1. TITLE PAGE

EVALUATION TITLE	:	To Assess the Safety and Performance of Intra-Articular Hyaluronic Acid (HA) in Patients with Knee Osteoarthritis (OA)
DEVICE	:	Biovisc Ortho Plus (Hyaluronic acid 40 mg/2ml)
INDICATION	:	Osteoarthritis of Knee
Evaluation Start Date	:	12/10/15
Evaluation Completion Date	:	27/06/16
Protocol No.	:	BTVCPL/07CL/BIOVISC_ORTHOP-150120
REPORT VERSION	:	1.0, Date: 27/07/16
Evaluation Phase	:	Clinical Evaluation (PMCF)

Evaluation Centre:

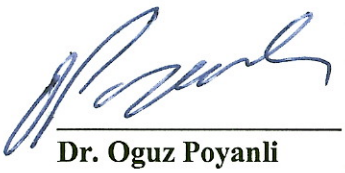
Dr. Oguz Poyanli
Goztepe Research and Training Hospital
Istanbul, Turkey.

Research Supported By:

Biotech Vision Care Pvt. Ltd.

1.1. Statement of Investigator for Good Clinical Practice compliance

The Evaluation has been conducted as per Declaration of Helsinki (Ethical principles for Medical Research Involving Human Subjects, revised by the WMA General Assembly, Fortaleza, Brazil, October 2013) and is consistent with ICH-GCP (E6-R1, Step 5) & ISO14155 guidelines along with the local regulatory requirements of GCP for Clinical Research and all relevant SOPs of Hospital. I accept the responsibility for scientific correctness of the project and the validity of the data produced in this report.



Date: 02.08.2016

Dr. Oguz Poyanli
Principal Investigator
Goztepe Research and Training Hospital
Istanbul, Turkey.

2. SYNOPSIS

Research Supported By: Biotech Vision Care Pvt. Ltd.	Individual Evaluation table referring to part of the dossier: Volume: Page:	For National Authority Use Only
Name of Finished Product: Biovisc Ortho Plus		
Name of Active Ingredient: Hyaluronic acid 40 mg/2ml		

Title of Evaluation	To Assess the Safety and Performance of the Intra-Articular Hyaluronic Acid (HA) in Patients with Knee Osteoarthritis (OA)
Recruitment period	3 months (12 weeks)
Evaluation period	7.5 months: Three intra-articular injection of hyaluronic acid and follow up after 3 and 6 months
Clinical Phase of Development	Clinical Evaluation (PMCF)
Objectives	To evaluate the performance and safety of the intra-articular hyaluronic acid treatment in patients with osteoarthritis of the knee.
Methodology	A total of 35 subjects will be enrolled in the Evaluation based on inclusion/exclusion criteria. Subjects will be given a Three injection of intra articular hyaluronic acid at a dose of 40mg/2ml and data will be analyzed for safety after the dose and during the follow up visits at 3 and 6 months. The performance will be assessed at 3 and 6 months of follow-up visits.
Number of subjects (planned and analyzed)	Total Patients Planned: 35 Total patients Enrolled: 35
Diagnosis and main criteria for inclusion	**Inclusion Criteria:** Patient must meet all of the below mentioned criteria: 1. Patients of either gender, ≥ 40 years and ≤ 85 years of age. 2. Mild to moderate documented diagnosis of knee osteoarthritis that fulfil the ACR (American College of Rheumatology) 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 osteoarthritis for at least 3 months prior to screening. If bilateral knee pain is present, the investigator

	will select 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. Patients who are willing to discontinue all non-steroidal anti-inflammatory drugs (NSAIDs) or other analgesic medication taken for any condition, including their knee pain. However patients will be allowed to use only acetaminophen or aspirin as a rescue pain medication during the Evaluation period. The patients must abstain from medication use 24 hours prior to any Evaluation visit. 7. Patients must be able to understand and follow the Evaluation procedures. **Exclusion criteria:** Patient will be excluded from the Evaluation if they fulfils any of the following criteria: 1. Patients with secondary osteoarthritis 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. Patients having previously undergone surgery on target knee, including arthroscopy. 4. Any severe systemic disease(s). 5. Any significant osteoarthritis symptoms in other joints apart from the target knee which may require pharmacological treatment during the Evaluation. 6. Patients who have received intra-articular hyaluronic acid within the previous 6 month and/or intra-articular steroids or articular lavage in the target knee within the previous 3 months prior to their inclusion in the Evaluation. 7. Administration of glucosamine sulphate, chondroitin sulphate and diacerein within the 3 months prior to their inclusion in the Evaluation. 8. History of allergy or hypersensitivity to hyaluronic acid. 9. Participation in any clinical Evaluation in the last 3 months and any surgery scheduled in the next 8 months that can affect directly the result of the present Evaluation.
Investigational Products	
Product	
Formulation (Generic Name)	Injection (Hyaluronic acid 40 mg/2ml)
Brand Name	Biovisc Ortho Plus

Strength	Hyaluronic acid 40 mg/2ml
Dosage form	Injection (Pre filled syringe)
Filled volume	2 ml PFS
Manufacturer	Biotech Vision Care Pvt. Ltd.
Mode of administration	Intra-articular injection
Duration of treatment	Approximately 21 days (Total Three Injections at weekly Interval)
Efficacy Parameters	Change in KOOS score (pain, stiffness with symptoms, function sub score) after 3 and 6 months from baseline visit.
Safety parameters	Adverse events (Starting from the baseline visit throughout to the follow-up visit)
Statistical analysis	Statistical analysis was performed using Statistical Analysis Software (SAS®). Frequency (N), mean (SD), median (minimum–maximum) were reported for continuous variables. Frequency and percentage were displayed for categorical variables. Percentage reduction in Pain, Stiffness with symptoms, Function sub score and KOOS Score at 3 and 6 months from the baseline visit was displayed and statistical significance for KOOS score was compared using unpaired t-test.
Summary of Results:	
Efficacy Results	Patient Mean Overall KOOS score was 34.85 ± 11.80 at baseline, which is significantly increased to 44.80 ± 12.69 at 3 months with mean change of 10.09 ± 7.07 ($p < 0.0001$), which was further increased to 54.79 ± 14.70 at 6 months with mean change of 19.68 ± 9.18 ($p < 0.0001$) from baseline. Overall KOOS score was improved by 29% at 3 months and 56% at 6 months from baseline. Patient Mean KOOS Pain score was 35.24 ± 15.81 at baseline, which is significantly increased to 47.38 ± 15.26 at 3 months with mean change of 12.53 ± 9.40 ($p < 0.0001$), which was further increased to 58.51 ± 17.33 at 6 months with mean change of 23.30 ± 11.22 ($p < 0.0001$) from baseline. KOOS Pain score was improved by 36% at 3 months and 66% at 6 months from baseline. Patient Mean KOOS stiffness with symptom score was 50.00 ± 17.62 at baseline, which is significantly increased to 56.71 ± 12.33 at 3 months with mean change of 7.14 ± 9.62 ($p < 0.0001$), which was further increased to 60.72 ± 12.02 at 6 months with mean change of 10.83 ± 10.81 ($p < 0.0001$) from baseline. KOOS stiffness with symptom score was improved by 14% at 3 months and 22% at 6 months from baseline. Patient Mean KOOS function daily living score was 43.52 ± 16.65 at baseline, which is significantly increased to 52.36 ± 16.65 at 3 months with mean change of 9.10 ± 6.68 ($p < 0.0001$), which was further increased to 61.57 ± 16.66 at 6

