2. Radiographic diagnosis of OA of the knee (Grade IV according to the Kellgren and Lawrence classification)
3. Having previously undergone surgery on target knee, including arthroscopy
4. Presence of any severe systemic disease(s)
5. Presence of significant OA symptoms in other joints apart from the target knee which would have required pharmacological treatment during the study.
6. History of receiving intra-articular HA within the previous 6 months and/or intra-articular steroids or articular lavage in the target knee within the previous 3 months prior to their inclusion in the study
7. Administration of glucosamine sulphate, chondroitin sulphate and diacerein within the 3 months prior to their inclusion in the study
8. History of allergy or hypersensitivity to HA

Participation in any clinical study in the last 3 months and any surgery scheduled in the next 8 months that could have affected directly the result of the present study.

9.4.3 Removal of patients from therapy or assessment

Not applicable, as it was a retrospective study.

9.5 Treatments

9.5.1 Treatment administered

The patients were administered with a single injection of HA 30 mg/ml by Intra-articular route.

9.5.2 Identity of investigational product(s)

Biovisc Ortho Single (Biotech Vision Care Pvt. Ltd, Ahmedabad, India) is a medical device comprising of:

- Cross Linked Sodium Hyaluronate - 30mg
- Phosphate Buffer Saline - pH 7.2

Manufactured by Bio-Tech Vision Care Pvt. Ltd

9.5.3 Method of assigning patients to treatment groups

Not applicable as it was non-interventional retrospective study.

9.5.4 Selection of doses in the study

Biovisc Ortho Single (Biotech Vision Care Pvt. Ltd, Ahmedabad, India) was supplied as a single use glass syringe of 3 ml in a sterile pack (containing Cross Linked Sodium Hyaluronate 30mg/ml)

9.5.5 Blinding

Not applicable, as this was a retrospective, non-interventional study.

9.5.6 Prior and concomitant therapy

The complete details of concomitant treatment were captured in the concomitant treatment log.

9.6 Efficacy and safety variables

9.6.1 Efficacy and safety measurements assessed and flow chart

9.6.1.1 Efficacy assessments

In this study changes in Western Ontario McMaster Universities Arthritis Index (WOMAC) score between baseline visit and 3 and 6 month follow-up were used to assess the efficacy of HA (3ml of 30mg/ml).

9.6.1.2 Safety assessments

Safety assessments consisted of collecting all adverse events (AE) and serious adverse events (SAE) with their severity and relationship to study device Safety profile of HA in this study was calculated by using Treatment Emergent Adverse Events (TEAE).

Adverse Event

An AE is the development of any untoward medical occurrence associated with the use of a drug in humans, whether or not considered causally related to the product.

Serious Adverse Event

A SAE is an adverse event occurring during any study phase and satisfies one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Is a congenital abnormality or birth defect
- Results in persistent or significant disability or incapacity
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

9.6.2 Appropriateness of measurements

In this retrospective, longitudinal study, disease profile of OA of knee patients with diagnosis, medical history and treatment history was evaluated. WOMAC pain score was used to assess the knee pain severity among OA patients. The WOMAC index is a patient-reported assessment of knee pain using 24 parameters. It comprises three components: pain, stiffness, physical function, which can be reported separately or as an overall index. The WOMAC measures five items for pain (score range 0–20), two for stiffness (score range 0–8), and 17 for functional limitation (score range 0–68). Changes in WOMAC score between baseline visit and 3-month and 6-month follow-up was used to assess the efficacy.

9.6.3 Study variables

9.6.3.1 Primary efficacy variable

WOMAC Index: The WOMAC index is a patient-reported assessment of knee pain using 24 parameters. Differences in WOMAC pain scores at follow-up Visits 3 month and 6 month from baseline visit, to assess the efficacy.

9.6.3.2 Other variables

Demographic information: The available information about Age, Gender, Weight and Height were captured.

Information regarding disease: Diagnosis of OA as per the ACR criteria, date of diagnosis, duration of disease and symptoms present for last 3 months were captured in the study.

Medical history: The details of past medical history were documented.

Treatment History: The details of any treatment taken in last 6 months were captured.

9.7 Data quality assurance

9.7.1 Data collection

After review of the patient's files, if the patient was found eligible for the study, then the patient was given a unique Identification number. All files of the eligible patients were identified and data were captured in a paper Case Report Form (CRF) from these files. The Investigators /designated site staff entered the data required by protocol in the CRF from patients' files. The protocol parameters were pre-designed in the CRF to facilitate the data entry. The participant's identification information including name, address and medical record numbers were secured and access was restricted only to the Investigator and study team.

9.7.2 Database management and quality control

The Clinical Research Associate (CRA)/ data management team raised queries, if found, the queries were addressed by the Investigator. Once the Investigators had resolved all queries and the database was declared complete and accurate, the database was locked.

