1 TITLE

Randomized, double blind, parallel group, placebo controlled study to evaluate the safety and efficacy of Arthronat in subjects with painful Osteoarthritis of hips, knees, shoulders, neck or wrists.

Name of the Investigational Medicinal Product	Arthronat
Indication Studied	Osteoarthritis
Sponsor Name	Rowtasha
Clinical Study Code	MA-CT-10-002
Development Phase of Study	Phase II
First Patient Enrolled	14 Jul, 2010
Last Patient Completed	02 Nov, 2010
Study Report Version & Date	Version 1.0, 15 Feb 2011

This study was conducted in accordance with the Good Clinical Practice guidelines as issued by the International Conference on Harmonization (ICH/135/95, Jul, 2002), Schedule Y, ICMR guidelines and the Declaration of Helsinki (current amendment).

SIGNATURE PAGE

I have prepared this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Author:

Signature — Date: 17/02/2011

Dr. Jyoti Rao Hegde
Senior Medical Monitor and Writer
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I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Biostatistician:

Signature — Date: 17/02/2011

Hemalatha S
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Sponsor's Representative:

Signature — Date: 17/02/2011.

Mr. Neville Wittenbaker
Clinical Study Manager
Sponsor's Representative

2 SYNOPSIS

Name of Sponsor/Company: Rowtasha, Bayswater, Western Australia **Name of Finished Product:** Arthronat **Name of Active Ingredient:** Otoliths	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*

TITLE OF STUDY:

Randomized, double blind, parallel group, placebo controlled study to evaluate the safety and efficacy of Arthronat in subjects with painful Osteoarthritis of hips, knees, shoulders, neck or wrists.

INVESTIGATORS AND STUDY CENTER(S):

Ethics committee approval was obtained for 1 study site (in 1 city of India).

SL NO.	PRINCIPAL INVESTIGATORS	STUDY CENTERS
1	Dr. N Prakash	N R N Orthopaedic Clinic, 2422, Kumarakrupa RPC Layout, 1st Main, Vijayanagar, Bangalore-560040. Karnataka, India.

PUBLICATION (REFERENCE):

Not Applicable

STUDY PERIOD:

DATE OF FIRST ENROLMENT	DATE OF LAST PATIENT COMPLETED
14 Jul, 2010	02 Nov, 2010

PHASE OF DEVELOPMENT:

Phase II

Name of Sponsor/Company: Rowtasha, Bayswater, Western Australia	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product: Arthronat		
Name of Active Ingredient: Otoliths		

OBJECTIVES:

Primary Objective:

- To evaluate the efficacy of Arthronat for the reduction in pain and improvement of mobility in subjects with painful osteoarthritis of the hip, knee, shoulders, neck .

Secondary Objective:

- To evaluate the efficacy of Arthronat for the relief of pain in treatment naive subjects as compared to subjects with history of NSAID usage for osteoarthritis of the hip, knee, shoulders, neck or wrists.

- To evaluate the safety of Arthronat in treatment of painful osteoarthritis of the hip, knee, shoulders, neck or wrists.

METHODOLOGY:

This was a 4 week prospective, randomized, double blind, parallel group, placebo controlled study. Subjects aged ≥ 18 yrs of age with painful osteoarthritis of hip, knee, shoulders, neck or wrists were randomized to treatment either with Arthronat or a matching placebo. The duration of the study treatment was of 4 weeks which was preceded by a screening period (with one week of single blind placebo run-in phase) not exceeding 14 days. Subject visits were scheduled at Screening (Visit 1), baseline/Day 0 (Visit 2), at Week 1 (Visit 3), Week 2 (Visit 4), Week 3 (Visit 5) and Week 4 (Visit 6 – End of the study visit).

DOSING SCHEDULE:

TREATMENT ARM	STRENGTH	ROUTE	DOSING SCHEDULE	TOTAL DAILY DOSE	DURATION
PLACEBO RUN IN PHASE					
Placebo	NA	Oral	3 capsules BID	6 capsules	1 week
ACTIVE TREATMENT PHASE					
Arthronat	500 mg	Oral	3 capsules BID	3000 mg	4 weeks
Placebo	NA	Oral	3 capsules BID	6 capsules	4 weeks

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NUMBER OF PATIENTS:

As planned, 80 subjects were enrolled from single center and all the 80 subjects completed the study.

	NO. OF PATIENTS
Screened	82
Enrolled	80
Completed	80
Included in MITT population	80
Included in PP population	80
Included in the safety population	80

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

The study population consisted of male or non-pregnant female patients aged ≥ 18 years of age with a previously diagnosed (at least 3 months prior to the screening visit) case of osteoarthritis of hip, knees based on the ACR (American College of Rheumatology) Clinical Classification criteria for osteoarthritis or a previously diagnosed (at least 3 months prior to screening visit) subjects on shoulders, neck and wrists based on the clinical and radiographic findings. Subjects should have been experiencing significant arthritic pain confirmed by screening WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index Scale) score between 10 - 40 (only for osteoarthritis of hip and knee) and a baseline VAS (Visual Analogue Scale) score of ≥ 4.

Criteria for exclusion from the study included pregnant or lactating females, any joint diseases, any history or trauma to the index joint, any obvious bony deformity or enlargement, any signs of acute inflammation or any serious and/or uncontrolled medical conditions interfering with the study or placing the patient at unacceptable risk. Only patients who fulfilled all of the inclusion criteria and did not meet any of the exclusion criteria were enrolled into the study.

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TEST AND REFERENCE PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

PRODUCT	TEST	COMPARATOR
Active Ingredient	Otoliths	Matching placebo
Brand name	Arthronat	Inactive substance
Dosage Form	Capsule	Capsule
Route	Oral	Oral
Strength	500 mg	NA
Dosing Regimen	3 capsules BID	3 capsules BID
Treatment duration	4 weeks	4 weeks
Manufacturer	Twilight Litaka Pharma Limited Pune	Twilight Litaka Pharma Limited Pune
Batch/Lot No.	452960	452960
Treatment ID	Product A	Product B
Manufacture Date	June 2010	June 2010
Expiration Date	Feb 2012	Feb 2012

DURATION OF TREATMENT:

The total duration of the active treatment was for 4 weeks which was preceded by 01 week of placebo run-in between screening and baseline visit.

CRITERIA FOR EVALUATION:

Efficacy Evaluation:

The primary efficacy endpoint:

- Change in the pain scores as evaluated by Visual Analogue Scale (VAS) at end of 1 week as compared to baseline (Day 0 / Visit 2)
- Improvement (change) in mobility at the end of Week 1 as compared to baseline (day 0 / Visit 2) evaluated by change in the WOMAC sub-scales of Stiffness and Physical function.

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Name of Active Ingredient: Otoliths		

The secondary efficacy endpoints:

- Change in the pain scores as evaluated by VAS at end of 2, 3 and 4 weeks as compared to baseline (Day 0 / Visit 2).
- Percentage of responders (defined as at least 70 % pain relief as compared to baseline) evaluated at the end of Week 1, 2, 3 and 4 using the VAS.
- Assessment of percentage responders at Week 1 stratified by prior history of Non Steroidal Anti – Inflammatory Drug (NSAID) use.
- Assessment of percentage responders at Week 2 stratified by prior history of NSAID use.
- Improvement (change) in mobility at the end of Week 2, 3 and 4 as compared to baseline (day 0 / Visit 2) evaluated by change in the WOMAC sub-scales of Stiffness and Physical function.
- Change from baseline to Week 1, 2, 3 and 4 in total WOMAC Index scale for hip and knee osteoarthritis.
- Change from baseline to Week 1, 2, 3 and 4 in SF-36 quality of life questionnaire.
- Change from baseline to Week 1, 2, 3 and 4 in Subject Global assessment of.
- OMERACT-OARSI responder index at Week 1, 2, 3 and 4.

  Number of subjects who use rescue medication in the treatment arm as compared to the placebo arm at end of week 1, 2 , 3 and 4 as compared to baseline.
- Number of days of use of rescue medication in the treatment arm as compared to the placebo arm.
- Amount (in mg) of first line rescue medication (Paracetamol) used in the treatment arm as compared to the placebo arm.
- Amount (in mg) of second line rescue medication (Ibuprofen) used in the treatment arm as compared to the placebo arm.

Safety Evaluation:

Safety evaluation included assessment of the following parameters:

- The type of AE(s), number of AE(s), frequency of AE(s) and proportion of patients with AE(s).
- Physical examination
- Assessment of vital signs
- Safety laboratory tests (Complete blood count, Liver function tests, urea, creatinine electrolytes and urine analysis)

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STATISTICAL METHODS

The SAS® package (SAS® Institute Inc., USA, and Version 9.2.) was used for statistical evaluation. All subjects in the study with relevant safety and efficacy data were considered for the analysis. Three populations were considered for the analyses: the modified intention-to-treat (MITT), the per-protocol (PP) population and safety population. All efficacy endpoints were analyzed for the MITT and PP population of which the MITT population analysis was the primary and PP was the secondary analyses sets and all safety endpoints were analyzed for the safety population.

For the primary efficacy endpoints, change in the pain scores as evaluated by Visual Analogue Scale (VAS) and improvement in mobility as evaluated by WOMAC sub-scales of Stiffness and Physical function at end of 1 week as compared to baseline (Day 0 / Visit 2) was calculated. For these efficacy endpoints, treatment effect was evaluated using an analysis of variance (ANOVA) model with factors for baseline and treatment. Treatment effects will be estimated using the least-square means and 95% CIs from the ANOVA model. The assumption of normality and homogeneity of variances was tested using the Shapiro-Wilks test and the Levenes test, respectively. If the assumptions are violated, Kruskal-Wallis test (non-parametric) was to be used to corroborate the results of the parametric analyses. If the two sided p-value of all primary efficacy endpoints (VAS scale and WOMAC subscale at the end of week 1 as compared to baseline) are less than 5%, then the hypothesis of superiority over placebo will be demonstrated. Since there were only two treatment arms in the study, and also for the non-parametric tests the factors don't consider, hence Wilcoxon rank sum test have been used instead of Kruskal Wallis test. The 95% CI have been reported for the LS Mean of the change from the baseline. Also the p value is presented from both ANOVA model and Wilcoxon rank sum test in tables. All other secondary efficacy endpoints were appropriately compared and summarized.

Adverse events that occurred subsequent to the first dose of study drug were summarized. The number and the proportion of subjects who experienced AEs were computed by treatment group, classified by MedDRA Primary System Organ Class and Preferred Terms. AEs were also summarized by each severity grade (mild, moderate, severe) and by each relationship grade (unrelated, unlikely, possibly, probably, definite) in a similar way. Vitals signs, physical examination, were summarized descriptively by treatment.

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SUMMARY – CONCLUSIONS

As planned, 80 patients enrolled from single center completed the clinical study. Forty subjects each were randomized into the two arms [Treatment A (Arthronat) and Treatment B (Placebo)] of the study. All the 80 randomized subjects were included for MITT, PP and safety analysis. The two treatment groups were comparable with respect to the demographic characteristics measured at baseline. The mean age of the subjects ranged from 27.3 to 69.4 years, with a mean of 53.0 years. 47 (58.75 %) of the subjects were females and 33 (41.25 %) of the subjects were males. And 8(10%) of the female subjects had child bearing potential. All subjects in the study were of Indian origin.

Efficacy Results:

The primary efficacy endpoints were the change in the pain scores as evaluated by Visual Analogue Scale (VAS) at end of Week 1 as compared to baseline (Day 0 / Visit 2) and Improvement (change) in mobility at the end of Week 1 as compared to baseline (day 0 / Visit 2) evaluated by change in the WOMAC sub-scales of Stiffness and Physical function.

There was a statistically significant reduction in pain in the subjects receiving Arthronat as compared to placebo at the end of week 1 as evaluated by VAS(p-value = 0.0013).

The mean value of WOMAC subscales of physical function for Arthonat treatment group at baseline was 26.8 and 27.0 at week 1 whereas the mean value for placebo group at baseline was 26.7 which increased to 29.0 at week 1. The LS mean difference observed between Arthronat and placebo groups was -2.050 (p=0.0090), which indicates that there was a statistically significant difference in physical function in the Arthronat treatment arm as compared to the placebo. The analysis of results at week 1 showed that the WOMAC subscales of physical function in Arthronat arm were better than placebo arm.There was no change seen in the mean value of WOMAC subscales of stiffness for Arthronat at baseline and week 1 (score = 3.1) however in the placebo arm the mean value increased from 3.2 at baseline to 3.4 at week 1. There was no statistically significant difference seen in the two treatment arms at week 1 (p= 0.3154).

There was no significant difference observed in absolute change from baseline to the end of week 1,2,3 and 4 in SF – 36 score between the two treatments. There was no significant difference observed in absolute change from baseline to the end of week 1, 2, 3 and 4 in Subject Global Assessment of Osteoarthritis between the two treatments.

At week 1, there were 39 (97.5%) responders in Arthronat group as compared to 27 (67.5%) responders in placebo group. At week 2, there were 40 (100.0%) responders in Arthronat group as compared to 26 (65.0%) responders in placebo group. At week 3, there were 39 (97.5%) responders in Arthronat group as compared to 28 (70.0%) responders in placebo group. At week

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4, there were 39 (97.5%) responders in Arthronat group as compared to 30 (75.0%) responders in placebo group.

Total number of tablets of rescue medication (paracetamol) consumed at each visit was lesser in Arthronat group (273) compared to Placebo (407) and reduced consistently from baseline to Week 4.This difference was statistically significant at all the visits .

Safety Results:

Safety data was presented for the safety population, which included all patients who had been randomized to receive the study medications.

Arthronat was well tolerated and was comparable with Placebo which was confirmed by the fewer incidences of adverse events and good compliance.

The number of adverse events and the number of patients reporting the adverse events were comparable between the treatment groups. Overall 2(2.5%) subjects experienced AEs related to system organ class - gastrointestinal disorders. Both the events were diarrhoea. One (2.5%) subject each in the Treatment A and Treatment B reported atleast one AE, which were moderate in nature and possibly related to the treatment. One subject each used concomitant medication Lactobacillus Sporogenes during Treatment A and Treatment B respectively.

No deaths, other SAEs and other significant AE(s) were reported in this study.

Vital signs were found to be within the normal range during the course of the study. There were no clinically significant abnormal findings at any of the visits in both the treatment groups. Physical examination was found to be normal during the course of the study for all the subjects. There were no clinically significant abnormal findings at any of the visits.

Conclusion:

The results of this study demonstrate that the Arthronat had a better efficacy profile compared to placebo, for the reduction in pain scores as evaluated by Visual Analogue Scale (VAS) at end of Week 1 in subjects with painful osteoarthritis of the hip, knee, shoulders, neck or the wrists and is safe and well tolerated.

DATE OF REPORT

15 Feb 2011

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4 LIST OF ABBREVIATIONS

LIST OF ABBREVIATIONS	
Abbreviation	**Description**
%	Percentage
°C	°Centigrade
°F	°Fahrenheit
ACR criteria	American College of Rheumatology criteria
AE	Adverse Event
ANOVA	Analysis of Variance
BP	Blood Pressure
CI	Confidence Interval
CM	Concomitant Medication
CRA	Clinical Research Associate
CRF	Case Record Form
CRO	Contract Research Organization
CVs	curriculum vitae
DCGI	Drugs Controller General of India
e.g.	for example
EC	Ethics Committees
ENT	Ear, Nose and Throat
EOS	End of Study
GCP	Good Clinical Practice
hCG	Human Chorionic Gonadotrophin
i.e.	that is
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMR	Indian Council of Medical Research
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board

ITT	Intention-to-Treat
IUD	Intra-uterine device
LS	Least square
MAL	Manipal AcuNova Ltd.
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intention-to-Treat
mIU/ml	Milli international units/milli litre
NA	Not Available
NSAID	Non Steroidal Anti – Inflammatory Drug
OA	Osteoarthritis
OMERACT – OARSI	Outcome Measures in Rheumatoid Arthritis Clinical Trials – Osteoarthritis Research Society International
OTC	Over the Counter
PIC	Patient Identity Code
PO	Per Oral
PP	Per-Protocol
PT	Preferred Term
QA	Quality Assurance
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SF – 36 QOL	Short Form – 36 Quality of Life questionnaire
SIC	Subject Identity Code
SOC	System Organ Class
SOP	Standard Operating Procedure
UPT	Urine Pregnancy Test
US FDA	United States Food and Drug Administration
V	Visit
WHO - DDE	World Health Organization Drug Dictionary Enhanced
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index Scale

5 ETHICS

5.1 INDEPENDENT ETHICS COMMITTEE (IEC) OR INSTITUTIONAL REVIEW BOARD

The version 1.0 of protocol of study code MA-CT-10-002 dated 10 May, 2010 and Informed Consent Form (ICF) dated 17 May, 2010 along with protocol amendment dated 18 May, 2010 were reviewed and approved by all the appropriate Ethics Committees (EC) prior to enrollment of the patients into the study. The names and addresses of all the three study sites along with EC approval letter and EC member details for each study site are provided Appendix 16.1.3.