	months with mean change of 17.75 ± 9.91 (p< 0.0001) from baseline. KOOS Function daily living score was improved by 21% at 3 months and 41% at 6 months from baseline. Patient Mean KOOS Function Sports and recreational activity score was 1.57 ± 5.11 at baseline, which is significantly increased to 9.39 ± 12.79 at 3 months with mean change of 7.73 ± 11.93 (p= 0.001), which was further increased to 21.29 ± 17.93 at 6 months with mean change of 19.52 ± 15.83 (p< 0.0001) from baseline. KOOS Function Sports and recreational activity score was improved by 492% at 3 months and 1243% at 6 months from baseline. Patient Mean KOOS Quality of life score was 12.86 ± 9.93 at baseline, which is significantly increased to 29.73 ± 16.16 at 3 months with mean change of 16.86 ± 12.35 (p< 0.0001), which was further increased to 47.78 ± 20.26 at 6 months with mean change of 34.68 ± 15.63 (p< 0.0001) from baseline. KOOS Quality of life score was improved by 131% at 3 months and 270% at 6 months from baseline. Results of present evaluation demonstrated significant improvement in KOOS score as well as pain, stiffness with symptom, function daily living, function sports and recreational activity and quality of life score at 3 and 6 months follow-up. Efficacy evaluation results of Biovisc Ortho Plus make it suitable for use in patients with OA.
Safety Results	As there is no treatment emergent adverse event reported while treatment and follow-up till 6 months, Biovisc Ortho Plus is found safe and effective.
Conclusion	This evaluation demonstrated that Biovisc Ortho Plus(Hyaluronic acid 40 mg/2ml) improves in KOOS score as well as pain, stiffness with symptom, function daily living, function sports and recreational activity and quality of life score at 3 and 6 months while exhibiting an excellent safety profile.

3. TABLE OF CONTENTS

4. LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
GCP	Good Clinical Practice
HA	Hyaluronic Acid
ICH	International Conference on Harmonization
ISO	International Organization for Standardization
NSAIDs	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
PMCF	Post Market Clinical Follow-up
SD	Standard Deviation
WMA	World Medical Association

5. ETHICS

5.1. INDEPENDENT ETHICS COMMITTEE (IEC)

Not applicable

5.2. ETHICAL CONDUCT OF THE EVALUATION

Not applicable

5.3. SUBJECT INFORMATION AND CONSENT

Not applicable

6. INVESTIGATORS AND EVALUATION ADMINISTRATIVE STRUCTURE

Present Evaluation was conducted at Goztepe Research and Training Hospital Istanbul, Turkey. The details of investigator and Evaluation administrative structure are given below in table 1.

Table 1: Evaluation administrative structure

Principal Investigator	**:**	Dr. Oguz Poyanli
Evaluation Center	**:**	Goztepe Research and Training Hospital Istanbul, Turkey
Evaluation supported by	**:**	Biotech Vision Care Pvt. Ltd.
Medical Writing and Statistical Services	**:**	Ethitrials Contract Research Pvt. Ltd. Ahmedabad

7. INTRODUCTION

Osteoarthritis (OA) of knee is the most common degenerative joint disease in older adults which causes joint pain and dysfunction, affecting quality life of individuals. It is characterized by deterioration and loss of articular cartilage, sub-chondral bone damage, inflammation/synovitis, osteophyte formation, and joint space loss [1]. Clinical symptoms of knee OA are mainly characterized by gradually increasing joint pain, stiffness and joint enlargement with limited mobility [1]. 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 radiographic knee OA affects 10% of adults over 55 years old [2]. The etiology of knee OA 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].

According to the American College of Rheumatology (ACR) guidelines for the treatment of knee OA, analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) are considered to be the first line treatment options [5]. 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 [5]. Intra-articular injection of hyaluronic acid (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 [6].

In the setting of knee joint, synovial fluid acts as a joint lubricant and shock absorber during shear and compressive stress [7]. Typically, synovial fluid mainly consists of HA that helps to maintain high fluid viscosity and the normal integrity of the joint [7]. In OA, viscoelastic properties of synovial fluid decreased due to the degradation of endogenous HA [8]. Intra-articular injection of exogenous HA stimulates production of endogenous HA which may relieve symptoms of knee OA via multiple pathways [9]. Besides structural benefits, HA has short term performance due to analgesic effect and also has long term effect which helps in pain and joint function [10]. The best therapeutic results of using low molecular weight HA were observed with a dose range between three to five weekly intra-articular injections, each with 2 to 2.5 ml of HA [11].

Both long and short term therapeutic effects of HA in knee OA patients have been shown in various clinical trials in comparison to intra-articular injection of corticosteroids and placebo [10]. The current Evaluation has been designed to support the safety and performance profile of HA in patients with osteoarthritis of knee thereby optimizing the HA treatment with the eventual aim of helping the physician in better managing the patients.

The present document is a clinical Evaluation report of Evaluation conducted to evaluate effect and safety of Biovisc Ortho Plus.

8. EVALUATION OBJECTIVE(S)

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

9. INVESTIGATION PLAN

9.1. OVERALL EVALUATION DESIGN AND PLAN-DESCRIPTION

Present Evaluation was single centric, non-randomized, open label post marketing evaluation in patients with osteoarthritis of knee.

A total of 35 patients who fulfilled inclusion/exclusion criteria were enrolled in present Evaluation. Patients were given three intra-articular injection of hyaluronic acid at a dose of 40mg/2ml at weekly intervals and efficacy data were collected during the follow-up visits at 3 and 6 months. Safety was evaluated throughout treatment visits as well as follow-up visits conducted after 3 and 6 months of

treatment. Data pertaining to performance (efficacy) were collected at follow-up visits conducted after 3 and 6 months of treatment.

A total of 6 visits were conducted during the evaluation. First visit is baseline visit, evaluation device (HA) administration was done on 3 visits and thereafter there were two follow-up visits. The follow-up visits were performed at 3 and 6 months after the completion of treatment.

Patients were screened as per the Inclusion/exclusion criteria before enrolment in present evaluation. Investigator had explained about the evaluation in detail to the patients. The Evaluation procedures are detailed in below table 2.

Table 2: Evaluation Schedule

	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Procedures	**Screening / Baseline**	**Injection Cycle 1**	**Injection Cycle 2**	**Injection Cycle 3**	**Follow-up 1**	**Follow-up 2**
	Day 1				**3 months ± 7 days after last injecti**	**6 months ± 7 days after last injection**
Inclusion/ Exclusion criteria	X					
Demographic information	X					
Medical history	X					
Treatment history	X					
Physical examination	X				X	
Vital signs	X					
Hyaluronic Acid intra- articular administration (Three injection cycle)		X	X	X		
KOOS Score	X				X	X
AE/SAE	X				X	X

Concomitant medication	X				X	X

Following data were planned to collect in present evaluation:

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

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

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

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

KOOS Score: The KOOS is 42-item patient-report questionnaire that assesses symptoms and problems associated with knee injury and osteoarthritis. It yields scores for five scales including Pain, Other Symptoms, Function in Daily Living, Function in Sport/Recreation, and Knee-Related Quality of Life. We used only the Pain scale which has a range of 0 to 100 where 100 represent the "best" score, i.e., no pain. We reported differences in baseline Pain scale score from Pain scale score at 6 months so these scores could theoretically range from -100 (moving from no pain to maximum pain) to 100 (moving from maximum pain to no pain). Positive change scores represent improvement from baseline.