9.8 Statistical methods planned in the protocol and determination of sample size

9.8.1 Statistical and analytical plans

All of the enrolled subjects who had signed the informed consent form constituted the safety population and considered for the analysis of safety parameters. For the efficacy analysis, the patients who had received HA dose and had undergone at least one follow up either at 3 or 6 months were included. The descriptive statistical methods were used to summarize the demographic and disease characteristics. For continuous variables measurements such as age, the mean, median, standard deviation and range were tabulated and for the categorical variable measurements such as gender, the frequencies were computed. All statistical analyses were conducted with the SAS System, version 9.2.

Analysis

The following analyses were performed for the analysis sets:

1. For continuous variables [n, mean ± SD, median (minimum–maximum)] and for categorical variables (frequency, %) were displayed. Following subjects, characteristics were summarized as age, height, and weight.
2. Number (percentage) of TEAE
3. Percentage reduction in the WOMAC pain score at follow-up visits from the baseline visit.

9.8.2 Determination of sample size

This was a non-interventional study therefore; no formal sample size calculation was performed. The study was planned to be performed on 30 male or female subjects with OA of knee.

9.9 Changes in the conduct of the study or planned analyses

9.9.1 Protocol amendments

No changes in protocol were made during the study

9.9.2 Other changes in study conduct

9.9.2.1 Changes in planned analysis

No changes in planned analyses were carried out during the conduct of the study.

10 Study patients

10.1 Disposition of patients

A total of 35 patients with OA of knee of either gender with age ≥ 40 years and ≤ 85 years were enrolled in this study after obtaining informed consent.

10.2 Protocol deviations

No protocol deviations were reported in this study.

11 Study evaluation

11.1 Data sets analyzed

A total of 35 patients were enrolled in the study. All enrolled patients were considered for analysis of safety. Of all enrolled patients, 97.1% patients were considered for analysis of efficacy. Details of the analyses sets are provided in Table 11-1 below.

Table 11-1: Analyzed Datasets (All enrolled)

	All Enrolled (N=35)
Efficacy Population	34 (97.1%)
Safety Population	35 (100%)

Source: Statistical Table 1

11.2 Demographic and other baseline characteristics

The Table 11-2 below provides an overview of demographic characteristics of all enrolled patients. The mean ± SD age of all enrolled patients was 62.7 ± 7.6 years. The majority of enrolled patients were females (91.4%). The mean ± SD height and weight of enrolled patients was 157.6 ± 6.4 cm and 84.2 ± 16.3 kg, respectively.

Table 11-2: Demographic Information (All enrolled)

	All Enrolled (N=35)
Age (Year)	
Mean ± SD	62.7 ± 7.6
Median (Min, Max)	62.0 (42,77.0)
Sex, n (%)	
Male	3 (8.6%)
Female	32 (91.4%)
Height (cm)	
Mean ± SD	157.6 ± 6.4
Median (Min, Max)	156.0 (144,175)
Weight (kg)	
Mean ± SD	84.2 ± 16.3
Median (Min, Max)	81.0 (53,114)

Source: Statistical Table 2
min = minimum, max = maximum, N = total number of patients enrolled, SD = Standard Deviation

The mean ± SD duration of OA was 5.7 ± 4.23 years. The most common symptom reported by the study participants was pain (100%), followed by swelling and morning stiffness, which were reported by 85.7% and 80.0% of patients, respectively. Details of the disease characteristics are provided in

Table 11-3.

Table 11-3: Disease Characteristics (All enrolled)

	All Enrolled (N=35)
Duration of Osteoarthritis (Year)	
Mean ± SD	5.7 ± 4.23
Median(Min, Max)	5.0 (1,15.0)
Symptoms of Osteoarthritis present for last 3 months, n (%)	
Pain	35 (100%)
Swelling	30 (85.7%)
Morning stiffness	28 (80.0%)
Body tenderness	5 (14.3%)
Crepitus on active motion	5 (14.3%)
Bony enlargement	1 (2.86%)
No Palpable warmth of synovium	0 (0.0%)
Others	0 (0.0%)

Source: Statistical Table 3
Max = Maximum, Min = Minimum, N = total number of patients enrolled, n = number of patients, SD = Standard Deviation

The symptoms of OA present for last 3 months are graphically illustrated in **Figure** 1 below.