5.2 ETHICAL CONDUCT OF THE STUDY

This study was carried out in accordance with the principles of Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, revised by the WMA General Assembly, Tokyo 2004 and Seoul 2008), International Conference on Harmonization (ICH) recommendation on Good Clinical Practice (GCP) (ICH/135/95, July 2002), 'Indian GCP', 'Schedule Y' of Indian Drugs and Cosmetics Rules 1945, and Ethical guidelines for biomedical research on human participants 2006, issued by ICMR.

5.3 PATIENT INFORMATION AND CONSENT

The investigator was responsible for obtaining signed and dated ICFs from the patients before any study specific procedures were performed within 14 days prior to study start. The patients were given adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Patients were given an opportunity to ask any questions and all the queries were clarified by the Principal Investigator / Co-investigator before decision making. The ICF described the study procedures and the possible potential hazards in non technical terms in conformity with regulatory requirements.

The ICFs were available in English and other required 3 native languages (i.e. Hindi, Kannada and Tamil). The ICF was translated in 3 languages from English and back translated to English by a certified translator. The patients were required to read and sign a consent form summarizing the discussion. The original copies of the signed and dated ICFs were retained in the institution's records, and were available for inspection by representatives of the sponsor, or representatives from competent authorities. Patients were given a copy of their written, signed and dated ICFs.

Copies of the ICF in English and other 3 native languages (i.e. Hindi, Kannada and Tamil) with translation and back translation certificates are provided in Appendix 16.1.3.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This clinical study was sponsored by Rowtasha. A single center participated in the clinical study. At the center, the principal investigator had the overall responsibility for the safety of patients in the study. The participating investigator and the study site details are provided in **Table 1.**

Table 1: Investigator and Study Centers

SERIAL NO.	PRINCIPAL INVESTIGATORS	STUDY CENTRES
1	Dr. N Prakash	N R N Orthopaedic Clinic, 2422, Kumarakrupa RPC Layout, 1st Main, Vijayanagar, Bangalore-560040. Karnataka, India.

Other Study Team & Study Facility Details

The Contract Research Organization, Manipal AcuNova Limited (MAL) was responsible for project management, clinical and medical monitoring, clinical data management, statistical analyses and preparation of the clinical study report. The clinical trial supplies along with the investigational products (IP) were provided by MAL. MAL distributed the IP to the study center, and the management of IP at study center was performed by the study site unblinded pharmacist. Details of the study team and study facility are provided in **Table 2 :**

Table 2 : Study Team and Facilities

Sponsor	Rowtasha 35/104, King William Street Bayswater – 6053 Western Australia
Sponsor's Authorized Representative	Mr. Neville Wittenbaker 35/104, King William Street Bayswater – 6053 Western Australia Tel: + 618 – 93710091 neville_trevor@bigpond.com
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The details of the study personnel were documented in the raw data sheets as log of staff at the trial sites. The curriculum vitae (CVs) of the principal investigators are provided in Appendix 16.1.4, and the folio of signatures is provided in Appendix 16.1.5.

7 INTRODUCTION

Osteoarthritis (also known as degenerative arthritis or degenerative joint disease) is a group of diseases and mechanical abnormalities involving the degradation of joints. It is a progressive disease resulting from stresses (normal joint + abnormal stresses or abnormal joint + normal stresses) that may be initiated from abnormality in any of the joint tissues (articular cartilage, subchondral bone, ligaments, menisci, periarticular muscles and peripheral bones and synovium) which results in breakdown of cartilage and bone.

Osteoarthritis (OA) can be classified into Primary / Idiopathic (where the underlying cause is not known) and Secondary (where the underlying cause is identifiable). OA commonly affects the hands, wrists, feet, spine, neck and the large weight bearing joints, such as the hips and knees, although in theory, any joint in the body can be affected. The commonest signs and symptoms of OA are joint pain, joint stiffness, joint tenderness, joint swelling / effusion, crepitus on movement of the joint, decreased range of movements, morning stiffness (< 30 minutes), joint deformity, joint instability, Heberden's nodes and Bouchard's nodes (in case of osteoarthritis of the hands). The risk factors of osteoarthritis are age (> 50 yrs of age), sex (females are more at risk for OA than men), obesity, previous joint injury, joint deformities, physical inactivity and family history of OA

Treatment of OA is usually a combination of therapies. The different therapies available are exercise (helps in maintaining the weight, increases the flexibility of joints and thereby reduces pain), weight reduction / control (helps by reducing the stress on the weight bearing joints which limits further injury and increase mobility), non drug pain therapy [can be achieved by application of heat or cold to the affected joint, massaging the affected area, transcutaneous electric nerve stimulation (acts by modifying pain perception), use of assistive devices – canes, braces, splints etc (acts by decreasing the pressure on the affected joints)], drugs (Paracetamol, NSAIDS – Diclofenac, ketorolac, ibuprofen, opioids analgesics, corticosteroids, hyaluronic acid - aim mainly at pain relief and reducing the inflammation) and surgery (removal of loose parts of the bone, bone fusion ,joint replacement). Alternate treatments also play a very important role in treatment of osteoarthritis. This includes nutritional supplementation chondroitin sulphate, antioxidants, vitamins B9/B12/D, acupuncture, etc. These therapies aim reducing the inflammation, pain relief and delay the progression of the disease. Extensive research is being performed to improvise the alternate treatments for OA.

One of the researched alternate treatments for OA is Arthronat. Arthronat is nutritional supplement which has shown promising effects in the treatment of osteoarthritis. It is even being used for the treatment of kidney stones, gout etc. The active component is derived from 'Otoliths' of salt water fishes. Otolith is a structure found in the saccule and the utricle of the inner ear. It is composed of layers of calcium carbonate (85-90 %) and gelatinous matrix (10-15 %). The exact mechanism of action of the drug is not known. However Arthronat has been found to reduce the pain and inflammation in the serous membranes of joints and damaged periosteum, relax periarticular ligaments, resolve

cartilage calcium build-ups, promote greater bone density, stimulates muscle tissue development and enhances muscle tone. The most common adverse effect reported is diarrhea (within the first 24 hours of the first dose) which is self resolving condition. The drug is indicated in Osteoarthritis, gout and kidney stones. Dosage for treatment of osteoarthritis is 3000 mg/ day in 2 equal divided doses. The medication is contraindicated in subjects who have a previous history of allergy to fish or fish products. Arthronat has shown very promising effects in the treatment of osteoarthritis without any major side effects. The medication is in use since from 10 years and has proved to be very effective in reduction in pain and improvement of joint mobility.

Our primary aim in conducting the study is to observe the potential benefits of the medication in a randomized, placebo controlled blinded study design, in accordance with recommended guidance by US FDA.

8 STUDY OBJECTIVES

Primary Objective of the study:

- To evaluate the efficacy of Arthronat for the reduction in pain and improvement of mobility in subjects with painful osteoarthritis of the hip, knee, shoulders, neck or the wrists.

Secondary Objective of the study:

- To evaluate the efficacy of Arthronat for the relief of pain in treatment naive subjects as compared to subjects with history of NSAID usage for osteoarthritis of the hip, knee, shoulders, neck or wrists.
- To evaluate the safety of Arthronat in treatment of painful osteoarthritis of the hip, knee, shoulders, neck or wrists.

9 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN DESCRIPTION

This was a randomized, double blind, parallel group, placebo controlled study to evaluate the efficacy and safety of Arthronat in subjects with painful osteoarthritis of hip, knee, shoulders, neck or wrists The duration of the study treatment was of 4 weeks which was preceded by a screening period (with one week of single blind placebo run-in phase) not exceeding 14 days.

The study population was planned to consist of subjects of either sex, aged ≥ 18 years who were previously diagnosed (at least for 3 months prior to screening) with osteoarthritis of hip (as per the ACR criteria for osteoarthritis of hip), knee (as per ACR

criteria for osteoarthritis of knee), shoulders, neck or the wrists (as per the clinical and radiographic findings of OA of shoulders, neck and wrists). A total of 80 subjects from a single centre were randomized into two groups in a 1:1 ratio. There were a total of 2 treatment arms in the study, details of which are presented in **Table 3**.

Table 3: Treatment Assignment

TREATMENT ARM	STRENGTH	ROUTE	DOSING SCHEDULE	TOTAL DAILY DOSE	DURATION
PLACEBO RUN IN PHASE					
Placebo	NA	Oral	3 capsules BID	6 capsules	1 week
ACTIVE TREATMENT PHASE					
Arthronat	500 mg	Oral	3 capsules BID	3000 mg	4 weeks
Placebo	NA	Oral	3 capsules BID	6 capsules	4 weeks

A subject was considered enrolled in the study after he/she signed the informed consent. The enrolled subject was considered randomized if he/she received the randomized treatment assignment number. A randomized subject was considered to have received treatment only after he/she receive at least one dose of the study medication. The duration of the treatment period for each subject was 4 weeks. A urine pregnancy test (UPT) was performed for all females of childbearing potential. Subjects receiving prior NSAID therapy were given appropriate wash –out as per protocol. Subjects had to complete a 1 week placebo run-in period where the compliance of the subjects was evaluated. Only subjects with 80% compliance during the run-in period were eligible to participate further in the study.

After establishing the eligibility of the subject, the subject was called for the Baseline visit (Randomization/Day 0) within 14 days after screening. The day of start of IP was considered as Day 0 and was recorded in the CRF. The first dose of the study medication was administered to the subject under supervision of the investigator or the investigator designated study personnel in the site after the completion of the randomization process. Study medication was dispensed to the subjects for the next 1 week. The rescue medications (first line – 15 tablets of Paracetamol 500 mg strength)) and subject diary was dispensed. Instructions regarding the regular intake of study medications were given. The subject was instructed to bring the used and unused medications and the completed subject diary in the next visit. The next visit of the subject was scheduled 1 week after the start of the treatment (with a window period of ± 1 day).

All adverse events occurring after the subject signs the Informed Consent Form (ICF) were captured in the adverse event module of the CRF. Any SAE occurring within 14 days of last dose of study treatment (Visit 6) was reported by the investigator.

Subject visits were scheduled at Screening (Visit 1), Baseline/Day 0 (Visit 2), at Week 1 (Visit 3), Week 2 (Visit 4), Week 3 (Visit 5) and Week 4 (Visit 6 – End of the study visit).

The protocol used in the study is provided in Appendix 16.1.1 and a sample case report form (CRF) in Appendix 16.1.2.

The study procedures /assessments performed at different visits have been mentioned below in **Table 4**.

Table 4: Study Visit Plan

S. No	Activities	Screening (V1 / -14 to -1 days)	Baseline (V2: Day 0)	Week 1 (V3)	Week 2 (V4)	Week 3 (V5)	Week 4 (V6)
1	Informed Consent Procedure	X					
2	Prior medical and surgical history	X					
3	Prior concomitant medications	X					
4	Demographic data (including height, weight and BMI)	X					X*
5	Vital Signs **	X	X	X	X	X	X
6	General physical examination (including complete systemic examination)	X					X
7	Orthopaedic examination of the index joint	X	X	X	X	X	X
8	Review of ACR criteria for OA of hip and knee	X	X				
9	Inclusion exclusion criteria	X	X				
10	Blood and urine samples collection ***	X					X
11	Urine pregnancy test for females of child bearing potential	X					
12	X- ray of the index joint	X					
13	Visual Analogue Scale for pain	X	X	X	X	X	X
14	SF – 36 Quality of Life questionnaire	X	X	X	X	X	X
15	WOMAC Index Questionnaire for subjects with hip and knee OA	X	X	X	X	X	X
16	Subject Global Assessment of OA	X	X	X	X	X	X
	Dispensing the run-in period medications	X					
17	Rescue medications dispensing****	X	X	X	X	X	
18	Dispensing of Subject diary	X	X	X	X	X	
19	Review and retrieval of Subject diary		X	X	X	X	X
20	Recording of AEs		X	X	X	X	X
21	Recording of Concomitant medications		X	X	X	X	X
22	Randomisation of subject and first dose administration		X				
23	Dispensing of study medications		X	X	X	X	
24	OMERACT – OARSI responder index			X	X	X	X
25	Review of Compliance		X$	X	X	X	X
26	Retrieval of unused medications		X$$	X	X	X	X

X = Activities applicable at the visit.
* - Only weight to be measured at Visit 6 (for calculation of BMI)
** - Vital signs includes – Sitting pulse rate and blood pressure, oral temperature and respiratory rate
*** - blood samples for complete blood count, liver function tests, urea, creatinine, electrolytes and urine samples for urine analysis (urine routine and microscopy)
**** - First line rescue medication – Paracetamol; second line rescue medication - Ibuprofen
$ - calculation of run-in period compliance $$ - retrieval of unused run-in period medications

9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

The randomized, double blind, parallel group, placebo controlled study design was chosen as an appropriate study design from a clinical methodology consideration. The efficacy of Arthronat in reduction in pain and improvement of mobility in painful osteoarthritis of hip, knee, shoulder, neck and wrists was compared to the effects of placebo. A double blind randomized, placebo controlled design was used to minimize any bias in the interpretation of the results of efficacy of the test products.

The placebo run-in period was included in the study to ensure the enrolment of potentially compliant subjects and to minimize withdrawals from the study due to non compliance to the study medications. The study was conducted as a clinical trial and with accordance to applicable regulatory requirements.

9.3 SELECTION OF STUDY POPULATION

Study population was drawn from outpatient hospital setting of the clinic. A total of 80 subjects with osteoarthritis of hip, knee, shoulders, neck or the wrists were recruited in this study based on inclusion/exclusion criteria.

9.3.1 Inclusion Criteria

Patients were eligible for enrolment in the study if they fulfilled the following criteria:

1. Male and female subjects ≥ 18 yrs of age in general good health
2. A previously diagnosed (atleast 3 months prior to the screening visit) case of osteoarthritis of hip, knees based on the ACR Clinical Classification criteria for osteoarthritis or a previously diagnosed (atleast 3 months prior to screening visit) case on shoulders, neck and wrists based on the clinical and radiographic findings.
3. Subjects who had been experiencing significant arthritic pain confirmed by:
    - Screening WOMAC score between 10 - 40 (only for osteoarthritis of hip and knee)
    - Baseline VAS score of ≥ 4
4. Subject who were willing to discontinue all the pain medications before starting the study drug except the rescue medications (Paracetamol or Ibuprofen) for the entire duration of the study.
5. Female subjects must have had fulfilled any one of the following criteria:
    - Considered to be of non-child bearing potential if she had undergone hysterectomy and/or bilateral Oopherectomy or if she had attained menopause (amenorrhea for the last consecutive 12 months).
    - If she was of child bearing potential – she must had not been pregnant (negative urine pregnancy test at screening) or lactating or planning to become pregnant during the study duration. She must have remained abstinent or used adequate contraception [oral contraceptives;

contraceptive patches/rings/implants/injected; Norplant®; Depo-Provera®; barrier methods (e.g., condom and spermicide); IUD]

6. All male subjects must have had agreed that they or their female spouses / partners would use adequate contraception or should remain sexually inactive throughout the study or their spouse / partner must have been of non – child bearing potential
7. Subjects must have demonstrated their willingness to participate in the study and comply with the study procedures and required visits.
8. Have had the ability to understand and sign a written informed consent form, which must be completed prior to study specific tasks being performed.
9. Must had been willing to authorize use and disclosure of protected health information collected for the study.

9.3.2 Exclusion Criteria

Patients were excluded from the study if they fulfilled any of the following:

1. Subject with history of disease which may have had involved the index joint including but not limited to rheumatoid arthritis, any inflammatory joint disease, metabolic bone disease (gout, pseudo gout etc), bone tumours, joint infections (reactive arthritis, septic arthritis), avascular necrosis (especially of neck of femur), neuropathic disorders etc.
2. Any history of trauma or surgery to the index joint (joint under the study) or any planned surgery (diagnostic or therapeutic intervention) to the index joint during the participation in the study.
3. Subjects belonging to Functional class IV as per the ACR criteria for functional status (Appendix XI of protocol).
4. Radiographic evidence of grade 4 osteoarthritis based on the Kellgren and Lawrence radiographic criteria for osteoarthritis (Appendix X of protocol).
5. Any obvious bony deformity or enlargement (including bony enlargement as per radiography, joint effusion etc) or any signs of acute inflammation of the joint due to arthritis.
6. Subject with history of any severe painful condition which requires the use of regular analgesia and confound the self assessments of pain caused by osteoarthritis.
7. Had any previous use of corticosteroids (oral or parentral), hyaluronic acid (intraarticular) for the treatment of osteoarthritis or any other medical condition.
8. Had used of prohibited medications for duration as specified in the protocol prior to baseline.
9. Subjects who had been consuming > 150mg/day of aspirin at screening. Subjects who had consumed ≤ 150 mg / day aspirin (for non-analgesic indications) should have had been on a stable dose for atleast 30 days prior to screening.