9.2. DISCUSSION OF EVALUATION DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

Not applicable.

9.3. SELECTION OF EVALUATION POPULATION

Subjects recruited to the Evaluation were taken from the standard population confirmed for following inclusion and exclusion criteria.

9.3.1. Inclusion Criteria

Subjects who fulfilled the below criteria were considered for inclusion into this Evaluation.

1. Patients of either gender, ≥ 40 years and ≤ 85 years of age.
2. Mild to moderate documented diagnosis of knee osteoarthritis that fulfill the ACR (American College of Rheumatology) 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 osteoarthritis for at least 3 months prior to screening. If bilateral knee pain is present, the investigator will select 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. Patients who are willing to discontinue all non-steroidal anti-inflammatory drugs (NSAIDs) or other analgesic medication taken for any condition, including their knee pain. However patients will be allowed to use only acetaminophen or aspirin as a rescue pain medication during the Evaluation period. The patients must abstain from medication use 24 hours prior to any Evaluation visit.
7. Patients must be able to understand and follow the Evaluation procedures.

9.3.2. Exclusion Criteria

The subjects were excluded based on the following criteria:

1. Patients with secondary osteoarthritis 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. Patients having previously undergone surgery on target knee, including arthroscopy.
4. Any severe systemic disease(s).
5. Any significant osteoarthritis symptoms in other joints apart from the target knee which may require pharmacological treatment during the Evaluation.
6. Patients who have received intra-articular hyaluronic acid within the previous 6 month and/or intra-articular steroids or articular lavage in the target knee within the previous 3 months prior to their inclusion in the Evaluation.
7. Administration of glucosamine sulphate, chondroitin sulphate and diacerein within the 3 months prior to their inclusion in the Evaluation.
8. History of allergy or hypersensitivity to hyaluronic acid.
9. Participation in any clinical Evaluation in the last 3 months and any surgery scheduled in the next 8 months that can affect directly the result of the present Evaluation.

9.3.3. Removal of Subjects from Therapy or Assessment

34 patients had completed evaluation treatment (3 injection) and were included for safety and efficacy assessment. One patient had not completed evaluation treatment (1 injection) as per protocol and was included for safety and efficacy assessment.

9.4. TREATMENTS

9.4.1. Treatments Administered

Patients were administered with a three injection of Hyaluronic acid 40 mg/2ml by the Intra-articular route at weekly interval. Total of 34 patients received three injections and 1 patient received one injection. All patients were included in the efficacy analysis.

9.4.2. Identity of Investigational Device(s)

Table 3: Summary of Investigational Device

Product	Evaluation test product
Formulation (Generic Name)	Hyaluronic Acid
Brand Name	Biovisc Ortho Plus
Strength	Hyaluronic acid 40 mg/2ml
Dosage form	Injection

9.4.2.1. Investigational Product (IP) Receipt, Dispensing and Handling

Not applicable

9.4.3. Methods of Assigning Subjects to Treatment Groups

Present Evaluation is single arm evaluation with only one treatment. A method of Assigning Subjects to Treatment Groups is not applicable.

9.4.4. Selection of Doses in the Evaluation

Biovisc Ortho Plus (Biotech Vision Care Pvt. Ltd, Ahmedabad, India) was supplied as a single use glass syringe of 2ml in a sterile pack (containing Hyaluronic acid 40 mg/2ml).

Three weekly injection administrations, is as per the Information for Use (IFU).

9.4.5. Selection and Timing of Dose for each Subject

Three Injections at weekly interval indicated for osteoarthritis of knee through intra-articular route.

9.4.6. Blinding

Not applicable, as present Evaluation is single arm open label Evaluation.

9.4.7. Prior and Concomitant Therapy

As per the protocol there was no any mandatory prior or concomitant therapy required during the Evaluation.

9.5. EFFICACY AND SAFETY VARIABLES

9.5.1. Efficacy and Safety Measurements Assessed and Flow Chart

Efficacy measurements

In this evaluation changes in KOOS score between baseline visit and 3 and 6 month follow-up were used to assess the efficacy of BIOVISC Ortho Plus (Hyaluronic acid 40 mg/2ml).

Safety measurements

Safety was measured by evaluation of treatment emergent adverse events and Serious Adverse Event (SAE).

Adverse Event (AE)
Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Serious Adverse Event (SAE)
Any untoward medical occurrence that at any dose:
- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
or
- is a congenital anomaly/birth defect

9.5.2. Appropriateness of Measurements

Not applicable

9.5.3. Primary Efficacy Variable(s)

Change in KOOS score and pain, stiffness with symptoms, function sub score after 3 and 6 months from baseline visit.

9.5.4. Device Concentration Measurements

Not applicable

9.5.5. Sample Collection & Processing

Not applicable

9.6. DATA QUALITY ASSURANCE

Not applicable

9.7. STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

9.7.1. Statistical and Analytical Plans

Statistical analysis was performed using Statistical Analysis Software (SAS®). Frequency (N), mean (SD), median (minimum–maximum) were reported for continuous variables. Frequency and percentage were displayed for categorical variables.

Percentage reduction in the Pain, Stiffness with symptoms, Function sub score and KOOS Score at 3 and 6 months from the baseline visit was displayed and statistical significance for KOOS score was compared using unpaired t-test.

9.7.2. Determination of Sample Size

Assuming mean reduction of 17 in KOOS score at 6 months from baseline and standard deviation 26, and considering one-sided alpha error of 0.05, power of 80%, sample size estimate is 32. Consideration of 10% of drop-out rate, we had planned to recruit 35 patients in present evaluation.

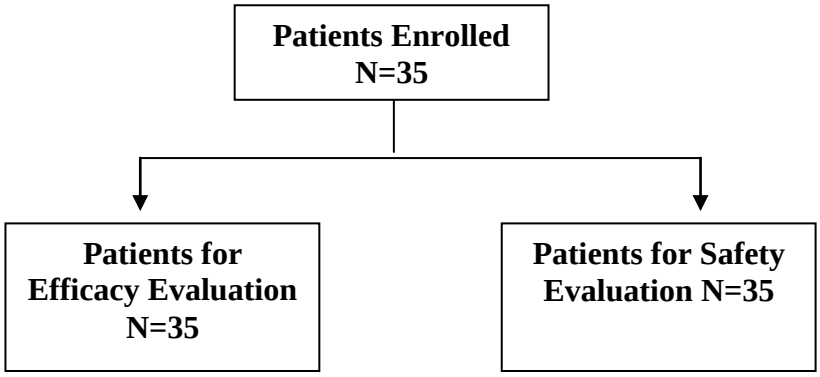
9.8. CHANGES IN THE CONDUCT OF THE EVALUATION OR PLANNED ANALYSES

There were no changes in the conduct of the Evaluation or planned analysis.

10. EVALUATION SUBJECTS

10.1. DISPOSITION OF SUBJECTS

A total of 35 patients with OA of knee of either gender with age ≥ 40 years and ≤ 85 years were enrolled in this Evaluation.



10.2. PROTOCOL DEVIATION(S)

There was no protocol deviations reported during conduct of evaluation.