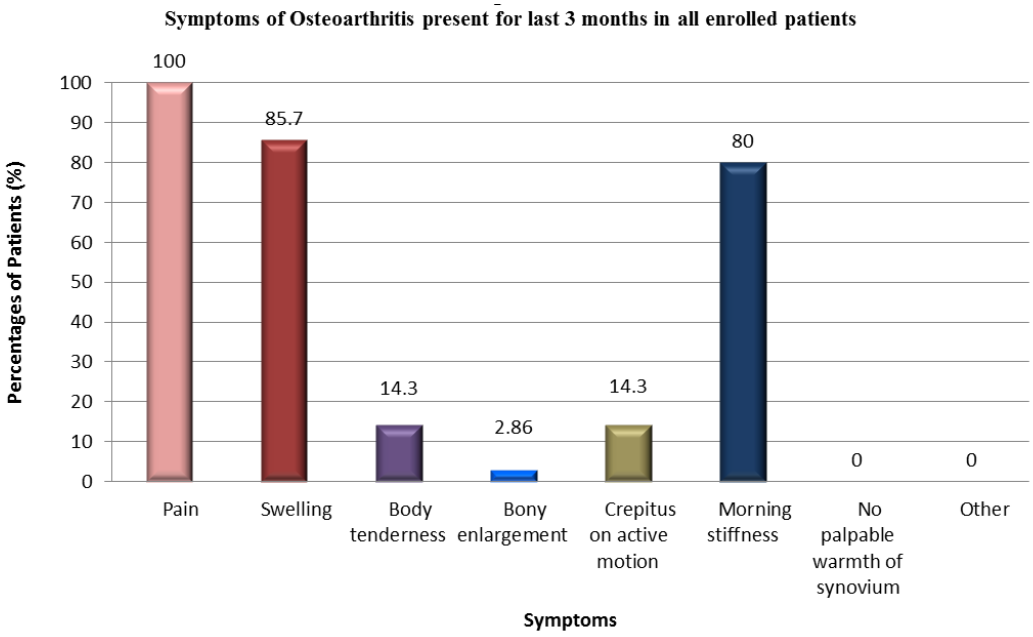

Figure 1: Symptoms of Osteoarthritis Present for Last 3 month in All Enrolled Patients
Source: Statistical table 3

Of all enrolled patients, 77.1% reported history of medical disease in the past. The most common condition reported was high blood pressure (51.9%) followed by diabetes which was present in about 22% of patients each. Details of the medical history are provided in Table 11-4.

Table 11-4: Summary of Medical History

	All Enrolled (N=35)
No. of patients with Medical History	
Yes	27 (77.1%)
No	8 (22.9%)
Medical Conditions	
High blood pressure	14 (51.9%)
Diabetes	6 (22.2%)
Osteoarthritis	6 (22.2%)
Atherosclerosis	1 (3.7%)
Cardiac arrhythmia	1 (3.7%)
Corneal artery disease	1 (3.7%)
Coronary artery disease	1 (3.7%)
Depression	1 (3.7%)
Fibroids	1 (3.7%)
Hyperthyroid	1 (3.7%)
Menopause	1 (3.7%)
Stomach ulceration	1 (3.7%)

Source: Statistical Table 5
N = total number of patients enrolled

Summary of medical history is graphically illustrated in **Figure 2** below

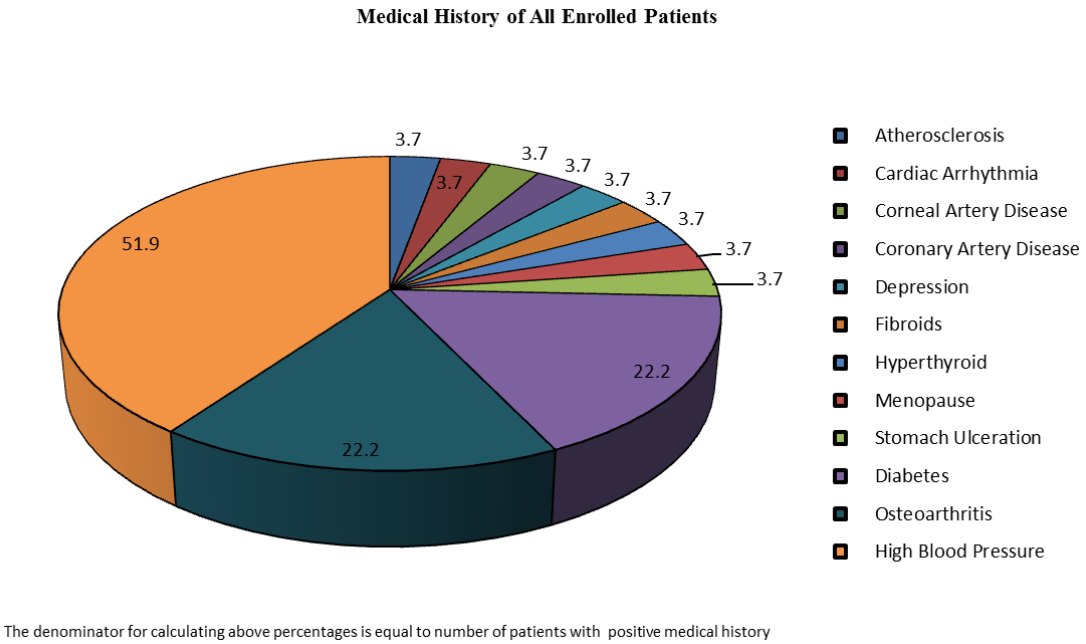

Figure 2: Medical History of All Enrolled patients
Source: Statistical table 5

11.3 Measurement of treatment compliance

All enrolled patients received intra-articular injection of HA.