10. Subjects who had significant medical conditions – chronic liver disease (AST / ALT ≥ 3xUNL or total bilirubin ≥ 2xUNL), renal disease (creatinine ≥ 1.5xUNL), significant cardiovascular or pulmonary disorder, severe hypertension (as per JNC VII classification – refer appendix XIII), HIV positive (by history), Hep B or Hep C positive (by history), any significant neurological and psychiatric disease (which may affect the participation and inference of endpoint of the study).
11. Subjects who had uncontrolled diabetes mellitus complicated with diabetic neuropathy, diabetics with prior history or concomitant usage of insulin.
12. Any previous history of alcohol abuse or any drug abuse.
13. Subjects who had any other disease or condition, or are using any medication, that in the judgment of the investigator would put the subject at unacceptable risk for participation in the study or may interfere with evaluations in the study or noncompliance with treatment or visits.
14. Subjects who have had participated in a study of an investigational drug 30 days prior to the baseline.
15. Any history or evidence of allergy to fish or any fish products in the past.
16. Subjects who were unable to comply with study requirements.

9.3.3 Removal of patients from therapy or Assessment

Criteria for discontinuation:

A. Subjects were free to drop out from the study at any time without stating any reason and they could choose not to receive the drug or equivalent after signing the consent. If the subject chooses not to receive the study drug after signing the consent, the subject must have had to notify the Investigator before dispensing of the study drug. However the subjects would continue to receive all the standard medical care, to which they are were entitled.

B. Investigator also, at their discretion, could withdraw the subject from participating in the study at any time. The subjects were withdrawn from therapy, if any of the following events occurred after giving the consent:

   a. Withdrawal of subjects due to lack of efficacy of the study medication where withdrawal was considered in the best interest of the subject.
   b. Subject suffered from significant intercurrent illness or undergoes surgery during the course of the study where continued participation in the study presented a significant safety concern.
   c. Subject experienced adverse event or laboratory abnormality, when withdrawal would have been in the best interest of the subject, as assessed by the investigator.
   d. The subject failed to comply with the requirements of the protocol (e.g., visit window deviation) the subject may be withdrawn at the discretion of investigator after discussion with medical monitor.

e. It was necessary to further protect the health of the subject or the integrity of the study.
f. Intake of any prohibited medications.
g. Pregnancy.
h. Repeated and frequent non-adherence to prescribed dosing regimen as reported in subject diary and/or assessed by the investigator and/or monitor.
i. Institution of additional medical rescue therapy.

9.4 TREATMENTS

9.4.1 Treatments Administered

During the run-in period all the subjects were provided with placebo for a 1 week period. A total of 80 patients were randomized into two treatment arms in the study. The treatment was given as per the randomization schedule generated. The total duration of the treatment was for 4 weeks and the subjects took the allotted treatment twice in a day orally.

9.4.2 Identity of Investigational Product

Rowtasha supplied the investigational products (IPs) used in the study. The drugs were manufactured complying with all required regulations. Sufficient quantities of the drug were supplied to the clinical study facility by the sponsor. The product identifiers on the bottles were letter designated as Product A or B along with other label information. The details of the investigational products are provided in **Table 5**.

Table 5: Investigational Product Details

Product	Test	Comparator
Active Ingredient	Otoliths	Matching placebo
Brand name	Arthronat	Inactive substance
Dosage Form	Capsule	Capsule
Route	Oral	Oral
Strength	500 mg	NA
Dosing Regimen	3 capsules BID	3 capsules BID
Treatment duration	4 weeks	4 weeks
Manufacturer	Twilight Litaka Pharma Limited, Pune	Twilight Litaka Pharma Limited, Pune
Batch/Lot No.	452960	452960
Treatment ID	Product A	Product B
Manufacture Date	Jun 2010	Jun 2010
Expiration Date	Feb 2012	Feb 2012

9.4.3 Method of assigning patients to treatment group

The randomization schedule was generated by MAL statistical team, using PROC PLAN in SAS, version 9.2, according to MAL standard operating procedures (SOPs) listing Enrolment-Id and treatment. Sites dispensed study medication in sequential order, as the subjects qualified for participation in the study. The investigator involved in conducting the study and performing the evaluation was blinded to treatment codes until the database is locked. The drug dispensing was done by Investigator designated site personnel. It was the responsibility of the site designee to ensure appropriate dispensing of study treatments.

All subjects who signed an IEC approved informed consent form and authorization for the use and disclosure of protected health information were assigned a unique subject identity code (SIC) consisting of 3 digit centre code. The subject initials and the randomization code were captured separately as an additional identity.

Copy of randomization schedule is attached as Appendix 16.1.7. The list of patients fulfilling all the inclusion and exclusion criteria, and who have been randomized is provided in Appendix 16.2.

9.4.4 Selection of Doses in the Study

During the run-in period, all the subjects were provided with placebo and were instructed to consume 3 capsules twice daily for a 1 week period. During the active treatment period, the dosing as per the randomization schedule started with dispensing and administration of drug. The first dose was administered to the subject on Day 0 at the study site under the supervision of the Investigator or the investigator designated study personnel after the randomization process. The subject were instructed to consume 3 capsules twice daily (i.e., total of 6 capsules per day) starting from Day 0 till the end of 4 weeks.

9.4.5 Selection and timing of doses in the study

IP administration:
During the run-in period, and the active treatment period, the dosing was BID and was to be taken before or after the two principal meals of the day. The capsules were taken along with plenty of fluids. The capsules were swallowed whole and not crushed, chewed, broken into pieces, or taken apart prior to administration. The treatment was given as per the randomization schedule generated. The total duration of the treatment was for 4 weeks and the subjects took the allotted treatment twice in a day orally.

Missed Doses:
The subjects were instructed to consume a total of 6 capsules (Arthronat / placebo as per the randomization schedule) per day. If the subject missed one dose of the medication,

he/she was instructed to consume 6 capsules during the next dose. The subject was advised to consume a total of 42 capsules per week (6 capsules per day X 7 days).

9.4.6 Blinding

This was a double blind study. The study was conducted under double blind conditions. To ensure double blind conditions the study medications (Arthronat capsules and the matching placebo) were dispatched in identical bottles marked as product "A" and "B". The investigators and the monitors were not informed about the identity of the study medication and had no copy of the randomization code. The investigator was supplied with a sealed emergency envelope for each subject number containing the identity of treatment sequence for each subject. The sealed envelopes were checked by the monitor during the study and were collected back at the end of the study. In case of emergency or occurrence of SAE, which required breaking of randomization code, the unblinding procedure as per MAL SOP's was to be followed.

Any accidental unblinding was to be recorded as a protocol deviation and the subject could continue in the study. Any need to open the investigator blinding of trial medication for clinical management of subjects health during the trial would also not be regarded as a withdrawal criterion, unless withdrawal would be in the best interest of the subject or study, as assessed by the investigator.

9.4.7 Prior and Concomitant Therapy

Concomitant therapy (except the prohibited medications as listed below) was permitted at the discretion of the physician. Detailed history of concomitant medications at the baseline was recorded in the CRF. All concomitant therapy taken by the subject during the study period was recorded in the CRF in the concomitant medications section in detail.

Subjects were instructed to report to the investigator any medication used over the course of the study. At the discretion of the investigator, these subjects continued the study participation if the medication was not anticipated to alter study integrity and interfere with the evaluation.

Prohibited medications:

1. Any medications used for pain relief (including but not limited to NSAIDs, topical analgesics, opioids, oral or parental (or topical to the index joint) corticosteroids, hyaluronic acid,
2. Any ayurvedic, homeopathic or herbal preparations etc) other than the rescue medications were prohibited throughout the study.

These medications were stopped at least 48 hrs prior to the baseline visit (Visit 2) or during the time prior to baseline visit that is at least 5 times the half life of the particular analgesic whichever is greater. Subjects with the history of any previous use of corticosteroids (oral, intramuscular, intraarticular, intravenous etc), hyaluronic acid (intra – articular) for treatment of osteoarthritis or any other medical condition in the past were not included in the study. Diabetic subjects with prior usage or concomitant usage of insulin were not included in the study. Subjects consuming > 150 mg/day aspirin at screening were not included in the study. Subjects consuming ≤ 150 mg / day aspirin (for non-analgesic indications) was on a stable dose for at least 30 days prior to screening and no changes in the dose was made during the study.

Rescue medications:

Paracetamol (first line) and Ibuprofen (second line) were the rescue medications to be used in the study. No other analgesics other than the two rescue medications were administered during the study. The details of rescue medication (number of rescue medications used per day, start and stop date of the medication and date of last dose of rescue medication consumed prior to the scheduled visit) were recorded in the subject diary.

Subjects could take Paracetamol upto a maximum of 4000 mg/day for pain relief. The medication was discontinued at least 48 hrs prior to any study assessment visit (specific instructions regarding the same were given to the subjects). If the subject did not experienced adequate pain relief with the first line rescue medication (Paracetamol), the subject was instructed to inform the study investigator or the designated study personnel and attend an unscheduled visit.. It was the investigator's discretion to start second line rescue medication (ibuprofen) or withdraw subject from study based on examination findings. Upto 3200 mg/Day Ibuprofen could be administered to the subject. The medication was to be discontinued at least 48 hrs prior to any study assessment visit.

9.4.8 Treatment Compliance

IP was dispensed by an authorized designee at the scheduled visits. Subjects were required to bring both used (empty medication bottles) and unused study medication to the study centre at their scheduled visits. Records were maintained of all medication dispensed, used and returned by each subject.

Compliance during the run-in phase was a minimum of 80%. If compliance was outside this range, the patient was carefully interviewed and, if necessary, re-informed about the purpose and the conduct of the trial. The final decision regarding the inclusion of the subject in the study based on the compliance of the run-in period was dependent on the Investigator's discretion. Subjects were asked about their compliance at each visit and the study diary was reviewed. This information was appropriately recorded at scheduled visit in the CRF. Compliance was assessed by drug history and the data was noted in the subject diary.

In the first and second week of treatment (Week 1 and Week 2), the subject who did not consume 42 capsules (6 capsules per day X 7 days) in the respective weeks were excluded from the per protocol population. Overall for the study, the compliance was between expected to be 90-110 %. Subjects judged to be non-compliant were planned to be counseled on the importance of daily study medication intake, as prescribed. Subjects who were repeatedly or severely non-compliant were discontinued, at investigator's discretion after discussion with the medical monitor. Also it was planned to discontinue subjects who were repeatedly or severely non-compliant, at investigators and medical monitor discretion.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Efficacy and Safety Measurements Assessed

- Efficacy evaluation included assessment of the following self administered scales.
  - -Visual Analogue Scale (VAS) for pain
  - - WOMAC index of osteoarthritis for subjects with hip and knee osteoarthritis
  - - SF – 36 Quality of Life questionnaire
  - - Patient Global Assessment of Osteoarthritis
- The OMERACT – OARSI responder index criteria was assessed to determine the clinical response.

Visual Analogue Scale for Pain:

A VAS is a measurement instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. It is a self administered scale. It is usually a horizontal line, 10 mm in length anchored with word descriptors at the end (where 0 represents 'No distress / pain' and 10 represents 'Unbearable distress / pain'). The subject marks on the line the point that they feel represents their perception of pain of their current state. The VAS score is determined by measuring in millimeters from the left hand end of the line to the point that the subject marks.

Pain assessment using the VAS for pain was performed during all the 6 visits of the study (Screening, Baseline, Visit 3, Visit 4, Visit 5 and Visit 6) and on daily basis too (in the subject diary).

Western Ontario and McMaster Universities (WOMAC) Index:

WOMAC Index scale is a disease-specific, tri-dimensional self-administered questionnaire, for assessing health status and health outcomes in osteoarthritis of hip and / or knee. It consists of 3 sub-scales: Pain sub-scale, Physical function sub-scale and Stiffness sub-scale. The pain sub-scale comprises of 5 questions regarding the amount of pain experienced by the subject due to osteoarthritis in the index joint in the past 48 hrs.

The scores are measured using the 5 point – Likert scale. Higher scores indicate higher pain. (0 indicates 'No pain' and 4 indicates 'Extreme pain').The stiffness sub-scale consisted of 2 questions regarding the amount of stiffness (resistance of the joint to movement characterized by difficulty in moving the joint along with pain and discomfort in the joint) experienced in the index joint in the past 48 hrs. The scores are measured using the 5 point – Likert scale. Higher scores indicate increased stiffness (0 indicates 'No stiffness' and 4 indicates 'Extreme stiffness'). The physical function sub-scale consists of 17 questions regarding the degree of difficulty experience in the index joint due to OA in the past 48 hrs. The scores are measured using the 5point – Likert scale. Higher scores indicate worse function. (0 indicates 'No difficulty' and 4indicates 'Extreme difficulty').

WOMAC index score was completed by subjects with osteoarthritis of knee and hip during each study visit (Screening, Baseline, Visit 3, Visit 4, Visit 5 and Visit 6).

SF – 36 Quality of Life Questionnaire:

SF – 36 questionnaire is a self administered questionnaire that measures the following 8 health concepts: physical functioning, role limitations due to physical problems, social functioning, bodily pain, mental health, role limitations due to emotional problems, vitality and general health perception. Higher scores represent well-being of the subject. SF – 36 questionnaire was completed by the subject during all the visits (screening, Baseline, Visit 3, Visit 4, Visit 5 and Visit 6).

The SF-36 includes 36 items and covers eight scales: physical functioning (PF), role limitations due to physical health problems (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH). All scales are linearly transformed to a 0–100 scale, with 0 indicating the least favorable status and 100 being the most favorable health status. Two summary measures, the physical component summary (PCS) and the mental component summary (MCS), aggregate the 8 scales. The three scales (PF, RP, and BP) contribute most to the scoring of the PCS measure, and three scales (MH, RE, SF) contribute most to the scoring of the MCS measure.

Subject Global Assessment of Osteoarthritis:

Subject Global Assessment of osteoarthritis is a self – administered scale which was completed by the subject during each study visit (Screening, Baseline, Visit 3, Visit 4, Visit 5 and Visit 6)

The subject had to assess on a scale of 1 (indicates 'Very good') to 5 (indicates 'Very poor') as to how severe the OA symptoms are and the severity of limitation of activities due to OA.

OMERACT – OARSI (Outcome Measures in Rheumatoid Arthritis Clinical Trials – Osteoarthritis Research Society International) responder index:

OMERACT – OARSI responder index is two sets of responder criteria to present the results of changes from baseline in three symptomatic domains (WOMAC Pain subscale, WOMAC Physical function subscale, and Subject's Global Assessment of Osteoarthritis.

The subjects were assessed to be 'OMERACT – OARSI Responder' or 'OMERACT – OARSI - Non – responder' at visit 3, visit 4, visit 5 and visit 6 for subjects of osteoarthritis of knee and hip.

Safety measurement:

Safety was assessed throughout the study via AE reporting, physical examination, monitoring of vital signs (heart rate, respiratory rate, blood pressure and temperature) and the laboratory investigations.

Treatment-emergent AEs were defined as events that occurred after the first dose of medication and up to end of treatment. AE(s) monitored using the solicited checklist as volunteered by the subject and as observed by the principal investigator will be categorized descriptively by total number of AE(s) based on their causality, as well as severity and compared between treatment and control arms. These events will be summarized and reported as appropriate. The number and the proportion of subjects who experienced AEs were computed by treatment group, classified by MedDRA Primary System Organ Class and Preferred Terms. AEs were also be summarized by each severity grade (mild, moderate, severe) and by each relationship grade (none, possibly, probably) in a similar way. Proportion of subjects who used concomitant medication during the study period were computed for each treatment group.

Vitals signs and physical examination were summarized descriptively by treatment. For the Safety laboratory tests the shift tables were present.

9.5.2 Appropriateness of Variables

The variables measured in this study were standard variables for clinical studies for treatment of osteoarthritis.

9.5.3 Primary Efficacy Variable (s)

The primary efficacy variables were changes in the pain scores as evaluated VAS and improvement in mobility as evaluated by WOMAC sub-scales of Stiffness and Physical function at end of 1 week as compared to Baseline (Day 0 / Visit 2).

9.5.4 Drug Concentration Measurements

The study did not include any drug concentration measurements.

9.6 DATA QUALITY ASSURANCE

Study Monitoring and Training

Site selection visits were made by the Clinical Research Associates (CRAs) of MAL. During site initiation, the investigator and the staff at the study site were trained on protocol, ICF procedure, ICH GCP guidelines, randomization procedure, AE and SAE reporting, source documentation and CRF filling, maintenance of the investigator site file, clinical supplies dispensing & accountability and storage procedures. During the study, the CRA had regular contact with the study site. These contacts included visits to confirm that facilities remained acceptable, that the site personnel adhered to the protocol, that data was accurately recorded in the CRFs and to provide information and support to the investigator. The CRA ensured that the regular updating of the inventory and maintenance of IP dispensing log for the individual patient, regular temperature control by maintaining temperature log, etc. which were required for drug accountability. Source data verification (a comparison of the data in the CRF with the hospital records and other records at the study site) was also done.