11. EFFICACY EVALUATION

11.1. DATA SETS ANALYSED

Table 4

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

Thirty five (35) patients with Osteoarthritis of Knee were enrolled in the Evaluation. Thirty four (34) patients had completed evaluation treatment (3 Injection) and one (1) patient had not completed evaluation treatment (1 injection) as per protocol.
Thirty three (33) patients had completed evaluation follow up at 3 months and Thirty one (31) patients had completed evaluation follow up at 6 months as per protocol and were included in efficacy analysis.

All of Thirty five (35) patients were included for safety evaluation.

11.2. DEMOGRAPHIC CHARACTERISTICS

Demographic variables included age and weight. It included Male as well as Female patients.

Frequency (N), mean (SD), median (minimum–maximum) of Age (In Years) and Weight (In Kg) are presented in below table 5(a):

Table 5(a): **Demographic and other baseline characteristics**

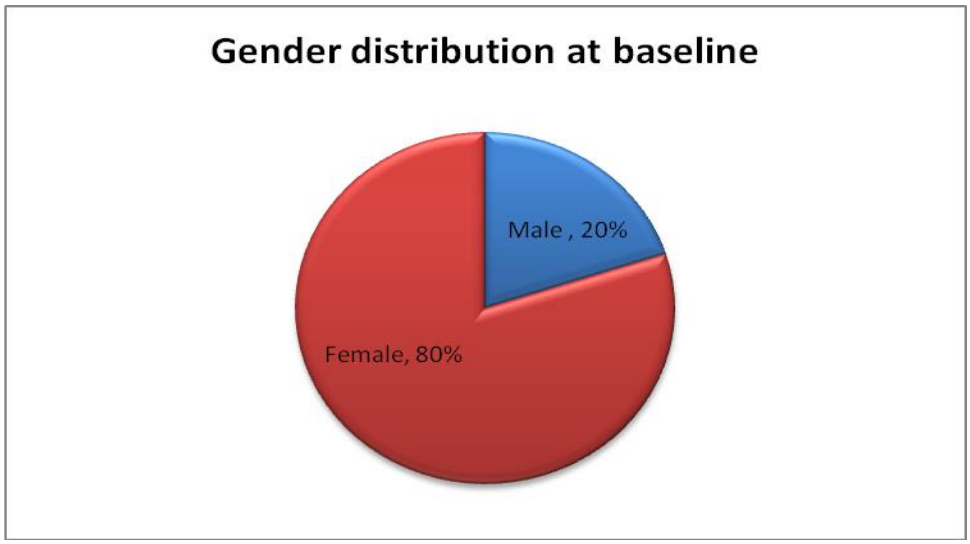
Demographic Data (N=35)		
Parameters	**Age**	**Weight**
Mean	62.83	83.31
SD	9.65	11.96
Min	45.0	49.0
Max	85.0	108.0
Median	63.0	85.0

Frequency and percent of male and female patient enrolled is presented in below table: (**Table 5**(b))

Table 5(b): Gender Demographic and other baseline characteristics

	N	(%)
Male	07	20.00
Female	28	80.00
Total	35	100

Figure 1: Gender distribution at baseline



Number of female patients (80.0%) enrolled in evaluation were higher than male (20.0%) patients.

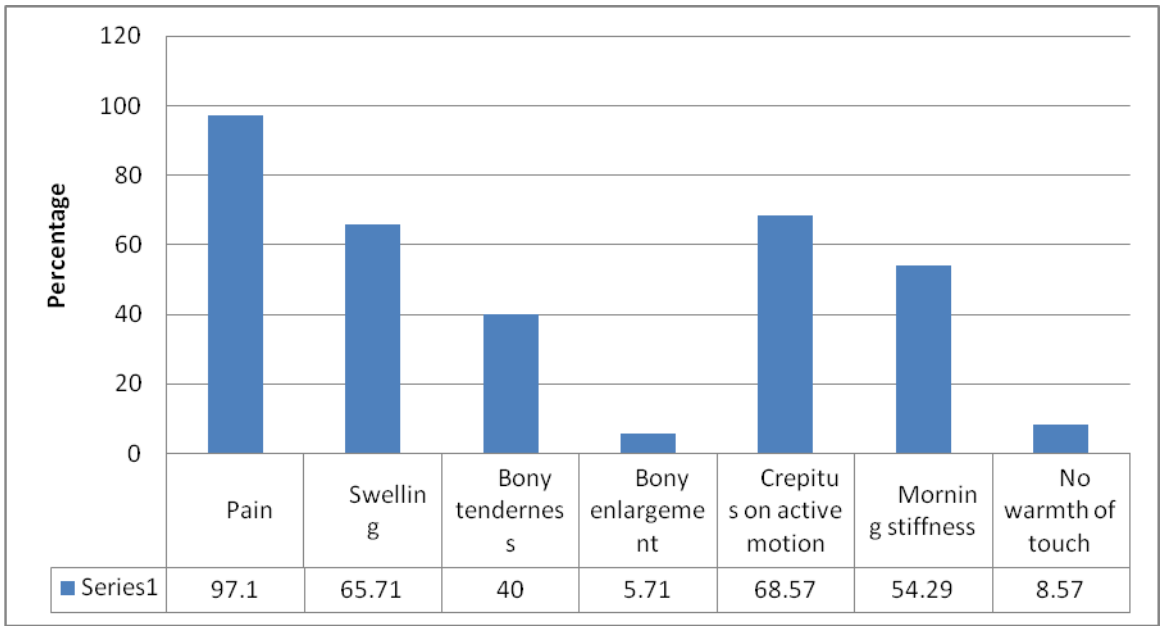
Osteoarthritis related symptoms of Pain, Bony enlargement, Crepitus on active motion was reported in all patients in last 3 months before evaluation. Other reported symptoms were Swelling, Bony tenderness, Morning stiffness and no warmth of touch.

Number and percentage of patients with specific symptoms are presented in below table 6:

Table 6: Symptoms of Osteoarthritis present for last 3 months

Symptoms of Osteoarthritis present for last 3 months	N=35 (%)
Pain	34 (97.10)
Swelling	23 (65.71)
Bony tenderness	14 (40.00)
Bony enlargement	2 (5.71)
Crepitus on active motion	24 (68.57)
Morning stiffness	19 (54.29)
No warmth of touch	3 (8.57)

Figure 2: Symptoms of Osteoarthritis present for last 3 months



11.3. EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL SUBJECT DATA

11.3.1. Analysis of Efficacy

In this evaluation changes in KOOS score between baseline visit and 3 and 6 month follow-up were used to assess the efficacy of BIOVISC Ortho Plus (Hyaluronic acid 40mg/2ml).

Patient Mean Overall KOOS score was 34.85 ± 11.80 at baseline, which is increased to 44.80 ± 12.69 at 3 months with mean change of 10.09 ± 7.07. P-value ($p < 0.0001$) between mean score at baseline and 3 months by unpaired t-test indicated highly significant improvement in Overall KOOS score. Patient Mean Overall KOOS score was further increased to 54.79 ± 14.70 at 6 months with mean change of 19.68 ± 9.18 from baseline. P-value ($p < 0.0001$) between mean score at baseline and 6 months by unpaired t-test indicated persistence of highly significant improvement in Overall KOOS score.