Table 11-5: Hyaluronic Acid Treatment

	All Enrolled (N=35)
Patients who received intra-articular injection of hyaluronic acid 30 mg/ml	35 (100%)

Source: Statistical Table 4
N = total number of patients enrolled

In total 71.4% of patients were on medication at the time of enrolment in the study. The details of medications are provided in the Table 11-6 below.

Table 11-6: Summary of Treatment History

	All Enrolled (N=35)
Patients currently on medication	
Yes	25(71.4%)
No	10(28.6%)
Medications	
Amlodipin (C08CA01)	1(4.0%)
Amlodipine And Valsartan (C09DB01)	1(4.0%)
Atorvastatin (C10AA05)	1(4.0%)
Caffeine (N06BC01)	1(4.0%)
Calcium Acetate (V03AE07)	1(4.0%)
Carvedilol (C70AG02)	1(4.0%)
Dexketoprofen (M01AE17)	1(4.0%)
Etodolac (M01AB08)	1(4.0%)
Insuline (A10AB01)	1(4.0%)
Isosorbide Mononitrate (C01DA14)	1(4.0%)
Levothyroxine (H03AA01)	1(4.0%)
Lisinopril (C09AA03)	1(4.0%)
Losartan Potassium And Hydrochlorothiazide (C03EA01)	1(4.0%)
Metformin (A10BA02)	1(4.0%)
Miglitol (A10BF02)	1(4.0%)
Pramipexole (N04BC05)	1(4.0%)
Ramipril (C09AA05)	1(4.0%)
Rosuvastatin (C10AA07)	1(4.0%)
Sertraline (N06AB06)	1(4.0%)
Sitagliptin / Metformin Hydrochloride (A10BD07)	1(4.0%)
Thiocolchicoside (M03BX05)	1(4.0%)
Verapamil (C08DA01)	1(4.0%)

Zinc Sulfate (A12CB01)	1(4.0%)
Zofenopril (C09AA15)	1(4.0%)
Acetylsalicylic Acid (B01AC06)	2(8.0%)
Diclofenac (M01AB05)	2(8.0%)
Hyaluronic Acid (M09AX01)	2(8.0%)
Candesartan (C09CA06)	3(12.0%)
Hydrochlorothiazide (C03AA03)	3(12.0%)

Source: Statistical Table 6
N = total number of patients enrolled

11.4 Efficacy results

11.4.1 Analysis of efficacy

Primary efficacy results

The change in the WOMAC Index score over the study period is illustrated in Table 11-7. There was a statistically significant reduction ($p \leq 0.0001$) in the WOMAC Index score from baseline to visit at month 3 and further reduction during visit at month 6. The mean ± SD change in WOMAC score was found to be 21.4 ± 10.0 at month 3 with percentage reduction of 28.7%. After 6 months, the mean ± SD change in WOMAC score was 29.6 ± 15.0 with percentage reduction of 39.7%.

Table 11-7: Change from Baseline in WOMAC Index Score by Visit.

	Efficacy Population (N=34)
Baseline	
Mean ± SD	74.6 ± 8.5
Median (Min, Max)	76.5 (48, 88.0)
Month 3	
Mean ± SD	53.2 ± 14.1
Median (Min, Max)	54.5 (20, 78.0)
Change from baseline	
Mean ± SD	21.4 ± 10.0
Median (Min, Max)	17.5 (8, 55.0)
p-value	<0.0001
Percentage reduction	28.7%
Month 6	
Mean ± SD	45.0 (18.2)
Median(Min, Max)	47.5 (9, 80.0)
Change from baseline	
Mean ± SD	29.6 ± 15.0
Median (Min, Max)	28.0 (6, 66.0)
p-value	<0.0001
Percentage reduction	39.7%

Source: Statistical Table 15 and 19
Max= Maximum, Min=Minimum, N = Efficacy Population, SD = Standard Deviation,

The change in the WOMAC Index score over the study period is graphically illustrated in **Figure 3** below:

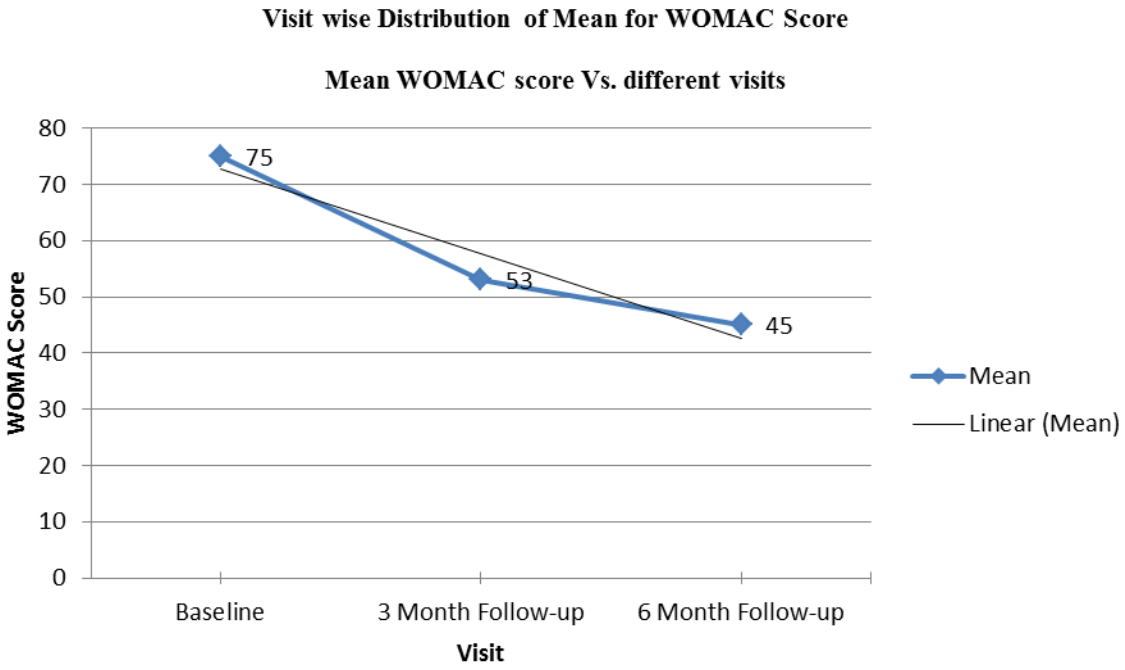

Figure 3: Visit wise Distribution of Mean WOMAC Score
Source: Statistical table 15

The three components of the WOMAC Index score viz, pain, stiffness and physical function were analyzed individually. The results of the analyses are presented below:

The change in the WOMAC Pain score over the study period is illustrated in Table 11-8. There was a statistically significant reduction ($p \leq 0.0001$) in WOMAC Pain score from baseline to visit at month 3 and further reduction during visit at month 6. The mean ± SD change in WOMAC Pain score was found to be 5.1 ± 2.8 at month 3 visit with percentage reduction of 29.3%. After 6 months, the mean ± SD change in WOMAC Pain score was 6.4 ± 3.8 with percentage reduction of 36.9%.

Table 11-8: Change from Baseline in WOMAC Pain Score by Visit.

	Efficacy Population (N=34)
Baseline	
Mean ± SD	17.5 ± 2.4
Median (Min, Max)	18.0 (12, 20.0)
Month 3	
Mean ± SD	12.4 ± 3.6
Median (Min, Max)	13.0 (5, 19.0)
Change from baseline	
Mean ± SD	5.1 ± 2.8
Median (Min, Max)	5.0 (1, 14.0)
p-value	<0.0001
Percentage reduction	29.3%
Month 6	
Mean ± SD	11.0 ± 4.7
Median (Min, Max)	11.0 (2,20.0)
Change from baseline	
Mean ± SD	6.4 ± 3.8
Median (Min, Max)	7.0 (0, 17.0)
p-value	<0.0001
Percentage reduction	36.9%

Source: Statistical Table 16 and 20.
Max= Maximum, Min=Minimum, N = Efficacy Population, SD = Standard Deviation,

The change in the WOMAC Pain score over study period is graphically illustrated in **Figure 4** below:

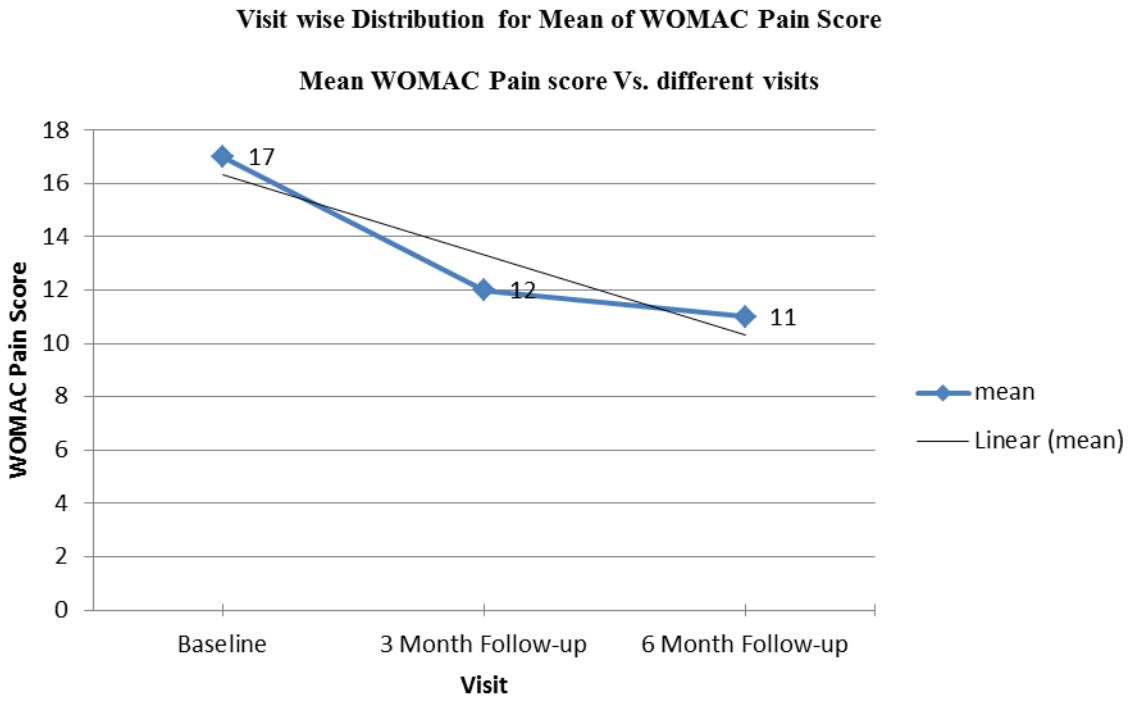

Figure 4: Visit wise Distribution of Mean WOMAC Pain Score
Source: Statistical Table 16

The change in the WOMAC Stiffness score over the study period is illustrated in

Table 11-9. There was a statistically significant reduction ($p \leq 0.0001$) in WOMAC Stiffness score from baseline to visit at month 3 and further reduction during visit at month 6. The mean ± SD change in WOMAC Stiffness score was found to be 2.1 ± 1.7 at month 3 visit with percentage reduction of 39.0%. After 6 months, the mean ± SD change in WOMAC Stiffness score was 2.6 ± 2.1 with percentage reduction of 48.9%.

Table 11-9: Change from Baseline in WOMAC Stiffness Score by Visit

	Efficacy Population (N=34)
Baseline	
Mean ± SD	5.4 ± 1.9
Median (Min, Max)	6.0 (1, 8.0)
Month 3	
Mean ± SD	3.3 ± 2.2
Median (Min, Max)	3.5 (0 ,8.0)
Change from baseline	
Mean ± SD	2.1 ± 1.7
Median (Min, Max)	2.0 (0, 6.0)
p-value	<0.0001
Percentage reduction	39.0%
Month 6	
Mean ± SD	2.7 ± 2.1
Median (Min, Max)	2.0 (0, 8.0)
Change from baseline	
Mean ± SD	2.6 ± 2.1
Median (Min, Max)	2.0 (-2, 6.0)
p-value	<0.0001
Percentage reduction	48.9%

Source: Statistical Table 17 and 21
Max= Maximum, Min=Minimum, N = Efficacy Population, SD = Standard Deviation,

The change in the WOMAC Stiffness score over study period is graphically illustrated **Figure 5** below.