All clinical studies conducted by MAL are subject to quality control and quality assurance measures as dictated by the appropriate department's operational documents like SOP's and process documents. The quality assurance activities were conducted by quality assurance personnel who after reviewing the data and the report declared the quality of the conduct of the study. Refer Appendix 16.1.8 for QA statement.

Audits and inspections

No audit/inspection has taken place till date for this study.

Data Management

Double Data entry, data validation and error rate calculation were done by Clinical Data Management personnel at Manipal AcuNova. The error rate for critical data was 0% and non-critical data was 0%. The data management personnel raised queries for discrepancies that required further clarification from the site and also for missing data using the "Data Clarification Form" as per the standard procedure. Resolution of data discrepancies was completed before the database was locked.

Dictionaries and coding terminology

AEs were classified according to the terminology of Medical Dictionary for Regulatory Activities (MedDRA Version 13.0) – Preferred Term (PT) and System Organ Class (SOC). Medications were classified using the World Health Organization Drug Dictionary (WHO-DD June 2009). Coding of all AEs and medications was completed before the database was locked.

9.7 STATISTICAL METHODS PLANNED AND DETERMINATION OF SAMPLE SIZE

9.7.1 Statistical and Analytical Plans

A comprehensive Statistical Analysis Plan (SAP) version 1.0 dated 26 Nov, 2010 was prepared for the study prior to the database being locked and performing the final analysis. A copy of SAP is provided in Appendix 16.1.9

9.7.1.1 Patients Included in the analysis

Three populations were considered for the analyses: the modified intention-to-treat (MITT) the per-protocol (PP) and the safety population. All efficacy endpoints were analyzed for the MITT and PP population of which the MITT population analysis was the primary and PP was the secondary analyses sets and all safety endpoints was analyzed for the safety population.

Modified Intention-to-treat population:
For efficacy evaluation, all subjects randomized and have at least one post treatment measurement were included in MITT population.

Per-Protocol population:
Subjects who complete both the baseline visit and end of treatment visit and who have no major protocol violations were included in the PP population.

Safety population:
For safety evaluation, all subjects randomized and received at least one dose of study medication were included in the safety population.

9.7.1.2 General Considerations

Statistical analyses were performed after all patients had ended their participation in the study and the database was locked.

The SAS® package (SAS® Institute Inc., USA, and Version 9.2) was used for statistical evaluation.

9.7.1.3 Demographic and Baseline Characteristics

The following demographic and baseline characteristics were summarized by treatment group: age, weight, gender, race, reproductive status and vital signs.

- For continuous measurements such as age, vital signs, height and weight the mean, median, standard deviation and range were tabulated.
- For categorical measurements such as gender, race and reproductive status the frequencies were calculated.

9.7.1.4 Analysis of Efficacy

The primary efficacy endpoint:

- Change in the pain scores as evaluated by Visual Analogue Scale (VAS) at end of 1 week as compared to Baseline (Day 0 / Visit 2)
- Improvement (change) in mobility at the end of Week 1 as compared to Baseline (day 0 / Visit 2) evaluated by change in the WOMAC sub-scales of Stiffness and Physical function.

The secondary efficacy endpoints:

- Change in the pain scores as evaluated by VAS at end of 2, 3 and 4 weeks as compared to Baseline (Day 0 / Visit 2).
- Percentage of responders (defined as atleast 70 % pain relief as compared to Baseline) evaluated at the end of Week 1, 2, 3 and 4 using the VAS
- Assessment of percentage responders at Week 1 stratified by prior history of NSAID use.
- Assessment of percentage responders at Week 2 stratified by prior history of NSAID use.
- Improvement (change) in mobility at the end of Week 2, 3 and 4 as compared to Baseline (day 0 / Visit 2) evaluated by change in the WOMAC sub-scales of Stiffness and Physical function.
- Change from baseline to Week 1, 2, 3 and 4 in total WOMAC Index scale for hip and knee osteoarthritis
- Change from baseline to Week 1, 2, 3,and 4 in SF-36 quality of life questionnaire
- Change from baseline to Week 1, 2, 3 and 4 in Subject Global assessment of Osteoarthritis
- OMERACT-OARSI responder index at Week 1, 2, 3 and 4.
- Number of subjects who use rescue medication in the treatment arm as compared to the placebo arm at end of week 1, 2 , 3 and 4 as compared to baseline
- Number of days of use of rescue medication in the treatment arm as compared to the placebo arm
- Amount (in mg) of first line rescue medication (Paracetamol) used in the treatment arm as compared to the placebo arm.
- Amount (in mg) of second line rescue medication (Ibuprofen) used in the treatment arm as compared to the placebo arm.

Analysis of primary efficacy endpoints:

For the primary efficacy endpoints, change in the pain scores as evaluated by Visual Analogue Scale (VAS) and improvement in mobility as evaluated by WOMAC sub-scales of Stiffness and Physical function at end of 1 week as compared to Baseline (Day 0

/ Visit 2) were calculated. For these efficacy endpoints, treatment effects were evaluated using an analysis of variance (ANOVA) model with factors for baseline and treatment. Treatment effects were estimated using the least-square means and 95% CIs from the ANOVA model. The assumption of normality and homogeneity of variances were tested using the Shapiro-Wilks test and the Levenes test, respectively. If the assumptions are violated, Kruskal-Wallis test (non-parametric) were used to corroborate the results of the parametric analyses. If the two sided p-value of all primary efficacy endpoints (VAS scale and WOMAC subscale at the end of week 1 as compared to Baseline) are less than 5%, then the hypothesis of superiority over placebo will be demonstrated.

Analysis of secondary efficacy endpoints:

The secondary efficacy endpoints were appropriately summarized and compared among the treatment and control arms.

9.7.1.5 Analysis of Safety and tolerability

The safety endpoints are:

- The type of AE(s), number of AE(s), frequency of AE(s) and proportion of subjects with AE(s).
- Physical examination
- Assessment of vital signs
- Safety laboratory tests (Complete blood count, Liver function tests, urea, creatinine and electrolytes and urine routine)

Analysis of safety endpoints:

Adverse events that occurred subsequent to the first dose of study drug were summarized. The number and the proportion of subjects who experienced AEs were computed by treatment group, classified by MedDRA Primary System Organ Class and Preferred Terms. AEs were also be summarized by each severity grade (mild, moderate, severe) and by each relationship grade (unrelated, unlikely, possibly, probably, definite) in a similar way. Vitals signs, physical examination, were summarized descriptively by treatment.

9.7.2 Handling of Drop-outs and Missing Data

Efficacy: For subjects with incomplete data (for dropping out or for any other reason), missing values were imputed for inclusion in the MITT population and no imputation was done for PP population.

Safety: No imputation was done on missing safety data, unless otherwise stated below.

Dates: Dates of remote events (e.g. AEs or concomitant medication) may be partially incomplete, as the day and/or month may be unknown. AEs with incomplete start dates were considered as treatment emergent, only if they are definitely known to have started after randomization. For treatment emergent AEs with incomplete start dates (unknown date and known month), the start date was taken as the first of the corresponding month or date of randomization, whichever is later. Incomplete dates for concomitant medications were not imputed.

9.7.3 Determination of Sample Size

As per the suggestion of sponsor, a sample size of 80 subjects (40 subjects in each treatment arm) was enrolled for the study.

9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

9.8.1 Changes in the study conduct

There were no changes in the conduct of the study from what was planned in the protocol.

9.8.2 Changes in the planned analysis

There were only two treatment arms in the study. Since for the non-parametric tests the factors are not considered Wilcoxon rank sum test have been used instead of Kruskal Wallis test to corroborate the results of the parametric analysis. The treatment effects were estimated using the 95% CI which have been reported for the Least – Square (LS) mean of the change from the baseline. Also the p value is presented from both ANOVA model and Wilcoxon rank sum test in tables.

In addition, the table template of Analysis of OMERACT-OARSI at each visit has been modified, as there is no baseline visit for the parameter. Only Number (and Percentage) of Responders and Non-Responders according to OMERACT-OARSI Responder Index at each visit has been presented.

10 STUDY PATIENTS

10.1 DISPOSITION OF PATIENTS

As planned, 80 patients enrolled from 01 center completed the clinical study. **Table 6** provided details of subject disposition by treatment group.

Table 6: Summary of subject disposition

	Treatment A n (%)	Treatment B n(%)	All n(%)
Number Of Subjects	40(100.0%)	40(100.0%)	80(100.0%)
Number Of Subjects Completed	40(100.0%)	40(100.0%)	80(100.0%)
Number Of Subjects Withdrawn	0(0.0%)	0(0.0%)	0(0.0%)
Enrolled = Number of subjects who were enrolled in the study Completed = Number of subjects who completed the visit 6 Withdrawn = Number of subjects who did not come for the Study Treatment A: Arthronat Treatment B: Placebo Source Listing: End of study form, Randomization			

All the enrolled 80 (100%) subjects completed all the scheduled study visits. **Table 7** provides the details about the number of patients at each visit.

Table 7: Number of subjects at each visits (MITT population)

Visit	Treatment A n (%)	Treatment B n (%)	All n (%)
Screening	40(100.0%)	40(100.0%)	80(100.0%)
Baseline (Randomization)	40(100.0%)	40(100.0%)	80(100.0%)
Week 1 (V3)	40(100.0%)	40(100.0%)	80(100.0%)
Week 2 (V4)	40(100.0%)	40(100.0%)	80(100.0%)
Week 3 (V5)	40(100.0%)	40(100.0%)	80(100.0%)
Week 4 (V6)	40(100.0%)	40(100.0%)	80(100.0%)
Treatment A: Arthronat Treatment B: Placebo Source Listing: Date of visit			

10.2 PROTOCOL DEVIATIONS

No major protocol deviations occurred during the conduct of the study.

11 EFFICACY EVALUATION

11.1 DATA SETS ANALYSED

Three populations were considered for the analyses: the modified intention-to-treat (MITT) the per-protocol (PP) and the safety population. All efficacy endpoints were analyzed for the MITT and PP population of which the MITT population analysis was the primary and PP was the secondary analyses sets and all safety endpoints was analyzed for the safety population.

Forty subjects each were randomized into the two arms [Treatment A (Arthronat) and Treatment B (Placebo)] of the study. All the 40 randomized subjects in both the treatment groups were included for MITT, PP and safety analysis. The **Table 8** provides the information about the number of subjects for MITT and safety population respectively.

Table 8: Summary of Study Population included for Analysis

	Number %		
Subject Status	**Treatment A (N=40)**	**Treatment B (N=40)**	**All (N=80)**
Number of subjects randomized	40(100.0%)	40(100.0%)	80(100.0%)
Included in the Modified intention-to-treat analysis	40(100.0%)	40(100.0%)	80(100.0%)
Included in the per-protocol analysis	40(100.0%)	40(100.0%)	80(100.0%)
Included in the safety analysis	40(100.0%)	40(100.0%)	80(100.0%)
Treatment A: Arthronat Treatment B: Placebo Source Listing: Randomization, End of study			

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

11.2.1 Demographic characteristics

The two treatment groups were comparable with respect to the demographic characteristics measured at baseline. **Table 9 and Table 10** provide the summaries of the subject characteristics at baseline for the MITT population, for the continuous and categorical characteristics, respectively.

The mean age of the subjects ranged from 27.3 to 69.4 years, with a mean of 53.0 years. 47 (58.75 %) of the subjects were females and 33 (41.25 %) of the subjects were males. And 8(10%) of the female subjects had child bearing potential. All subjects in the study were of Indian origin.

Table 9: Summary of subject demographic characteristics at baseline: continuous variables (MITT population)

Treatment	Treatment A(N=40)	Treatment B (N=40)	All (N=80)
Age (Years)			
N	40	40	80
Mean	54.7	51.3	53.0
SD	9.13	10.03	9.69
Minimum	28.3	27.3	27.3
Median	54.3	50.3	52.5
Maximum	69.4	69.0	69.4
Height (in cm)			
N	40	40	80
Mean	159.1	162.1	160.6
SD	8.20	10.12	9.27
Minimum	148.0	150.0	148.0
Median	156.0	160.0	158.0
Maximum	180.0	195.0	195.0
Weight (in kg)			
N	40	40	80
Mean	67.3	66.2	66.8
SD	9.33	11.35	10.34
Minimum	48.0	41.0	41.0
Median	66.0	68.0	66.0
Maximum	92.0	84.0	92.0
BMI			
N	40	40	80
Mean	26.6	24.9	25.8
SD	3.53	3.61	3.64
Minimum	19.7	18.2	18.2
Median	26.7	24.8	25.9
Maximum	37.2	34.8	37.2

Treatment A: Arthronat
Treatment B: Placebo
Source Listing: Demography

Table 10: Summary of subject demographic characteristics at baseline: categorical variables (MITT population)

		Treatment A (N=40)		Treatment B (N=40)		All (N=80)	
Variable	**Categories**	n	%	n	%	n	%
Gender	**Female**	20	50.00	27	67.50	47	58.75
	Male	20	50.00	13	32.50	33	41.25
If Female Child bearing potential	**Yes**	5	12.50	3	7.50	8	10.00
	No	15	37.50	24	60.00	39	48.75
If Yes	**Surgically Sterile**	2	5.00	1	2.50	3	3.75
	Double Barrier Method	3	7.50	2	5.00	5	6.25
If No	**Post Menopausal**	14	35.00	16	40.00	30	37.50
	Hysterectomy And/Or B/L Oopherectomy	1	2.50	8	20.00	9	11.25
Race	**Indian**	40	100.00	40	100.00	80	100.00

N = total number of subjects
n = number of subjects in a given category
% = (n / Number of subjects with available results) x 100
Treatment A: Arthronat
Treatment B: Placebo
Source Listing: Demography

11.2.2 Medical History

All relevant medical history was recorded at the screening visit. **Table 11** provides the summary of patient's medical history classified by involved System Organ Class (SOC) and MedDRA preferred term for the MITT population.

Overall 24 (30.0%) and 15 (18.8%) subjects had a medical history of hypertension and Type 2 diabetes mellitus in the study respectively. Both the treatment arms were comparable in terms of medical history.

A listing of medical conditions for each patient is provided in Appendix 16.2.

Table 11: Summary of the subjects' medical history classified by MedDRA preferred term (MITT population)

		Treatment A (N=40)		Treatment B (N=40)		ALL (N=80)	
System Organ Class	MedDRA Preferred Term	n	%	n	%	n	%
Metabolism And Nutrition Disorders	Diabetes Mellitus	4	10.0	1	2.5	5	6.3
	Type 2 Diabetes Mellitus	10	25.0	5	12.5	15	18.8
Surgical And Medical Procedures	Angioplasty	1	2.5	1	2.5	2	2.5
	Caesarean Section	2	5.0	0	0.0	2	2.5
	Cataract Operation	3	7.5	2	5.0	5	6.3
	Cholecystectomy	1	2.5	1	2.5	2	2.5
	Gallbladder Operation	0	0.0	1	2.5	1	1.3
	Haemorrhoid Operation	1	2.5	2	5.0	3	3.8
	Hysterectomy	8	20.0	1	2.5	9	11.3
	Inguinal Hernia Repair	0	0.0	1	2.5	1	1.3
	Renal Stone Removal	0	0.0	1	2.5	1	1.3
	Salpingectomy	5	12.5	8	20.0	13	16.3
Vascular Disorders	Hypertension	11	27.5	13	32.5	24	30.0

N = Total number of subjects in the specified group
n/% = Number / percentage of subjects reporting the specified medical history preferred term
Treatment A: Arthronat
Treatment B: Placebo
Source Listing: Medical History

11.2.3 Prior medication

Both the treatment arms Arthonat and placebo were comparable in terms of prior NSAIDs usage. The most commonly used prior medication was NSAIDs, Galenic (combination of Ibuprofen/Paracetamol) by 15(37.5%) and 8(20%) subjects in Arthonat and placebo groups respectively. Details of Percentage of subjects who used prior medication (MITT population) are provided in **Table 12**.