Mean of Overall KOOS score at baseline, 3 months and 6 months change in score is presented in below table 7:

Table 7 : Descriptive Statistics for Overall KOOS Scores by Visit (Efficacy Population)

Baseline	
N	35
Missing	0
Mean (S.D)	34.85 (11.80)

Month 3	
N	33
Missing	2
Mean (S.D)	44.80 (12.69)
Change from baseline	
N	33
Missing	2
Mean (S.D)	10.09 (7.07)
p-value	< 0.0001
Month 6	
N	31
Missing	4
Mean (S.D)	54.79 (14.70)
Change from baseline	
N	31
Missing	4
Mean (S.D)	19.68 (9.18)
p-value	< 0.0001

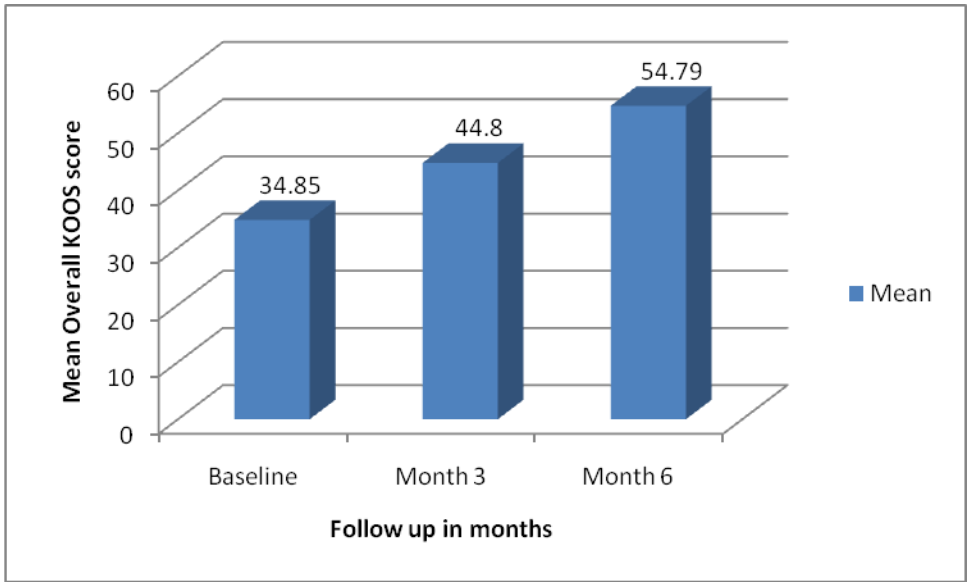
Overall KOOS score was increased by 29% at 3 months and 56% at 6 months from baseline.

Table 8 : Percentage Improvement in Overall KOOS Scores by Visit (Efficacy Population)

	Mean (SD)	**Percentage (%)**
Baseline	34.85 (11.80)	-
Month 3	44.80 (12.69)	29
Month 6	54.79 (14.70)	56

Graphical illustration of change in Overall KOOS score at 3 and 6 months from baseline is depicted in figure 3.

Figure 3: Change in mean Overall KOOS score at 3 and 6 months



Patient Mean KOOS Pain score was 35.24 ± 15.81 at baseline, which is increased to 47.38 ± 15.26 at 3 months with mean change of 12.53 ± 9.40. P-value ($p< 0.0001$) between mean score at baseline and 3 months by unpaired t-test indicated highly significant improvement in KOOS pain score. Patient Mean KOOS Pain score was further increased to 58.51 ± 17.33 at 6 months with mean change of 23.30 ± 11.22 from baseline. P-value ($p< 0.0001$) between mean score at baseline and 6 months by unpaired t-test indicated persistence of highly significant improvement in KOOS pain score.

Mean of KOOS pain score at baseline, 3 months and 6 months change in score is presented in below table 9:

Table 9 : Descriptive Statistics for KOOS Pain Scores by Visit (Efficacy Population)

Baseline	
N	35
Missing	0
Mean (S.D)	35.24 (15.81)
Month 3	
N	33
Missing	2
Mean (S.D)	47.38 (15.26)

Change from baseline	
N	33
Missing	2
Mean (S.D)	12.53 (9.40)
p-value	< 0.0001
Month 6	
N	31
Missing	4
Mean (S.D)	58.51 (17.33)
Change from baseline	
N	31
Missing	4
Mean (S.D)	23.30 (11.22)
p-value	< 0.0001

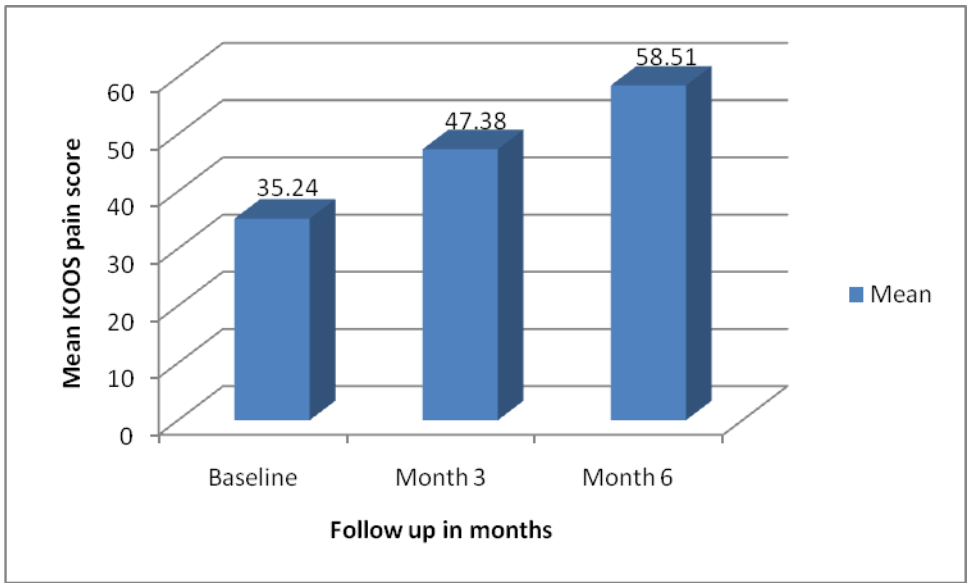
KOOS Pain score was increased by 36% at 3 months and 66% at 6 months from baseline.

Table 10 : Percentage Improvement in KOOS Pain Scores by Visit (Efficacy Population)

	Mean (SD)	**Percentage (%)**
Baseline	35.24 (15.81)	-
Month 3	47.38 (15.26)	36
Month 6	58.51 (17.33)	66

Graphical illustration of change in KOOS Pain score at 3 and 6 months from baseline is depicted in figure 4.

Figure 4: Change in mean KOOS Pain score at 3 and 6 months



Patient Mean KOOS stiffness with symptoms score was 50.00 ± 17.62 at baseline, which is increased to 56.71 ± 12.23 at 3 months with mean change of 7.14 ± 9.62. P-value ($p< 0.0001$) between mean score at baseline and 3 months by unpaired t-test indicated highly significant improvement in KOOS stiffness with symptoms score. Patient Mean KOOS stiffness with symptoms score was further increased to 60.72 ± 12.02 at 6 months with mean change of 10.83 ± 10.81 from baseline. P-value ($p< 0.0001$) between mean score at baseline and 6 months by unpaired t-test indicated persistence of highly significant improvement in KOOS stiffness with symptoms score.