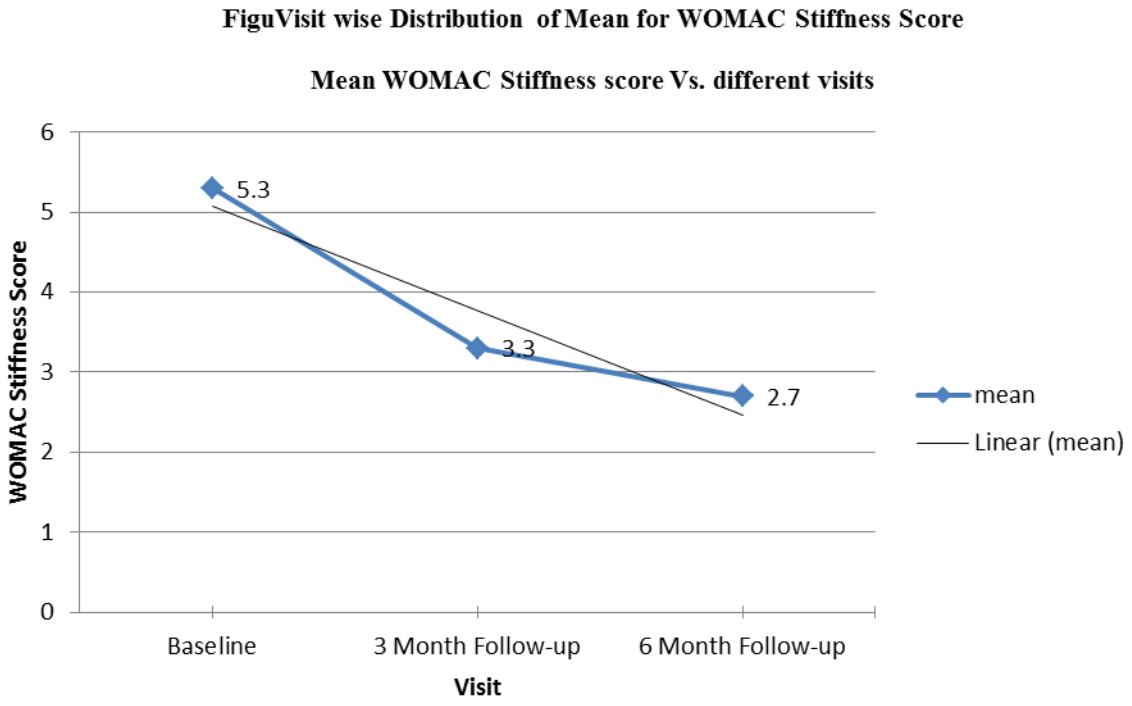

Figure 5: Visit wise Distribution of Mean WOMAC Stiffness Score
Source: Statistical table 17

The change in the WOMAC Physical Function score over the study period is illustrated in Table 11-10. There was a statistically significant reduction ($p \leq 0.0001$) in WOMAC Physical Function score from baseline to visit at month 3 and further reduction during visit at month 6. The mean ± SD change in WOMAC Physical Function score was found to be 14.2 ± 7.3 at month 3 visit with percentage reduction of 27.4%. After 6 months, the mean ± SD change in WOMAC Physical Function score was 20.6 ± 10.9 with percentage reduction of 39.7%.

Table 11-10: Change from Baseline in WOMAC Physical Function Score by Visit

	Efficacy Population (N=34)
Baseline	
Mean ± SD	51.8 ± 6.1
Median (Min, Max)	53.0 (34,62.0)
Month 3	
Mean ± SD	37.6 ± 10.2
Median (Min, Max)	39.5 (14, 54.0)
Change from baseline	
Mean ± SD	14.2 ± 7.3
Median(Min, Max)	12.0 (4, 38.0)
p-value	<0.0001
Percentage reduction	27.4%
Month 6	
Mean ± SD	31.2 ± 12.9
Median (Min, Max)	33.0 (6,56.0)
Change from baseline	
Mean ± SD	20.6 ± 10.9
Median(Min, Max)	17.0 (2, 47.0)
p-value	<0.0001
Percentage reduction	39.7%

Source: Statistical Table 18 and 22
Max= Maximum, Min=Minimum, N = Efficacy Population, SD = Standard Deviation,

The change in the WOMAC Stiffness score over the study period is graphically illustrated in **Figure 6** below.