Table 12: Percentage of subjects who used prior medication (MITT population)

	Treatment A (N=40)		Treatment B (N=40)	
Preferred Term	n	%	n	%
Acarbose	1	2.5	0	0
Aceclo Plus	6	15.0	9	22.5
Aceclofenac	8	20.0	9	22.5
Acetylsalicylic Acid	0	0	1	2.5
Amlodipine	5	12.5	3	7.5
Atenolol	1	2.5	2	5.0
Atorvastatin Calcium	1	2.5	0	0
Calcitrol /00508501/	1	2.5	0	0
Calcium	5	12.5	4	10.0
Calcium Carbonate	1	2.5	1	2.5
Calcium Citrate	0	0	3	7.5
Calcium With Vitamin D /01233101/	1	2.5	0	0
Clopidogrel Sulfate	0	0	1	2.5
Diapride Forte	3	7.5	0	0
Diclofenac Deanol	1	2.5	1	2.5
Diclofenac Sodium	7	17.5	9	22.5
Enalapril Maleate	1	2.5	1	2.5
Etoricoxib	0	0	1	2.5
Fixocard	0	0	1	2.5
Galenic /Ibuprofen/Paracetamol/	15	37.5	8	20.0
Gemcal	0	0	1	2.5
Gemer-P	1	2.5	0	0
Glibenclamide	1	2.5	0	0
Glimepiride	0	0	1	2.5
Glucosamine Sulfate	0	0	1	2.5
Glynase Mf	2	5.0	0	0
Hyzaar /01284801/	3	7.5	1	2.5
Ibuprofen	0	0	1	2.5
Indometacin	0	0	1	2.5
Lekovit Ca	9	22.5	7	17.5
Lornoxicam	1	2.5	1	2.5
Losartan Potassium	1	2.5	0	0
Mecobalamin	2	5.0	2	5.0
Metaglip	2	5.0	1	2.5
Metformin	2	5.0	3	7.5
Metformin Hydrochloride	0	0	1	2.5
Metoprolol Succinate	1	2.5	0	0
Metoprolol Tartrate	1	2.5	2	5.0

	Treatment A (N=40)		Treatment B (N=40)	
Nephrovite	1	2.5	0	0
Nifedipine	0	0	1	2.5
Osteocare /01424301/	1	2.5	1	2.5
Paracetamol	8	20.0	5	12.5
Pritor /01506701/	0	0	1	2.5
Propranolol Hydrochloride	1	2.5	0	0
Ramipril	0	0	2	5.0
Rejoint	0	0	1	2.5
Sil-Norboral	2	5.0	0	0
Telmisartan	0	0	2	5.0

n/% = Number/percentage of subjects with the given characteristics
Treatment A: Arthronat
Treatment B: Placebo
Source Listing: Prior Concomitant Medication

11.3 MEASUREMENTS OF TREATMENT COMPLIANCE

The treatment compliance was measured as 100% in both the treatment groups of Arthronat and Placebo respectively. Treatment compliance have been categorized and summarized for the MITT population in the **Table 13**.

Table 13: Summary of treatment compliance (MITT population)

Summary of Treatment Compliance			
Visit		**Treatment A**	**Treatment B**
WEEK 1 (V3)	N	40	40
	Mean	100.0	100.0
	SD	0.00	0.00
	Minimum	100.0	100.0
	Maximum	100.0	100.0
WEEK 2 (V4)	N	40	40
	Mean	100.0	100.0
	SD	0.00	0.00
	Minimum	100.0	100.0
	Maximum	100.0	100.0
WEEK 3 (V5)	N	40	40
	Mean	100.0	100.0
	SD	0.00	0.00
	Minimum	100.0	100.0
	Maximum	100.0	100.0
WEEK 4 (V6)	N	40	40

Summary of Treatment Compliance			
Visit		**Treatment A**	**Treatment B**
	Mean	100.0	100.0
	SD	0.00	0.00
	Minimum	100.0	100.0
	Maximum	100.0	100.0
Treatment A: Arthronat Treatment B: Placebo Source Listing: Treatment Compliance			

11.4 EFFICACY RESULTS AND TABULATION OF DATA

11.4.1 Analysis of Efficacy

11.4.1.1 Analysis of pain scores as evaluated by Visual Analogue Scale (VAS)

The VAS scale was used in the study as a measurement instrument that tries to measure a characteristic or attitude that was believed to range across a continuum of values and cannot easily be directly measured. Please refer to Section 9.5.1 and Appendix V of the protocol for more details on VAS scale.

VAS pain scores were reduced more in Arthronat group from the baseline compared to placebo which infers that there was improvement in the pain scores in the Arthronat group. The mean pain scores as evaluated by VAS at baseline were 68.6 which came down to 65.4 in Arthronat arm and from 70.1 increased to 70.5 in placebo arm at week 1.

The summary of pain scores as evaluated by VAS by visit for MITT population is provided in **Table 14**. Mean percent change in VAS from baseline is presented in **Table 15** and **Figure 1**. Analysis of absolute change from baseline in VAS pain scores is provided in **Figure 2**.

Post-text Table 1: and **Post-text Table 2** provide the summary of pain scores as evaluated by percent change in Visual Analogue Scale (VAS) from baseline of MITT population and PP population respectively. **Post-text Table 3** provides the summary of pain scores as evaluated by Visual Analogue Scale (VAS) by visit for PP population.

Table 14: Summary of pain scores as evaluated by VAS (MITT population)

Visit	Categories	Treatment A (N=40)	Treatment B (N=40)
Screening	**N**	40	40
	Mean	68.6	69.4
	SD	8.11	9.48
	Median	70.0	70.0
	Minimum	50.0	50.0
	Maximum	90.0	95.0
Baseline	**N**	40	40
	Mean	68.0	70.1
	SD	7.90	8.32
	Median	70.0	70.0
	Minimum	50.0	50.0
	Maximum	80.0	86.0
Visit 3	**N**	40	40
	Mean	65.4	70.5
	SD	7.99	7.07
	Median	65.0	70.0
	Minimum	45.0	58.0
	Maximum	80.0	88.0
Visit 4	**N**	40	40
	Mean	61.6	69.1
	SD	9.05	7.80
	Median	60.0	70.0
	Minimum	45.0	55.0
	Maximum	90.0	90.0
Visit 5	**N**	40	40
	Mean	59.8	68.2
	SD	10.00	8.51
	Median	60.0	68.5
	Minimum	40.0	52.0
	Maximum	80.0	90.0
Visit 6	**N**	40	40
	Mean	56.6	65.2
	SD	11.51	8.21
	Median	55.0	65.0
	Minimum	40.0	50.0
	Maximum	80.0	80.0

Treatment A: Arthronat;
Treatment B: Placebo
Source Listing: Visual Analogue Scale for Pain

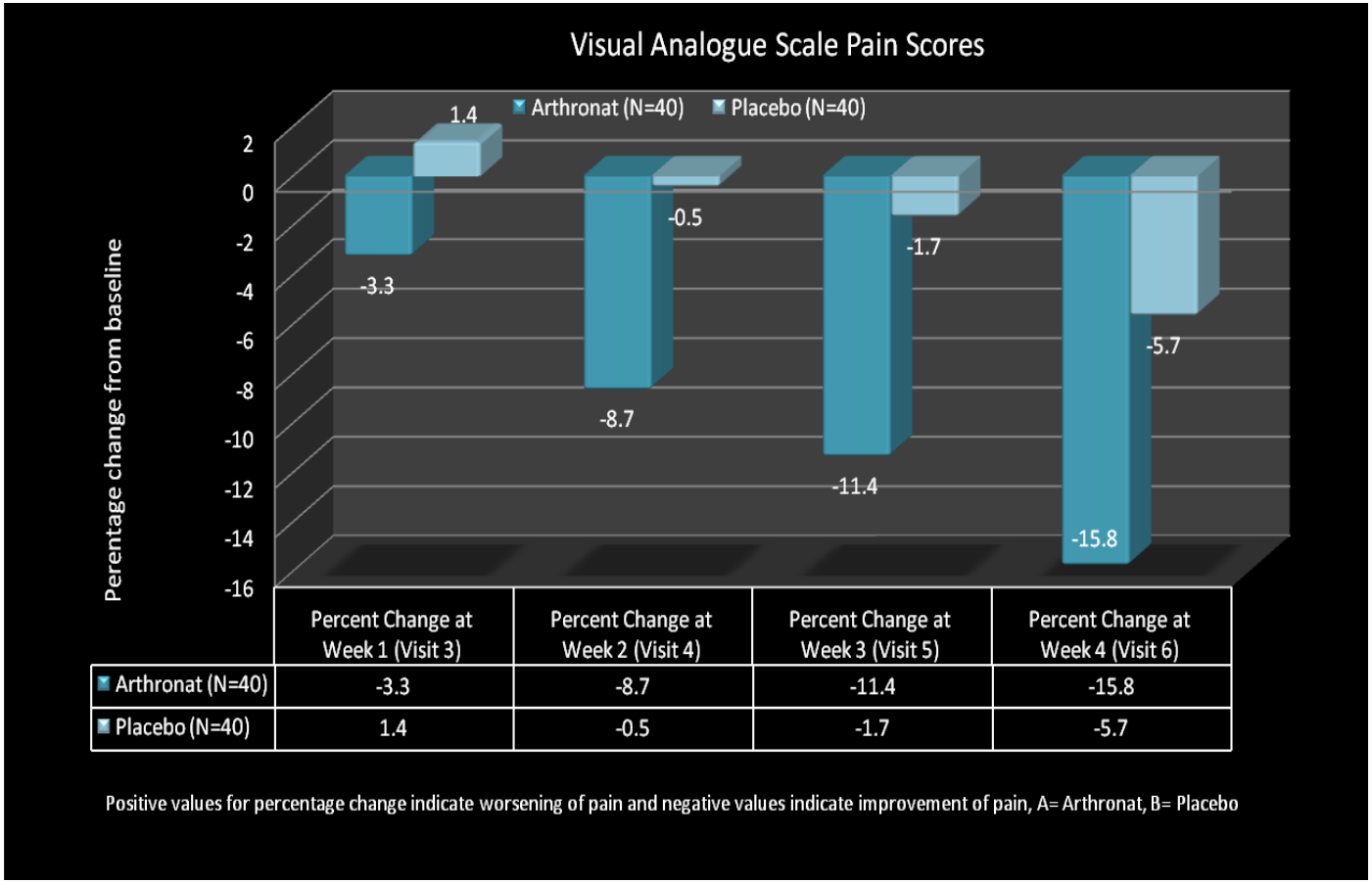
Table 15: Mean Percentage change in VAS scores from baseline

VAS SCORES FOR PAIN*		
	Arthronat (N=40)	**Placebo (N=40)**
Mean Percent Change at Week 1 (Visit 3)	-3.3	1.4
Mean Percent Change at Week 2 (Visit 4)	-8.7	-0.5
Mean Percent Change at Week 3 (Visit 5)	-11.4	-1.7
Mean Percent Change at Week 4 (Visit 6)	-15.8	-5.7

* Positive values for percentage change indicate worsening of pain and negative values indicate improvement of pain

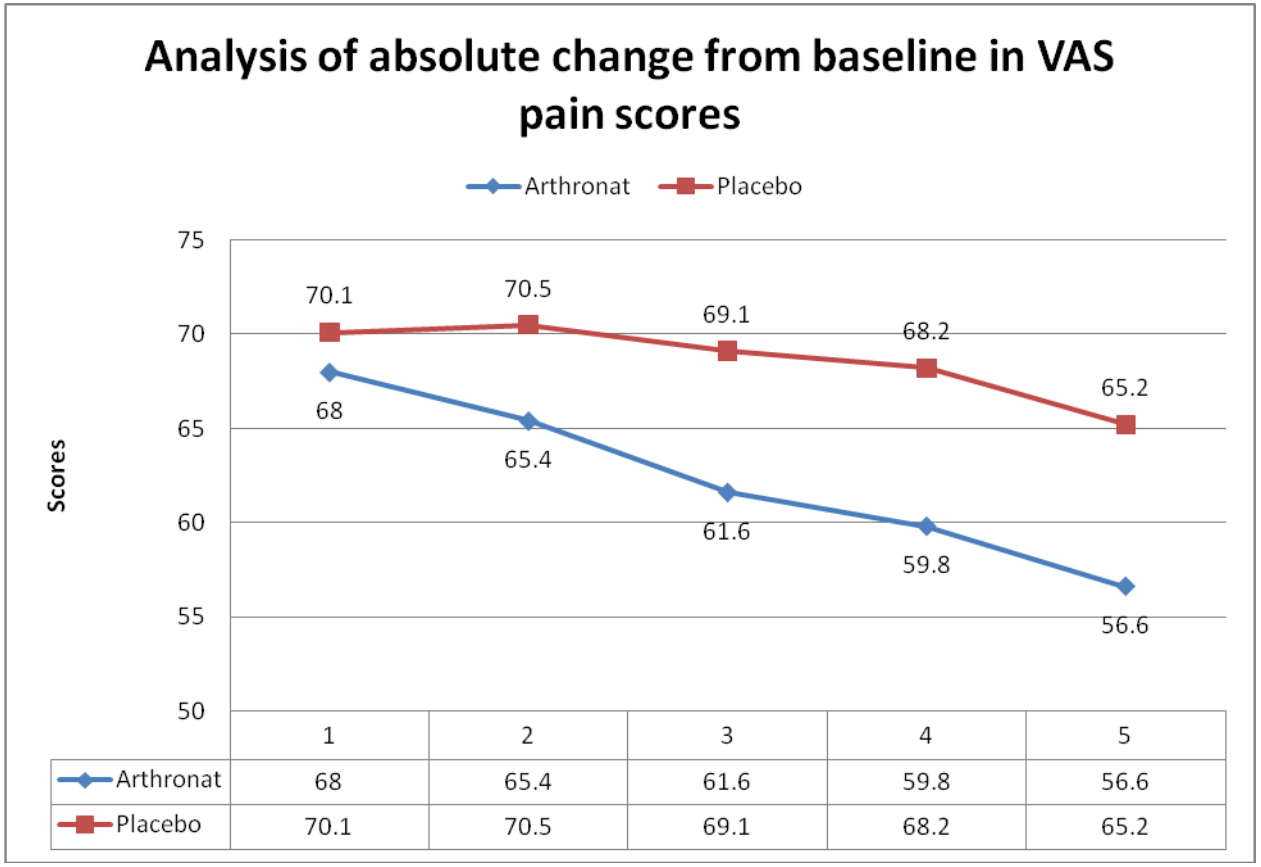
Source : Table VAS PCT_MITT

Figure 1: Mean percent change in Visual Analogue Scale (VAS) from baseline



	Percent Change at Week 1 (Visit 3)	Percent Change at Week 2 (Visit 4)	Percent Change at Week 3 (Visit 5)	Percent Change at Week 4 (Visit 6)
Arthronat (N=40)	-3.3	-8.7	-11.4	-15.8
Placebo (N=40)	1.4	-0.5	-1.7	-5.7

Figure 2: Analysis of absolute change from baseline in VAS pain scores



	1	2	3	4	5
Arthronat	68	65.4	61.6	59.8	56.6
Placebo	70.1	70.5	69.1	68.2	65.2

Table 16 provides the analysis of absolute change from baseline in pain scores as evaluated by Visual Analogue Scale (VAS) at end of week 1 as compared to baseline (Day 0 / Visit 2) for MITT population.

The LS mean difference obtained for the treatment comparison of Arthronat and placebo at week 1was -3.878. The p-value of 0.0013 indicates that there was a significant difference in absolute change from baseline in pain scores as evaluated by Visual Analogue Scale (VAS) at end of week 1 as compared to baseline (Day 0 / Visit 2) between the treatments.

Table 16: Analysis of absolute change from baseline in pain scores as evaluated by Visual Analogue Scale (VAS) at end of week 1 as compared to Baseline (Day 0 / Visit 2) (MITT population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	68.0	7.90	40	70.1	8.32	-1.1	6.93	-3.878	(-6.539,-1.217)	0.0048	0.0013
Week 1	40	65.4	7.99	40	70.5	7.07			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: Visual Analogue Scale for Pain

Post-text Table 4 provides the analysis of absolute change from baseline in pain scores as evaluated by Visual Analogue Scale (VAS) at end of week 1 as compared to Baseline (Day 0 / Visit 2) for PP population.

Table 17 provides the analysis of absolute change from baseline in pain scores as evaluated by Visual Analogue Scale (VAS) at end of week 2 as compared to baseline (Day 0 / Visit 2) for MITT population.

The LS mean difference obtained for the treatment comparison of Arthronat and placebo at week 2 was -6.600. The p-value of 0.0001 indicates that there was a significant difference in absolute change from baseline in pain scores as evaluated by Visual Analogue Scale (VAS) at end of week 2 as compared to baseline (Day 0 / Visit 2) between the treatments.

Table 17:Analysis of absolute change from baseline in pain scores as evaluated by Visual Analogue Scale (VAS) at end of week 2 as compared to Baseline (Day 0 / Visit 2) (MITT population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	68.0	7.90	40	70.1	8.32	-3.7	9.37	-6.600	(-10.09,-3.114)	0.0003	0.0001
Week 2	40	61.6	9.05	40	69.1	7.80			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: Visual Analogue Scale for Pain

Post-text Table 5: provides the analysis of absolute change from baseline in pain scores as evaluated by Visual Analogue Scale (VAS) at end of week 2 as compared to Baseline (Day 0 / Visit 2) for PP population.

Table 18 provides the analysis of absolute change from baseline in pain scores as evaluated by Visual Analogue Scale (VAS) at end of week 3 as compared to baseline (Day 0 / Visit 2) for MITT population.