Mean of KOOS stiffness with symptoms score at baseline, 3 months and 6 months change in score is presented in below table 11:

Table 11 : Descriptive Statistics for KOOS Stiffness with symptoms scores by Visit (Efficacy Population)

Baseline	
N	35
Missing	0
Mean (S.D)	50.00 (17.62)
Month 3	
N	33
Missing	2
Mean (S.D)	56.71 (12.23)

Change from baseline	
N	33
Missing	2
Mean (S.D)	7.14 (9.62)
p-value	< 0.0001
Month 6	
N	31
Missing	4
Mean (S.D)	60.72 (12.02)
Change from baseline	
N	31
Missing	4
Mean (S.D)	10.83 (10.81)
p-value	< 0.0001

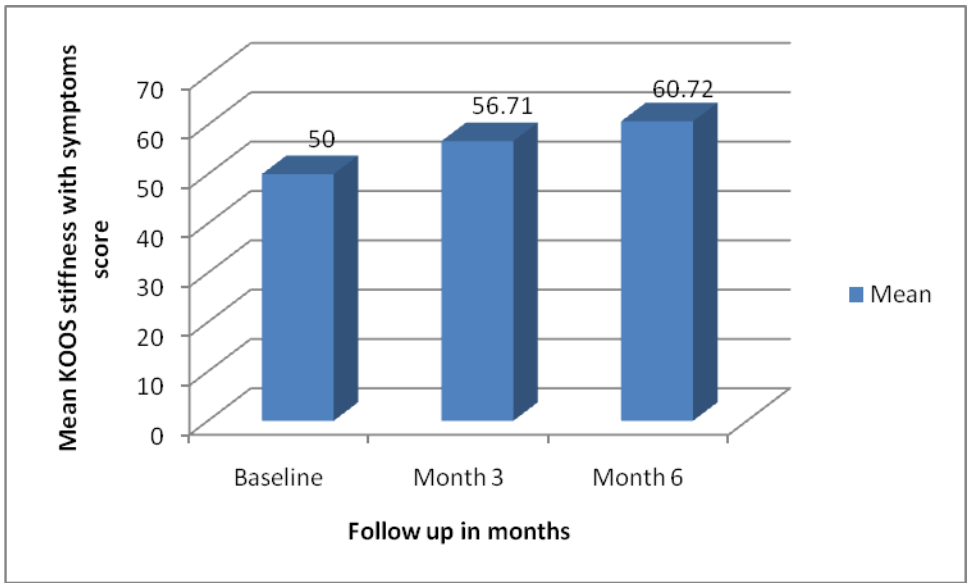
KOOS Stiffness with symptoms score was increased by 14% at 3 months and 22% at 6 months from baseline.

Table 12 : Percentage Improvement in KOOS Stiffness with symptoms scores by Visit (Efficacy Population)

	Mean (SD)	**Percentage (%)**
Baseline	50.00 (17.62)	-
Month 3	56.71 (12.23)	14
Month 6	60.72 (12.02)	22

Graphical illustration of change in KOOS stiffness with symptoms score at 3 and 6 months from baseline is depicted in figure 5.

Figure 5: Change in mean KOOS stiffness with symptoms score at 3 and 6 months



Patient Mean KOOS function daily living score was 43.52 ± 16.65 at baseline, which is increased to 52.36 ± 16.65 at 3 months with mean change of 9.10 ± 6.68. P-value ($p< 0.0001$) between mean score at baseline and 3 months by unpaired t-test indicated highly significant improvement in KOOS function daily living score. Patient Mean KOOS function daily living score was further increased to 61.57 ± 16.66 at 6 months with mean change of 17.75 ± 9.91 from baseline. P-value ($p< 0.0001$) between mean score at baseline and 6 months by unpaired t-test indicated persistence of highly significant improvement in KOOS function daily living score.

Mean of KOOS function daily living score at baseline, 3 months and 6 months change in score is presented in below table 13:

Table 13 : Descriptive Statistics for KOOS Function daily living score by Visit (Efficacy Population)

Baseline	
n	35
Missing	0
Mean (S.D)	43.52 (16.65)
Month 3	
n	33
Missing	2
Mean (S.D)	52.36 (16.65)

Change from baseline	
n	33
Missing	2
Mean (S.D)	9.10 (6.68)
p-value	< 0.0001
Month 6	
n	31
Missing	4
Mean (S.D)	61.57 (16.66)
Change from baseline	
n	31
Missing	4
Mean (S.D)	17.75 (9.91)
p-value	< 0.0001

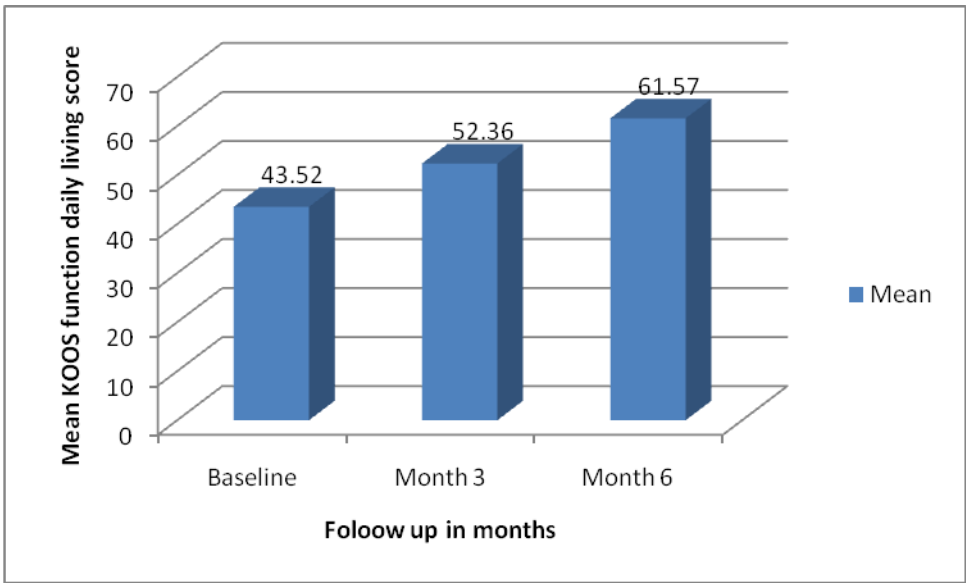
KOOS Function daily living score was increased by 21% at 3 months and 41% at 6 months from baseline.

Table 14 : Percentage Improvement in KOOS Function daily living Scores by Visit (Efficacy Population)

	Mean (SD)	**Percentage (%)**
Baseline	43.52 (16.65)	-
Month 3	52.36 (16.65)	21
Month 6	61.57 (16.66)	41

Graphical illustration of change in KOOS function daily living score at 3 and 6 months from baseline is depicted in figure 6.

Figure 6: Change in mean KOOS function daily living score at 3 and 6 months



Patient Mean KOOS Function Sports and recreational activity score was 1.57 ± 5.11 at baseline, which is increased to 9.39 ± 12.79 at 3 months with mean change of 7.73 ± 11.93. P-value (p = 0.001) between mean score at baseline and 3 months by unpaired t-test indicated highly significant improvement in KOOS Function Sports and recreational activity score. Patient Mean KOOS Function Sports and recreational activity score was further increased to 21.29 ± 17.93 at 6 months with mean change of 19.52 ± 15.83 from baseline. P-value (p< 0.0001) between mean score at baseline and 6 months by unpaired t-test indicated persistence of highly significant improvement in KOOS Function Sports and recreational activity score.