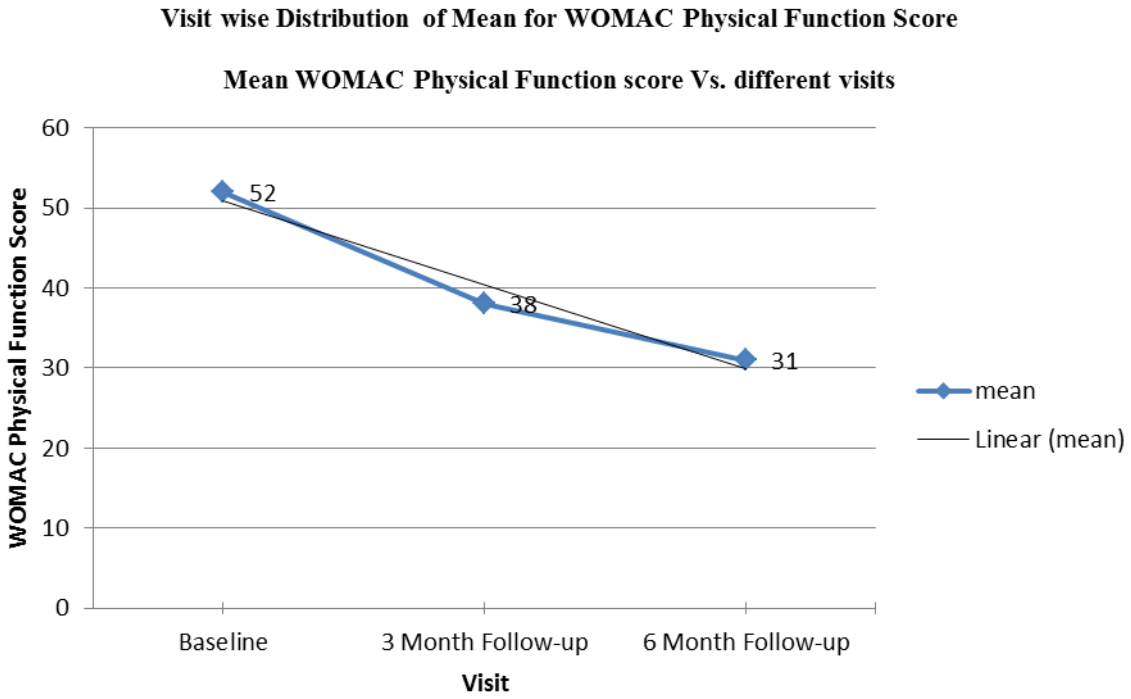

Figure 6: Visit wise Distribution of mean WOMAC Physical function score.
Source: Statistical table 18

11.4.2 Efficacy conclusions

There was statistically significant reduction ($p \leq 0.001$) in the individual WOMAC pain, stiffness and physical function scores from baseline to the visit at month 3 and further reduction during the visit at month 6. The overall WOMAC score also reduced significantly ($p \leq 0.001$) from baseline to the visit at month 3 and month 6. In the light of our results the Biovisc Ortho Single (Biotech Vision Care Pvt. Ltd, Ahmedabad, India) (with HA 3ml of 30mg/ml) is found to be efficacious in treatment of OA of knee.

12 Safety evaluation

12.1 Extent of exposure

Not applicable.

12.2 Adverse events

No AE, SAE, deaths, and TEAEs were reported in this study. Please refer to statistical table 8–14

12.3 Clinical laboratory evaluation

No laboratory evaluations were performed in this study.

12.4 Vital signs, physical findings, and other observations related to safety

Not applicable.

12.5 Safety conclusions

The Intra-articular HA injection was found to be safe and tolerated well.

13 Discussion and overall conclusions

Discussion

Osteoarthritis of knee is a progressive joint disease in older adults characterized by joint inflammation affecting quality of life of individuals (1). OA of knee is one of the top five most disabling conditions that affects more than one-third of the elderly population (14). Intra-articular injection of HA is currently recommended by the main therapeutic guideline in the treatment of OA and is recommended to those patients who do not respond to non-pharmacological therapy, NSAIDs or analgesics (9). This retrospective longitudinal study was conducted to support the safety and efficacy profile of intra-articular injection of HA (3ml of 30mg/ml) in patients of OA of knee with an aim to help the physicians in managing the patients.

The higher prevalence of OA in female patients observed in this study is compatible with results of previous studies (4, 6, 15). However, the sample size of the population in this study is small to reach this kind of conclusion. Similarly, the major symptoms of pain, swelling, and morning stiffness reported in our study were also reported in other studies in the past. (16).

Osteoarthritis is a disease with a high rate of comorbidity. Around 3 out of 4 subjects from our study suffered from at least one disease, with high blood pressure being the most common followed by, diabetes mellitus. The prevalence of comorbidity in this study population is similar to the study results reported by Reeuwijk et al. (68% to 85%) (17).

The current study found that pain and joint movement improved significantly following treatment with HA with the beneficial effects lasting up to 6 months after single intra-articular injection. Published data showed that HA caused significant improvement in pain and joint mobility (18, 19). Several reports have shown that the HA treated patients had lower mean WOMAC pain, stiffness and physical function sub-score at 6 months. Our findings are similar to that of literature. The WOMAC Index score showed significant improvement with a reduction of 39.7% by 6 months.

Unlike corticosteroids, the beneficial effects of HA were long lasting (2–6 months in most studies) after treatment interruption indicating a long carry-over effect. Due to its mode of action, the International League for Associations against Rheumatism (ILAR) has defined intra-articularly administered HA as a Symptomatic Slow Acting Drug for Osteoarthritis (SYSADOA)(20). No AEs were observed throughout the study. In addition, no patient showed deterioration in his or her condition. Hence, the data of our study reveals that Biovisc Ortho Single device (Biotech Vision Care Pvt. Ltd, Ahmedabad, India) is safe and effective in patients with OA.

Our results suggest that intra-articular injection of HA should be the treatment option for those patients who do not respond to non-pharmacological therapy, NSAIDs or analgesics. Therefore, Biovisc Ortho Single (Biotech Vision Care Pvt. Ltd, Ahmedabad, India), which contains HA (3ml of 30mg/ml) is a valuable treatment option for OA of the knee.

Conclusion:

We found that Biovisc Ortho Single device (Biotech Vision Care Pvt. Ltd, Ahmedabad, India) intra-articular HA injection is safe and effective in patients with OA of knee. The findings of this study could be helpful for clinicians in developing strategies for treatment and management of OA of knee.

14 Tables, Figures and Graphs Referred to but not Included in the Text

Not Applicable

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16 Appendices

This section will be provided as separate document.