The LS mean difference obtained for the treatment comparison of Arthronat and placebo at week 3 was -7.615. The p-value of 0.0004 indicates that there was a significant difference in absolute change from baseline in pain scores as evaluated by Visual Analogue Scale (VAS) at end of week 3 as compared to baseline (Day 0 / Visit 2) between the treatments.

Table 18: Analysis of absolute change from baseline in pain scores as evaluated by Visual Analogue Scale (VAS) at end of week 3 as compared to Baseline (Day 0 / Visit 2) (MITT population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	68.0	7.90	40	70.1	8.32	-5.0	10.38	-7.615	(-11.54,-3.691)	0.0002	0.0004
Week 3	40	59.8	10.00	40	68.2	8.51			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: Visual Analogue Scale for Pain

Post-text Table 6: provides the analysis of absolute change from baseline in pain scores as evaluated by Visual Analogue Scale (VAS) at end of week 3 as compared to baseline (Day 0 / Visit 2) for PP Population.

Table 19 provide the analysis of absolute change from baseline in pain scores as evaluated by Visual Analogue Scale (VAS) at end of week 4 as compared to baseline (Day 0 / Visit 2) for MITT population.

The LS mean difference obtained for the treatment comparison of Arthronat and placebo at week 4 was -8.172. The p-value of 0.0019 indicates that there was a significant difference in absolute change from baseline in pain scores as evaluated by Visual Analogue Scale (VAS) at end of week 4 as compared to Baseline (Day 0 / Visit 2) between the treatments.

Table 19: Analysis of absolute change from baseline in pain scores as evaluated by Visual Analogue Scale (VAS) at end of week 4 as compared to Baseline (Day 0 / Visit 2) (MITT population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	68.0	7.90	40	70.1	8.32	-8.1	12.15	-8.172	(-12.63,-3.719)	0.0005	0.0019
Week 4	40	56.6	11.51	40	65.2	8.21			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: Visual Analogue Scale for Pain

Post-text Table 7: provide the analysis of absolute change from baseline in pain scores as evaluated by Visual Analogue Scale (VAS) at end of week 4 as compared to Baseline (Day 0 / Visit 2) for PP Population.

11.4.1.2 Analysis of improvement in mobility as evaluated by WOMAC sub-scales of Stiffness and Physical function

WOMAC Index scale used in the study is a disease-specific, tri-dimensional self-administered questionnaire, for assessing health status and health outcomes in osteoarthritis of hip and / or knee. It consists of 3 sub-scales: Pain sub-scale, Physical function sub-scale and Stiffness sub-scale. Please refer to Section 9.5.1 and APPENDIX VII of the protocol for more details on WOMAC Index scale.

WOMAC pain and physical function scores were reduced more in Arthronat compared to placebo which infers that Arthronat group had improvement in the WOMAC pain and physical function scores from the baseline compared to placebo. However no improvement was seen in stiffness scores in Arthronat group from the baseline compared to Placebo.

The mean WOMAC sub-scales of stiffness at baseline were 3.1 and 3.2 and at week 1 were 3.1 and 3.4 for Arthronat and placebo group respectively. The mean WOMAC sub-scales of physical function at baseline were 26.8 and 26.7 and at week 1 were 27.0 and 29.0 for Arthronat and placebo group respectively.

The summary of improvement in mobility as evaluated by WOMAC sub-scales of Stiffness and Physical Function by visit for MITT population is provided in **Table 20**. Percentage change in WOMAC index sub-scales of Pain, Stiffness & Physical Function from baseline are presented in **Table 21, Figure 3**, **Figure 4** and **Figure 5**.

Post-text Table 8 provides the summary of improvement in mobility as evaluated by percent change in WOMAC sub-scales of Pain, Stiffness & Physical Function and total-scale from baseline (PP population). **Post-text Table 9** provides the Summary of improvement in mobility as evaluated by WOMAC sub-scales of Stiffness and Physical Function by visit for PP Population.

Table 20: Summary of improvement in mobility as evaluated by WOMAC sub-scales of Stiffness and Physical Function (MITT population)

Visit	Subscale	Categories	Treatment A (N=40)	Treatment B (N=39)
Screening	**Stiffness**	N	40	39
		Mean	3.0	2.8
		SD	0.62	0.74
		Median	3.0	3.0
		Minimum	1.0	1.0
		Maximum	5.0	4.0
Baseline		N	40	39
		Mean	3.1	3.2

Visit	Subscale	Categories	Treatment A (N=40)	Treatment B (N=39)
		SD	0.74	0.99
		Median	3.0	3.0
		Minimum	2.0	1.0
		Maximum	5.0	5.0
Visit 3		N	40	39
		Mean	3.1	3.4
		SD	0.67	0.99
		Median	3.0	3.0
		Minimum	2.0	1.0
		Maximum	5.0	5.0
Visit 4		N	40	39
		Mean	3.2	3.3
		SD	0.70	0.94
		Median	3.0	3.0
		Minimum	2.0	1.0
		Maximum	5.0	5.0
Visit 5		N	40	39
		Mean	3.2	3.3
		SD	0.62	1.00
		Median	3.0	3.0
		Minimum	2.0	1.0
		Maximum	5.0	5.0
Visit 6		N	40	39
		Mean	3.1	3.2
		SD	0.69	0.92
		Median	3.0	3.0
		Minimum	2.0	1.0
		Maximum	5.0	5.0
Screening	**Physical Function**	N	40	39
		Mean	25.9	26.3
		SD	2.54	3.16
		Median	26.0	27.0
		Minimum	21.0	16.0
		Maximum	31.0	32.0
Baseline		N	40	39
		Mean	26.8	26.7
		SD	3.88	4.29
		Median	26.5	27.0
		Minimum	18.0	15.0
		Maximum	36.0	37.0

Visit	Subscale	Categories	Treatment A (N=40)	Treatment B (N=39)
Visit 3		N	40	39
		Mean	27.0	29.0
		SD	3.20	2.79
		Median	26.0	29.0
		Minimum	19.0	23.0
		Maximum	35.0	36.0
Visit 4		N	40	39
		Mean	26.4	29.0
		SD	2.78	2.74
		Median	26.5	29.0
		Minimum	19.0	24.0
		Maximum	32.0	37.0
Visit 5		N	40	39
		Mean	26.6	27.7
		SD	3.11	2.89
		Median	26.0	27.0
		Minimum	21.0	22.0
		Maximum	34.0	33.0
Visit 6		N	40	39
		Mean	26.5	28.2
		SD	3.39	2.42
		Median	26.0	28.0
		Minimum	16.0	25.0
		Maximum	34.0	34.0

Treatment A: Arthronat
Treatment B: Placebo
Source Listing: WOMAC Index Questionnaire for Hip and Knee OA

Table 21 : Mean Percentage change in WOMAC index sub-scales of Pain, Stiffness & Physical Function from baseline

WOMAC SCORES		
Pain	**Treatment A (N=40)**	**Treatment B (N=39)**
Percent Change at Week 1 (Visit 3)	1	7.1
Percent Change at Week 2 (Visit 4)	-3.2	2.8
Percent Change at Week 3 (Visit 5)	-3.3	4.6
Percent Change at Week 4 (Visit 6)	-4.3	6.1
Stiffness		
Percent Change at Week 1 (Visit 3)	1.9	10.3
Percent Change at Week 2 (Visit 4)	8	8.9
Percent Change at Week 3 (Visit 5)	5.9	10
Percent Change at Week 4 (Visit 6)	3.4	7.2
Physical function		
Percent Change at Week 1 (Visit 3)	1.7	11.6
Percent Change at Week 2 (Visit 4)	-0.3	12.1
Percent Change at Week 3 (Visit 5)	0.6	7.3
Percent Change at Week 4 (Visit 6)	-0.2	9.2
Positive values for percentage change indicate worsening of pain/stiffness and physical function and negative values indicate improvement of pain/stiffness and physical function Source: Table WOMAC PCT_MITT		

Figure 3: Percentage change in WOMAC index sub-scales of Pain scores from baseline

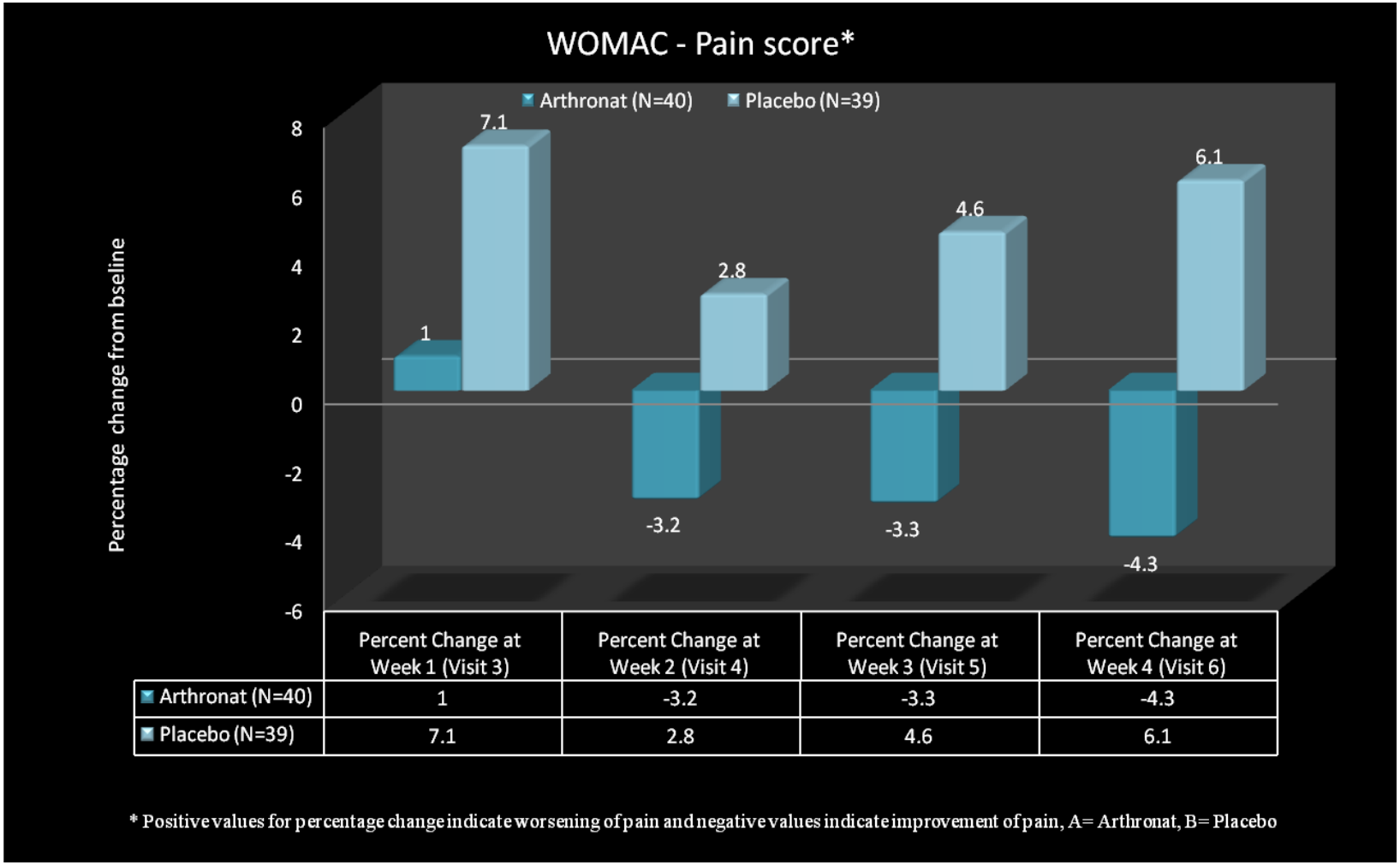


Figure 4 : Percentage change in WOMAC index sub-scales of Stiffness scores from baseline

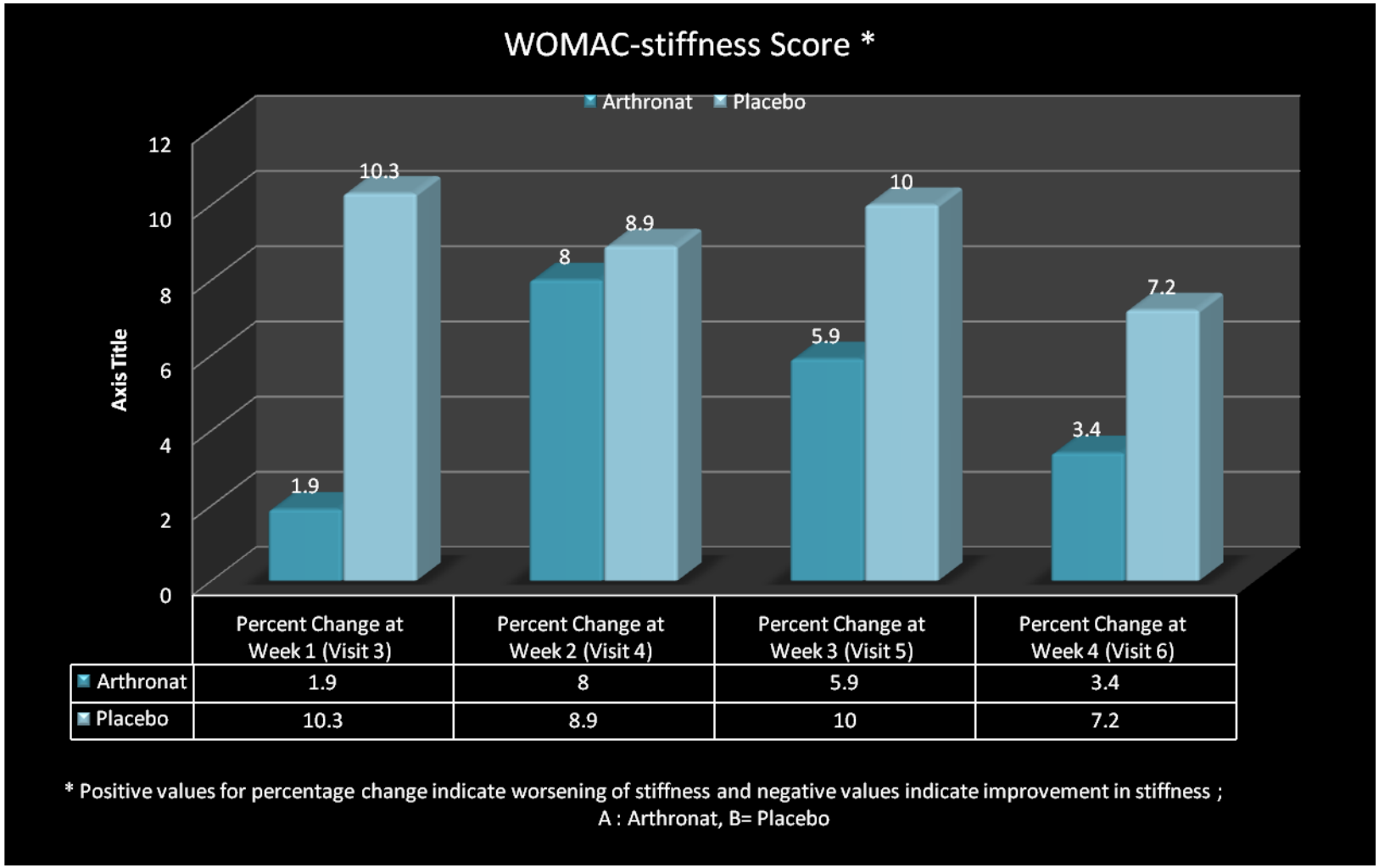
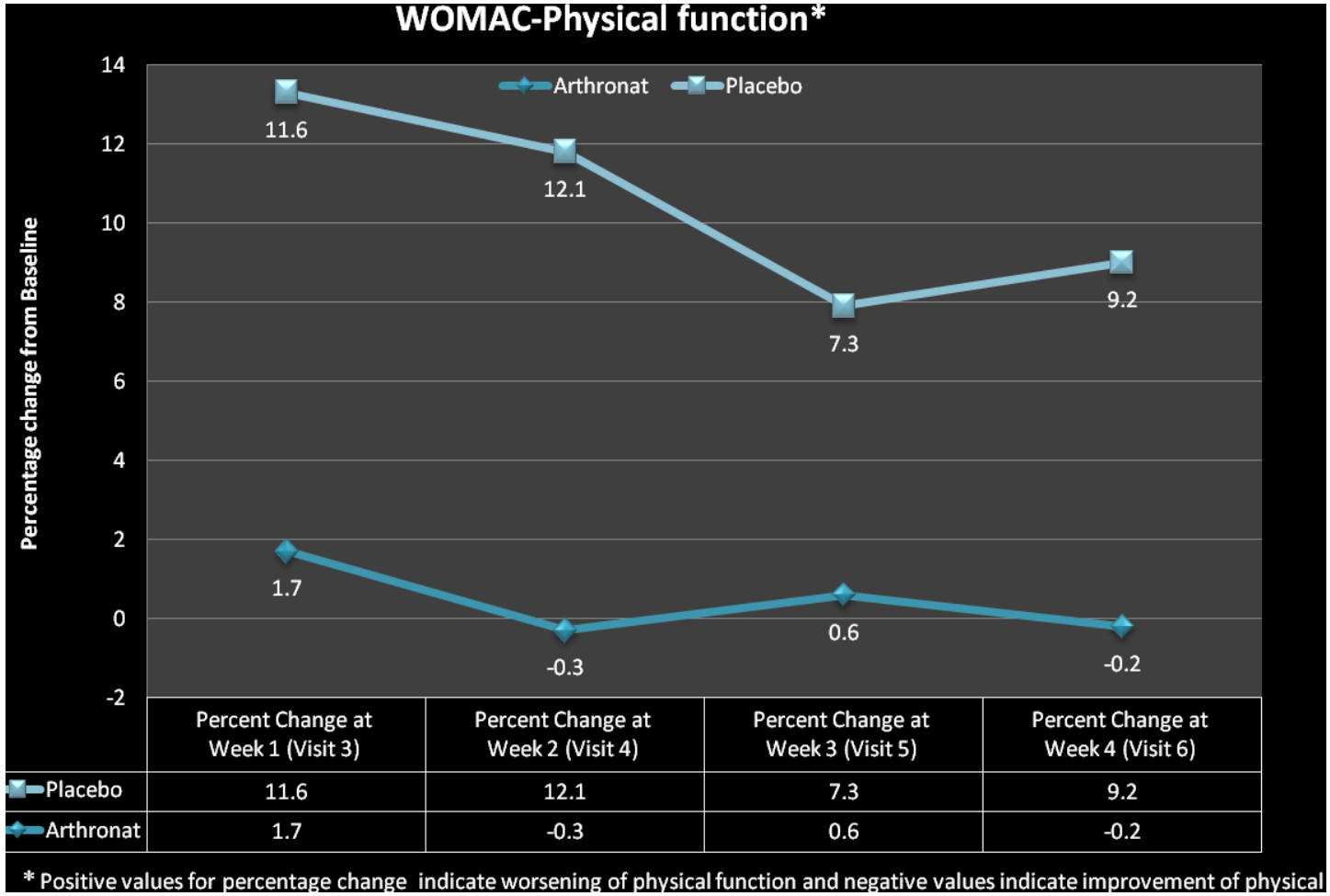