Mean of KOOS Function Sports and recreational activity score at baseline, 3 months and 6 months change in score is presented in below table 15:

Table 15 : Descriptive Statistics for KOOS Function Sports and recreational activity score by Visit
(Efficacy Population)

Baseline	
n	35
Missing	0
Mean (S.D)	1.57 (5.11)
Month 3	
n	33
Missing	2

Mean (S.D)	9.39 (12.79)
Change from baseline	
n	33
Missing	2
Mean (S.D)	7.73 (11.93)
p-value	0.001
Month 6	
n	31
Missing	4
Mean (S.D)	21.29 (17.93)
Change from baseline	
n	31
Missing	4
Mean (S.D)	19.52 (15.83)
p-value	< 0.0001

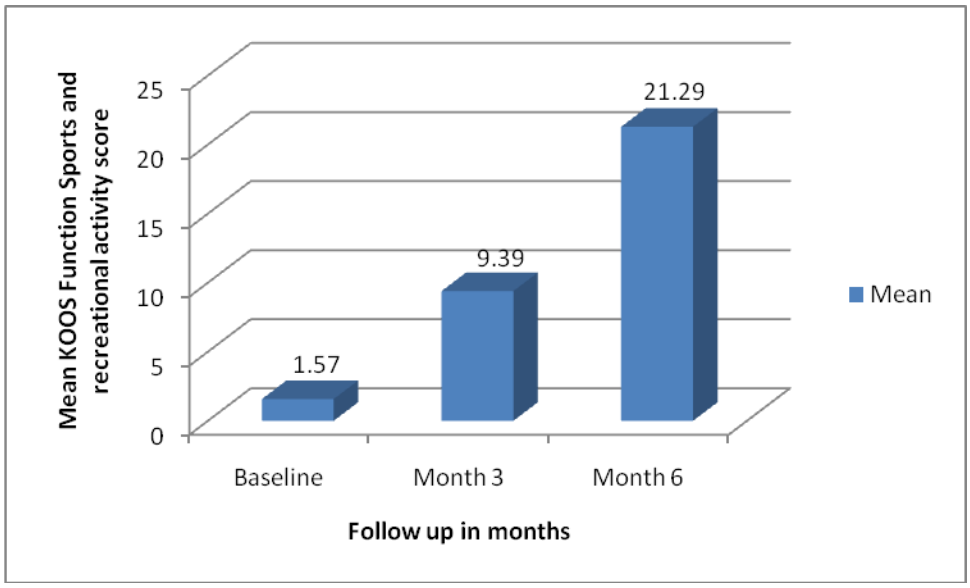
KOOS Function Sports and recreational activity score was increased by 492% at 3 months and 1243% at 6 months from baseline.

Table 16 : Percentage Improvement in KOOS Function Sports and recreational activity Scores by Visit
(Efficacy Population)

	Mean (SD)	**Percentage (%)**
Baseline	1.57 (5.11)	-
Month 3	9.39 (12.79)	492
Month 6	21.29 (17.93)	1243

Graphical illustration of change in KOOS Function Sports and recreational activity score at 3 and 6 months from baseline is depicted in figure 7.

Figure 7: Change in mean KOOS Function Sports and recreational activity score at 3 and 6 months



Patient Mean KOOS Quality of life score was 12.86 ± 9.93 at baseline, which is increased to 29.73 ± 16.16 at 3 months with mean change of 16.86 ± 12.35. P-value ($p < 0.0001$) between mean score at baseline and 3 months by unpaired t-test indicated highly significant improvement in KOOS Quality of life score. Patient Mean KOOS Quality of life score was further increased to 47.78 ± 20.26 at 6 months with mean change of 34.68 ± 15.63 from baseline. P-value ($p < 0.0001$) between mean score at baseline and 6 months by unpaired t-test indicated persistence of highly significant improvement in KOOS Quality of life score.

Mean of KOOS Quality of life score at baseline, 3 months and 6 months change in score is presented in below table 12:

Table 17: Descriptive Statistics for KOOS Quality of life score by Visit (Efficacy Population)

Baseline	
n	35
Missing	0
Mean (S.D)	12.86 (9.93)
Month 3	
n	33
Missing	2
Mean (S.D)	29.73 (16.16)

Change from baseline	
n	33
Missing	2
Mean (S.D)	16.86 (12.35)
p-value	< 0.0001
Month 6	
n	31
Missing	4
Mean (S.D)	47.78 (20.26)
Change from baseline	
n	31
Missing	4
Mean (S.D)	34.68 (15.63)
p-value	< 0.0001

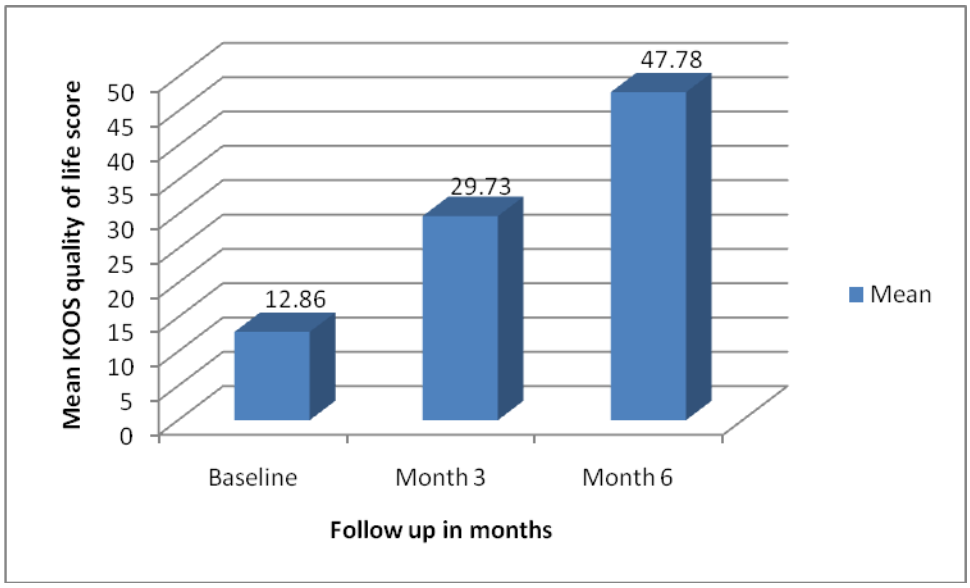
KOOS Quality of life score was increased by 131% at 3 months and 270% at 6 months from baseline.

Table 18 : Percentage Improvement in KOOS Quality of life Scores by Visit (Efficacy Population)

	Mean (SD)	**Percentage (%)**
Baseline	12.86 (9.93)	-
Month 3	29.73 (16.16)	131
Month 6	47.78 (20.26)	270

Graphical illustration of change in KOOS Quality of life score at 3 and 6 months from baseline is depicted in figure 8.

Figure 8: Change in mean KOOS Quality of life score at 3 and 6 months



11.3.2. Statistical/Analytical Issue

Not Applicable.

11.3.2.1. Adjustments for Covariates

Not Applicable.

11.3.2.2. Handling of Dropouts or Missing Data

2 patients data was missing at 3 month follow up and 4 patients data was missing at 6 month follow up in the evaluation.

11.3.2.3. Interim Analyses and Data Monitoring

Not applicable.

11.3.2.4. Multicentre Studies

Not applicable.

11.3.2.5. Multiple Comparison/Multiplicity

Not applicable.

11.3.2.6. Use of an "Efficacy Subset" of Subjects

Not applicable.

11.3.2.7. Active-Control Studies Intended to Show Equivalence

Not applicable.

11.3.2.8. Examination of Subgroups

Not applicable.