Figure 5: Percentage change in WOMAC index sub-scales Physical Function score from baseline



	Percent Change at Week 1 (Visit 3)	Percent Change at Week 2 (Visit 4)	Percent Change at Week 3 (Visit 5)	Percent Change at Week 4 (Visit 6)
Placebo	11.6	12.1	7.3	9.2
Arthronat	1.7	-0.3	0.6	-0.2

Table 22 provides the analysis of absolute change from baseline in improvement in mobility as evaluated by WOMAC subscales of stiffness and physical function at end of week 1 as compared to Baseline (Day 0 / Visit 2) for modified intention-to-treat population.

The mean value of WOMAC subscales of physical function for Arthonat treatment group at baseline was 26.8 and 27.0 at week 1 whereas the mean value for placebo group at baseline was 26.7 which increased to 29.0 at week 1. The LS mean difference observed between Arthronat and placebo groups was -2.050 (p=0.0090), which indicates that there was a statistically significant difference in physical function in the Arthronat treatment arm as compared to the placebo. The analysis of results at week 1 showed that the WOMAC subscales of physical function in Arthronat arm were better than placebo arm.

There was no change seen in the mean value of WOMAC subscales of stiffness for Arthronat at baseline and week 1 (score = 3.1) however in the placebo arm the mean value increased from 3.2 at baseline to 3.4 at week 1. There was no statistically significant difference seen in the two treatment arms at week 1 (p= 0.3154).

Table 22 : Analysis of absolute change from baseline in improvement in mobility as evaluated by WOMAC subscales of stiffness and physical function at end of week 1 as compared to Baseline (Day 0 / Visit 2) (MITT population)

		Treatment A			Treatment B			Absolute change from baseline					
Visit	**Subscale**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**Mean**	**SD**	**LS Mean**	**95% CI***	**P-value***	**P-value****
Baseline	**Stiffness**	40	3.1	0.74	39	3.2	0.99	0.1	0.65	-0.222	(-0.488,0.044)	0.1005	0.3154
Week 1		40	3.1	0.67	39	3.4	0.99			.		.	.
Baseline	**Physical Function**	40	26.8	3.88	39	26.7	4.29	1.2	4.05	-2.050	(-3.281,-0.819)	0.0014	0.0090
Week 1		40	27.0	3.20	39	29.0	2.79			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: WOMAC Index Questionnaire for Hip and Knee OA

Post-text Table 10: provides the analysis of absolute change from baseline in improvement in mobility as evaluated by WOMAC subscales of stiffness and physical function at end of week 1 as compared to baseline (Day 0 / Visit 2) for Per-Protocol Population.

Table 23 provides the analysis of absolute change from baseline in improvement in mobility as evaluated by WOMAC subscales of stiffness and physical function at end of week 2 as compared to baseline (Day 0 / Visit 2) for modified intention-to-treat population.

The LS mean difference obtained for the treatment comparison of Arthronat and placebo at week 2 was -0.009. The p-value of 0.6845 indicates that there was no significant difference in absolute change from baseline in improvement in mobility as evaluated by WOMAC subscales of stiffness at end of week 2 as compared to baseline (Day 0 / Visit 2) between the treatments.

The LS mean difference obtained for the treatment comparison of Arthronat and placebo at week 2 was -2.614. The p-value of 0.0069 indicates that there was a significant difference in absolute change from baseline in improvement in mobility as evaluated by WOMAC subscales of physical function at end of week 2 as compared to baseline (Day 0 / Visit 2) between the treatments.

Table 23: Analysis of absolute change from baseline in improvement in mobility as evaluated by WOMAC subscales of stiffness and physical function at end of week 2 as compared to Baseline (Day 0 / Visit 2) (MITT population)

		Treatment A			Treatment B			Absolute change from baseline					
Visit	**Subscale**	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	**Stiffness**	40	3.1	0.74	39	3.2	0.99	0.1	0.89	-0.009	(-0.343,0.325)	0.9579	0.6845
Week 2		40	3.2	0.70	39	3.3	0.94			.		.	.
Baseline	**Physical Function**	40	26.8	3.88	39	26.7	4.29	0.9	4.51	-2.614	(-3.821,-1.407)	<.0001	0.0069
Week 2		40	26.4	2.78	39	29.0	2.74			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: WOMAC Index Questionnaire for Hip and Knee OA

Post-text Table 11: provides the analysis of absolute change from baseline in improvement in mobility as evaluated by WOMAC subscales of stiffness and physical function at end of week 2 as compared to baseline (Day 0 / Visit 2) for Per-Protocol Population.

Table 24 provides the analysis of absolute change from baseline in improvement in mobility as evaluated by WOMAC subscales of stiffness and physical function at end of week 3 as compared to baseline (Day 0 / Visit 2) for modified intention-to-treat population.

The LS mean difference obtained for the treatment comparison of Arthronat and placebo at week 3 was -0.114. The p-value of 0.7415 indicates that there was no significant difference in absolute change from baseline in improvement in mobility as evaluated by WOMAC subscales of stiffness at end of week 3 as compared to baseline (Day 0 / Visit 2) between the treatments.

The LS mean difference obtained for the treatment comparison of Arthronat and placebo at week 3 was -1.152. The p-value of 0.2373 indicates that there was no significant difference in absolute change from baseline in improvement in mobility as evaluated by WOMAC subscales of physical function at end of week 3 as compared to baseline (Day 0 / Visit 2) between the treatments.

Table 24: Analysis of absolute change from baseline in improvement in mobility as evaluated by WOMAC subscales of stiffness and physical function at end of week 3 as compared to Baseline (Day 0 / Visit 2) (MITT population)

		Treatment A			Treatment B			Absolute change from baseline					
Visit	**Subscale**	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	**Stiffness**	40	3.1	0.74	39	3.2	0.99	0.1	0.96	-0.114	(-0.464,0.236)	0.5190	0.7415
Week 3		40	3.2	0.62	39	3.3	1.00			.		.	.
Baseline	**Physical Function**	40	26.8	3.88	39	26.7	4.29	0.4	4.70	-1.152	(-2.492,0.188)	0.0909	0.2373
Week 3		40	26.6	3.11	39	27.7	2.89			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: WOMAC Index Questionnaire for Hip and Knee OA

Post-text Table 12: provides the analysis of absolute change from baseline in improvement in mobility as evaluated by WOMAC subscales of stiffness and physical function at end of week 3 as compared to baseline (Day 0 / Visit 2) for Per-Protocol Population.

Table 25 provides the analysis of absolute change from baseline in improvement in mobility as evaluated by WOMAC subscales of stiffness and physical function at end of week 4 as compared to baseline (Day 0 / Visit 2) for modified intention-to-treat population.

The LS mean difference obtained for the treatment comparison of Arthronat and placebo at week 4 was -0.111. The p-value of 0.5346 indicates that there was no significant difference in absolute change from baseline in improvement in mobility as evaluated by WOMAC subscales of stiffness at end of week 4 as compared to baseline (Day 0 / Visit 2) between the treatments.

The LS mean difference obtained for the treatment comparison of Arthronat and placebo at week 4 was -1.746. The p-value of 0.0958 indicates that there was no significant difference in absolute change from baseline in improvement in mobility as evaluated by WOMAC subscales of physical function at end of week 4 as compared to baseline (Day 0 / Visit 2) between the treatments.

Table 25: Analysis of absolute change from baseline in improvement in mobility as evaluated by WOMAC subscales of stiffness and physical function at end of week 4 as compared to Baseline (Day 0 / Visit 2) (MITT population)

		Treatment A			Treatment B			Absolute change from baseline					
Visit	**Subscale**	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	**Stiffness**	40	3.1	0.74	39	3.2	0.99	0.0	0.94	-0.111	(-0.453,0.230)	0.5176	0.5346
Week 4		40	3.1	0.69	39	3.2	0.92			.		.	.
Baseline	**Physical Function**	40	26.8	3.88	39	26.7	4.29	0.6	4.43	-1.746	(-3.030,-0.462)	0.0084	0.0958
Week 4		40	26.5	3.39	39	28.2	2.42			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: WOMAC Index Questionnaire for Hip and Knee OA

Post-text Table 13: provides the analysis of absolute change from baseline in improvement in mobility as evaluated by WOMAC subscales of stiffness and physical function at end of week 4 as compared to baseline (Day 0 / Visit 2) for Per-Protocol Population.

11.4.1.3 Analysis of WOMAC total score

WOMAC mean total scores reduced more in Arthronat group compared to placebo which infers that there was more improvement in WOMAC total score in the Arthronat group from the baseline compared to Placebo at the end of the study at Week 4 (Visit 6).The mean WOMAC total score at baseline was 37.9 and 37.7 in Arthronat and Placebo group respectively and end of the study at visit 6 was 37.2 and 39.5 in Arthronat and Placebo group respectively. Please refer to Section 9.5.1 of the protocol in for more details on WOMAC total score.

The summary of WOMAC total score by visit for MITT population is provided in **Table 26**. Mean Percentage change in WOMAC index Total-Score from baseline is provided in **Table 27** and **Figure 6**.

Post-text Table 14: provides the Summary of WOMAC total score by visit for Per-Protocol Population**.**

Table 26: Summary of WOMAC total score (MITT population)

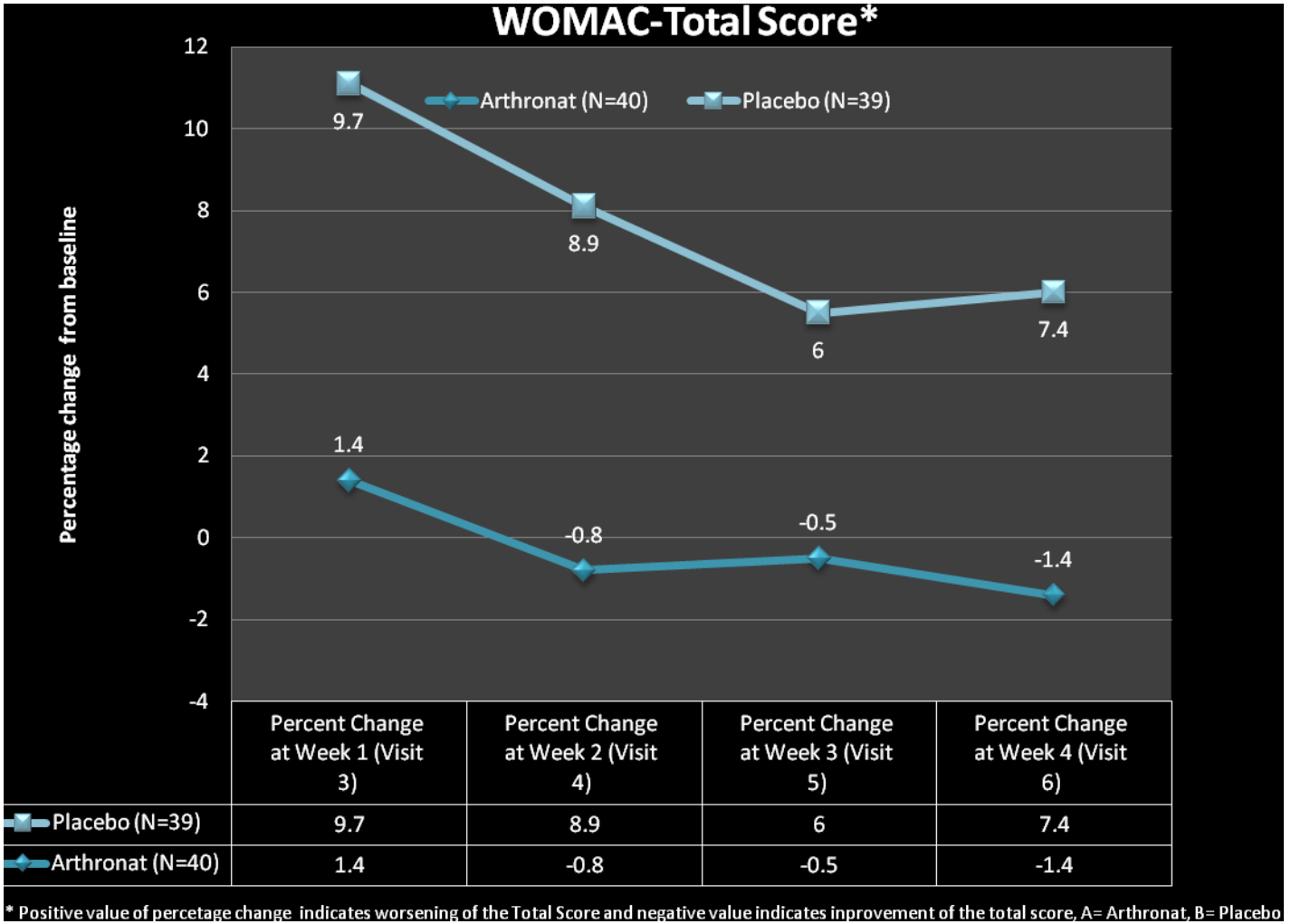
Visit	Categories	Treatment A (N=40)	Treatment B (N=39)
Screening	N	40	39
	Mean	36.7	36.8
	SD	2.72	3.54
	Median	37.0	37.0
	Minimum	30.0	23.0
	Maximum	42.0	43.0
Baseline	N	40	39
	Mean	37.9	37.7
	SD	4.44	5.45
	Median	37.0	38.0
	Minimum	27.0	23.0
	Maximum	47.0	49.0
Visit 3	N	40	39
	Mean	38.2	40.6
	SD	4.22	4.20
	Median	37.0	39.0
	Minimum	30.0	33.0
	Maximum	52.0	50.0
Visit 4	N	40	39
	Mean	37.3	40.1
	SD	4.15	4.54
	Median	37.0	39.0
	Minimum	26.0	32.0
	Maximum	49.0	52.0
Visit 5	N	40	39
	Mean	37.4	39.0
	SD	4.49	4.62

Visit	Categories	Treatment A (N=40)	Treatment B (N=39)
	Median	36.5	38.0
	Minimum	28.0	29.0
	Maximum	49.0	49.0
Visit 6	N	40	39
	Mean	37.2	39.5
	SD	4.92	3.85
	Median	37.0	39.0
	Minimum	24.0	35.0
	Maximum	49.0	49.0
Treatment A: Arthronat Treatment B: Placebo Source Listing: WOMAC Index Questionnaire for Hip and Knee OA			

Table 27 : Mean Percentage change in WOMAC index Total-Score from baseline

WOMAC SCORES		
Percent Change at Week 1 (Visit 3)	1.4	9.7
Percent Change at Week 2 (Visit 4)	-0.8	8.9
Percent Change at Week 3 (Visit 5)	-0.5	6
Percent Change at Week 4 (Visit 6)	-1.4	7.4
Positive values for percentage change indicate worsening of pain/stiffness and physical function and negative values indicate improvement of pain/stiffness and physical function Source: Table WOMAC PCT_MITT		

Figure 6: Percentage change in WOMAC index sub-scales of Total-score from baseline



	Percent Change at Week 1 (Visit 3)	Percent Change at Week 2 (Visit 4)	Percent Change at Week 3 (Visit 5)	Percent Change at Week 4 (Visit 6)
Placebo (N=39)	9.7	8.9	6	7.4
Arthronat (N=40)	1.4	-0.8	-0.5	-1.4

* Positive value of percetage change indicates worsening of the Total Score and negative value indicates inprovement of the total score, A= Arthronat, B= Placebo

Table 28 provides the analysis of absolute change from baseline in WOMAC total score at end of week 1 as compared to Baseline (Day 0 / Visit 2) for modified intention-to-treat population.