11.3.3. Device Dose, Device Concentration, and Relationships to Response

All the patients evaluable for efficacy received the same dose of Evaluation treatment.
So, Dose-concentration relationship is not applicable.

11.3.4. Interactions

Not Applicable

11.3.5. Efficacy Conclusions

In present evaluation, three injections of Biovisc Ortho Plus is found effective in treatment of Osteoarthritis Knee.

12. SAFETY EVALUATION

12.1. EXTENT OF EXPOSURE

34 patients received three injections of Evaluation treatment and 1 patient received one injection of evaluation treatment.

12.2. ADVERSE EVENTS (AEs)

No adverse event was reported during conduct of present Evaluation.

Table 19: Treatment Emergent AE

	Safety Population (N= 35)		
	n	**%**	**E**
Any event	0	0.0%	0

Table 20: Evaluation of Treatment Emergent Adverse Events (TEAE)

	Safety Population (N= 35)
Total no. of subjects who had Adverse event, n (%)*	
Yes	0(0.0%)
No	0(0.0%)
Total no .of Adverse reaction, n	0
Total no. of subjects having Serious Adverse event, n (%)*	0
Yes	0(0.0%)
No	0(0.0%)
Total no .of Serious Adverse event, n	0
Ongoing status of Adverse event, n (%)**	
Yes	0(0.0%)
No	0(0.0%)
Severity, n (%) **	
Mild	0(0.0%)
Moderate	0(0.0%)
Severe	0(0.0%)
Relationship with evaluation device, n (%) **	
Definite	0(0.0%)
Probable	0(0.0%)
Possible	0(0.0%)
Probably Not	0(0.0%)
Not Related	0(0.0%)
Action taken, n (%) **	
None	0(0.0%)
Concomitant Medication	0(0.0%)
Non-Drug Treatment	0(0.0%)
Outcome, n (%) **	
Recovered/resolved without sequelae	0(0.0%)
Recovered/resolved with sequelae	0(0.0%)

	Safety Population (N= 35)
Worsened	0(0.0%)
Death	0(0.0%)
Unknown	0(0.0%)

12.3. DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

No death, other SAE or other significant AE were reported during the Evaluation

12.4. CLINICAL LABORATORY EVALUATION

Not performed in present Evaluation.

12.4.1. Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value

Not Applicable

12.4.2. Evaluation of Each Laboratory Parameter

Not Applicable

12.4.2.1. Laboratory Values over Time

Not Applicable.

12.4.2.2. Individual Subject Changes

Not Applicable

12.4.2.3. Individual Clinically Significant Abnormalities

Not Applicable

12.5. VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

Measurement of Vital signs (Blood pressure and pulse) and physical examination was performed for all patients at baseline.

No clinically significant abnormalities reported in baseline vitals and examination as per Investigator's discretion. Baseline clinical evaluation of all patients ensured that no patient with undiagnosed serious medical condition was enrolled in Evaluation.

12.6. SAFETY CONCLUSIONS

In present evaluation, Biovisc Ortho Plus is found safe and effective without any incidence of treatment emergent adverse events.

13. DISCUSSION AND OVERALL CONCLUSIONS

The present clinical evaluation was performed in Patients with Knee Osteoarthritis (OA) with objective to assess the safety and performance of the Intra-Articular Hyaluronic Acid (Biovisc Ortho Plus) at Goztepe Research and Training Hospital Istanbul, Turkey. Intra-articular HA injections have been demonstrated to be beneficial in the treatment of OA, improving joint lubrication and synovial fluid viscosity, normalizing hyaluronan synthesis, inhibiting proteoglycan degradation and exhibiting analgesic and anti-inflammatory effects [10]. The best therapeutic results of using low molecular weight HA were observed with a dose range between three to five weekly intra-articular injections, each with 2 to 2.5 ml of HA [11]. In present evaluation, three weekly intra-articular injections, each with 2 ml of HA were administered and KOOS score data were analyzed to assess effectiveness of Biovisc Ortho Plus formulation.

In other study 168 patients with knee osteoarthritis, who were followed for 24 weeks, were randomized to receive HyalOne® which was provided in prefilled syringes each containing 60mg/4ml of hyaluronic acid sodium salt for intra-articular injection. Patients received the injection at baseline (T0) and were followed-up at 4 (T1), 12 (T2), and 24 (T3) weeks after the first injection. Before treatment patient mean KOOS pain score was 23.6 (SD 11.66), mean KOOS function daily living score was 26.8 (SD 8.06) and KOOS sports/recreational mean score was 19.0 (SD 9.40). Whereas in the present study, patient mean KOOS pain score, mean KOOS function daily living score and KOOS function sports/recreational activity score was 35.24 (SD 15.81), 43.52 (SD 16.65) and 1.57 (SD 5.11), respectively. Mean baseline values of all KOOS subscales progressively increased at each study time point to reach the highest value at T3. The analysis of variance for repeated measures conducted on each KOOS subscale showed a significant improvement against baseline in all scales at T1, T2 and T3 ($p<0.001$). While in the present study, Biovisc Ortho Plus treatment all KOOS subscales progressively increased after 3 and 6 months from baseline ($p< 0.0001$). [12. Vetro A et al., *pain relief and functional recovery over a six-month period after intra-articular injection with sodium hyaluronate (MW 1500-2000KDA) in osteoarthritis of the knee*, European journal of musculoskeletal diseases, 2014. **3**(1): p. 25-33.]

As there is no treatment emergent adverse event reported while treatment and follow-up till 6 months, Biovisc Ortho plus is found safe and effective. Results of present evaluation demonstrated significant improvement in KOOS score as well as pain, stiffness, function daily living, function sports and recreational activity and quality of life score at 3 and 6 months follow-up. An efficacy evaluation result of Biovisc Ortho plus makes it suitable for use in patients with OA.

14. REFERENCES

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11. Bellamy, N., et al., *Viscosupplementation for the treatment of osteoarthritis of the knee.* Cochrane Database Syst Rev, 2006(2): p. CD005321.

15 APPENDICES

15.1 EVALUATION INFORMATION

15.1.1 Protocol and protocol amendments
15.1.2 Sample case report form
15.1.3 IEC Approval letter and sample ICFs (Not Applicable)
15.1.4 CV of Principal Investigator and other important participants in the Evaluation.
15.1.5 Signature of principal investigator(s)
15.1.6 Listing of patients receiving test device(s)/investigational product(s) from specific batches, where more than one batch was used
15.1.7 Randomization scheme and codes (subject identification and treatment assigned)(Not Applicable)
15.1.8 Audit certificate (Not Applicable)
15.1.9 Documentation of statistical methods
15.1.10 Documentation of inter-laboratory standardization methods and quality assurance procedures if used (Not Applicable)
15.1.11 Publications based on the Evaluation. (Not Applicable)
15.1.12 Important publications referenced in the report

15.2 PATIENT DATA LISTINGS

15.2.1 Discontinued patients
15.2.2 Protocol deviations
15.2.3 Subjects excluded from the efficacy analysis
15.2.4 Demographic data
15.2.5 Compliance and/or device concentration data (Not Applicable)
15.2.6 Individual efficacy response data
15.2.7 Adverse event listings (each subject)
15.2.8 Listing of individual laboratory measurements by subject, when required by regulatory Authorities

15.3 CASE REPORT FORMS

15.3.1 CRFs for deaths, other serious adverse events and withdrawals for AE
15.3.2 Other CRFs submitted

15.4 INDIVIDUAL SUBJECT DATA LISTING