The LS mean difference obtained for the treatment comparison of Arthronat and placebo at week 1was -2.438. The p-value of 0.0029 indicates that there was a significant difference in absolute change from baseline in WOMAC total score at end of week 1 as compared to baseline (Day 0 / Visit 2) between the treatments.

Table 28: Analysis of absolute change from baseline in WOMAC total score at end of week 1 as compared to baseline (Day 0 / Visit 2) (MITT population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	37.9	4.44	39	37.7	5.45	1.5	5.04	-2.438	(-4.148,-0.728)	0.0058	0.0029
Week 1	40	38.2	4.22	39	40.6	4.20			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: WOMAC Index Questionnaire for Hip and Knee OA

Post-text Table 15: provides the analysis of absolute change from baseline in WOMAC total score at end of week 1 as compared to baseline (Day 0 / Visit 2) for Per-Protocol Population.

Table 29 provides the analysis of absolute change from baseline in WOMAC total score at end of week 2 as compared to Baseline (Day 0 / Visit 2) for modified intention-to-treat population.

The LS mean difference obtained for the treatment comparison of Arthronat and placebo at week 2 was -2.804. The p-value of 0.0522 indicates that there was no significant difference in absolute change from baseline in WOMAC total score at end of week 2 as compared to Baseline (Day 0 / Visit 2) between the treatments.

Table 29: Analysis of absolute change from baseline in WOMAC total score at end of week 2 as compared to Baseline (Day 0 / Visit 2) (MITT population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	37.9	4.44	39	37.7	5.45	0.9	5.93	-2.804	(-4.710,-0.898)	0.0045	0.0522
Week 2	40	37.3	4.15	39	40.1	4.54			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: WOMAC Index Questionnaire for Hip and Knee OA

Post-text Table 16: provides the analysis of absolute change from baseline in WOMAC total score at end of week 2 as compared to baseline (Day 0 / Visit 2) for Per-Protocol Population.

Table 30 provides the analysis of absolute change from baseline in WOMAC total score at end of week 3 as compared to Baseline (Day 0 / Visit 2) for modified intention-to-treat population.

The LS mean difference obtained for the treatment comparison of Arthronat and placebo at week 3 was -1.571 for the treatment comparison of Arthronat and placebo. The p-value of 0.2816 indicates that there was no significant difference in absolute change from baseline in WOMAC total score at end of week 3 as compared to Baseline (Day 0 / Visit 2) between the treatments.

Table 30: Analysis of absolute change from baseline in WOMAC total score at end of week 3 as compared to baseline (Day 0 / Visit 2) (MITT population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	37.9	4.44	39	37.7	5.45	0.4	6.11	-1.571	(-3.591,0.449)	0.1254	0.2816
Week 3	40	37.4	4.49	39	39.0	4.62			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: WOMAC Index Questionnaire for Hip and Knee OA

Post-text Table 17: provides the analysis of absolute change from baseline in WOMAC total score at end of week 3 as compared to baseline (Day 0 / Visit 2) for Per-Protocol Population.

Table 31 provides the analysis of analysis of absolute change from baseline in WOMAC total score at end of week 4 as compared to Baseline (Day 0 / Visit 2) for modified intention-to-treat population.

The LS mean difference obtained for the treatment comparison of Arthronat and placebo at week 4 was -2.371. The p-value of 0.0767 indicates that there was no significant difference in absolute change from baseline in WOMAC total score at end of week 4 as compared to Baseline (Day 0 / Visit 2) between the treatments.

Table 31: Analysis of absolute change from baseline in WOMAC total score at end of week 4 as compared to Baseline (Day 0 / Visit 2) (MITT population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	37.9	4.44	39	37.7	5.45	0.5	5.73	-2.371	(-4.285,-0.458)	0.0158	0.0767
Week 4	40	37.2	4.92	39	39.5	3.85			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: WOMAC Index Questionnaire for Hip and Knee OA

Post-text Table 18: provides the analysis of absolute change from baseline in WOMAC total score at end of week 4 as compared to Baseline (Day 0 / Visit 2) for Per-Protocol Population.

11.4.1.4 Analysis of Responders (defined as at least 70% pain relief as compared to Baseline)

One subject in Arthronat group had more than 70% pain relief at Week 2 as compared to Baseline.

No subject had at least 70% pain relief at Week 1 as compared to Baseline, at Week 3 as compared to Baseline and at Week 4 as compared to Baseline.

Since there were no subject with at least 70% pain relief in Placebo group, analysis within both the groups could not be made.

11.4.1.5 Analysis of SF – 36 score

SF – 36 questionnaires was a self administered questionnaire used in the study that measured the following 8 health concepts: physical functioning, role limitations due to physical problems, social functioning, bodily pain, mental health and role limitations due to emotional problems, vitality and general health perception. Higher scores represented well-being of the subject. Please refer to Section 9.5.1 and APPENDIX VI of the protocol in for more details on SF – 36 questionnaires.

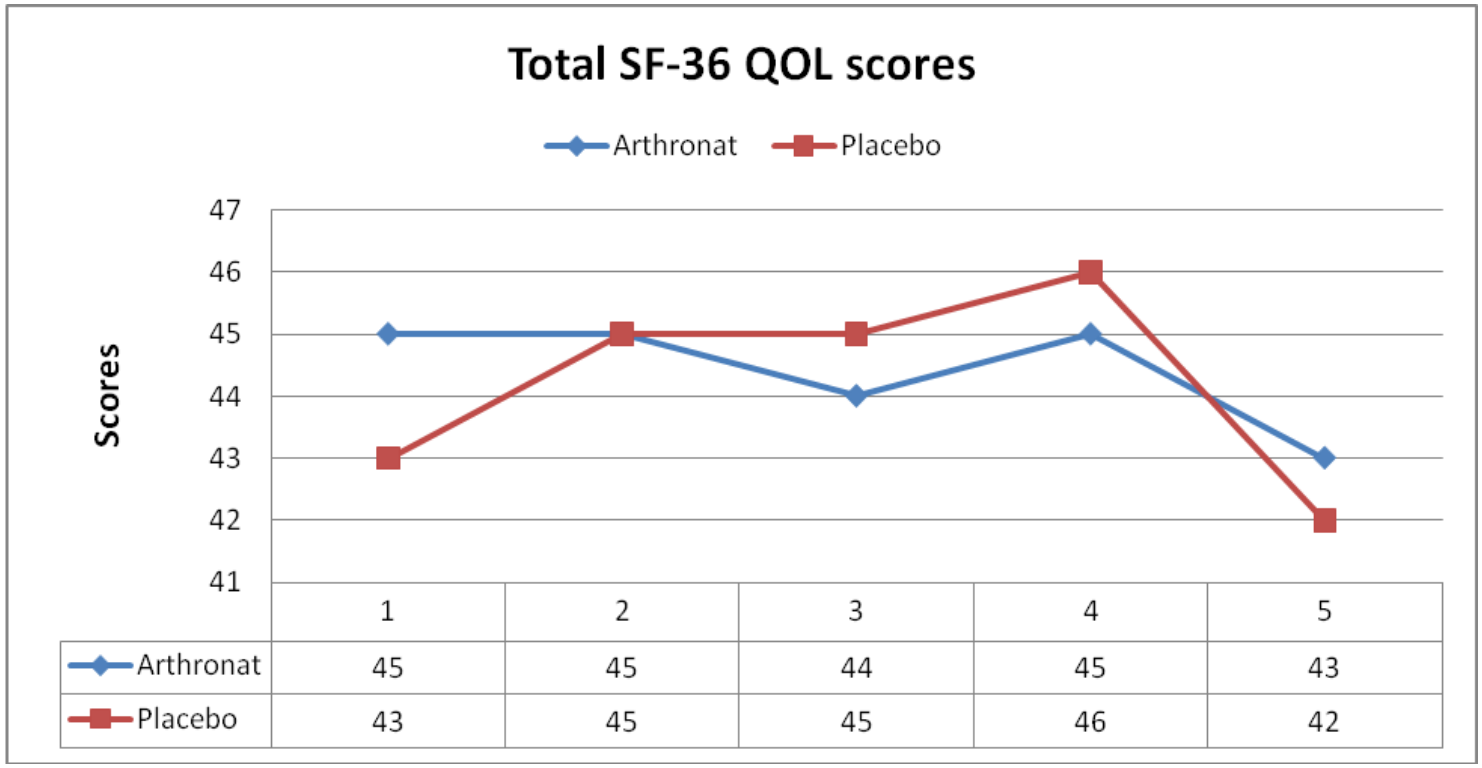
There was no clear pattern shown in the Total SF-36 scores between Arthronat and Placebo groups during the study from Baseline to end of the study at Week 4. The SF-36 scores were similar in both the groups. However the Physical and Mental health scores in the Arthronat group were found to be slightly higher than the placebo group at the end of the study at Week 4.

Summary and comparison of Total SF-36 scores are provided in **Table 32**, **Table 33**, **Figure 7** and **Figure 8**.

Table 32 : Summary of SF-36 scores scales between Arthronat and Placebo group at Baseline, Week 1, 2, 3 and 4.

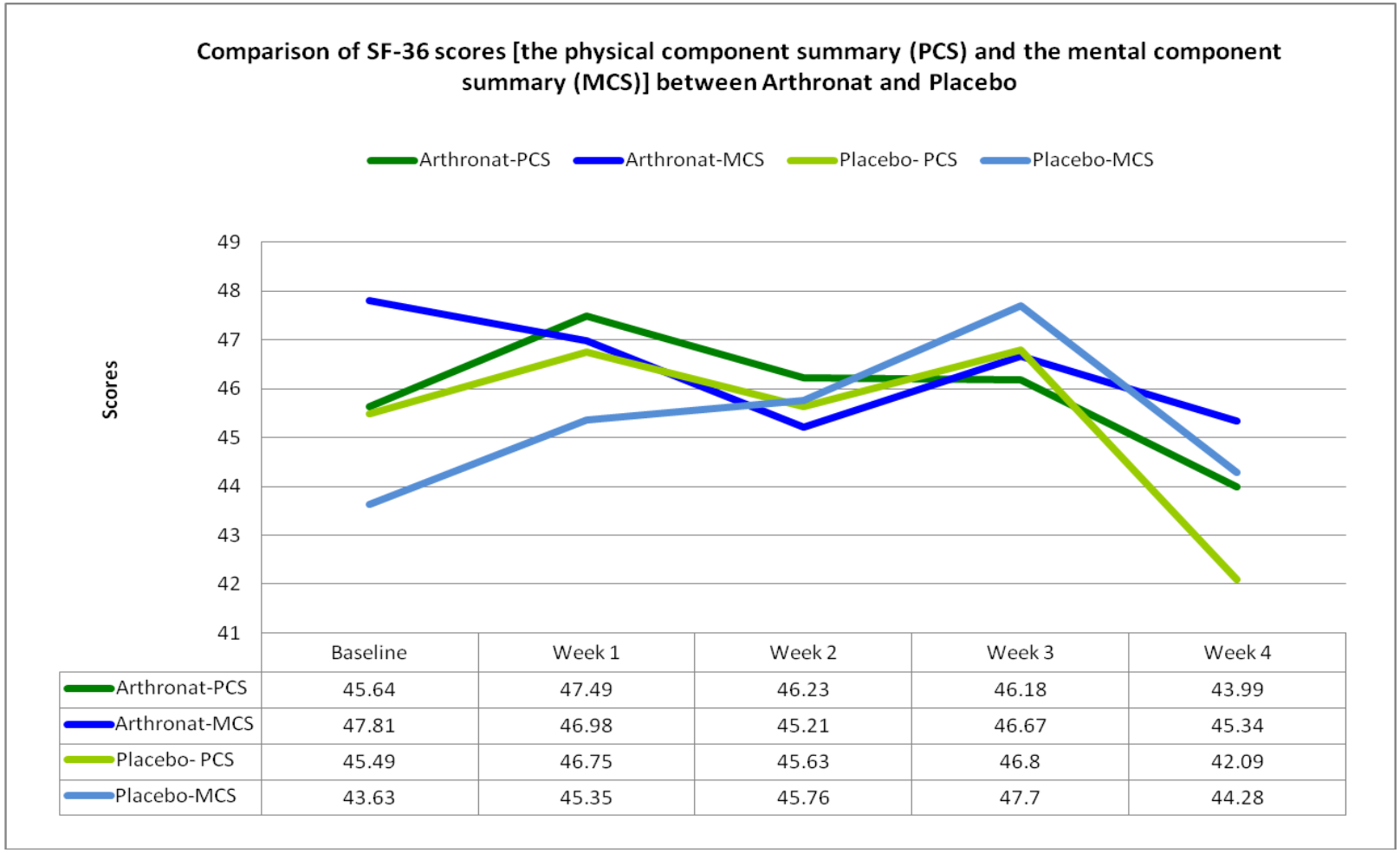
SF-36 SCORES													
Groups	**Week**	**Physical Function**	**Role-Physical**	**Body Pain**	**General Health**	**Vitality**	**Social Functioning**	**Role Emotional**	**Mental Health**	**Reported Health**	**Physical Health**	**Mental Health**	**TOTAL SF-36 Score**
Arthronat	Baseline	47.31	40.94	36.25	50.1	53.63	50	34.17	51.15	27.5	45.646	47.81	**45**
	Week 1	47.56	43.75	37.5	51.55	57.13	45.75	29.17	51.3	27.5	47.498	46.98	**45**
	Week 2	47.88	43.13	32.5	51.15	56.5	46.5	21.67	50.23	26.25	46.232	45.21	**44**
	Week 3	47.81	40.31	35	52.55	55.25	53.75	22.5	49.28	52.55	46.184	46.666	**45**
	Week 4	46.81	39.06	27.5	53.23	53.38	49	21.67	49.43	25.63	43.996	45.342	**43**
Placebo	Baseline	47.69	45.63	36.25	49.53	48.38	41.25	30	49	27.5	45.496	43.632	**43**
	Week 1	48.63	43.44	38.75	51.58	51.38	45.75	30.83	47.25	26.25	46.756	45.358	**45**
	Week 2	47.63	40.94	38.75	50.7	50.13	43.5	35	49.48	27.5	45.63	45.762	**45**
	Week 3	47.38	41.25	41.25	52.75	51.38	46.75	39.17	48.5	27.5	46.802	47.71	**46**
	Week 4	45.25	39.38	26.25	52.08	47.5	45.75	30.83	45.28	27.5	42.092	44.288	**42**

Figure 7 : Total SF-36 Scores between Arthronat and Placebo group during the study



	1	2	3	4	5
Arthronat	45	45	44	45	43
Placebo	43	45	45	46	42

Figure 8: Comparison of SF-36 scores [the physical component summary (PCS) and the mental component summary (MCS)] between Arthronat and Placebo



	Baseline	Week 1	Week 2	Week 3	Week 4
Arthronat-PCS	45.64	47.49	46.23	46.18	43.99
Arthronat-MCS	47.81	46.98	45.21	46.67	45.34
Placebo- PCS	45.49	46.75	45.63	46.8	42.09
Placebo-MCS	43.63	45.35	45.76	47.7	44.28

Table 33 : Summary of mean percent change from baseline of SF-36 score by various scale

SUMMARY OF MEAN PERCENT CHANGE FROM BASELINE OF SF-36 SCORE BY VARIOUS SCALE			
Scale	Visit	Treatment A	Treatment B
Physical Functioning	Week 1 (Visit 3)	1.76	5.25
	Week 2 (Visit 4)	2.57	3.32
	Week 3 (Visit 5)	2.35	3.72
	Week 4 (Visit 6)	0.57	-0.47
Physical Health	Week 1 (Visit 3)	13.83	1.24
	Week 2 (Visit 4)	12.44	-2.70
	Week 3 (Visit 5)	3.65	-0.70
	Week 4 (Visit 6)	3.75	-5.50
Emotional Problems	Week 1 (Visit 3)	-30.00	1.28
	Week 2 (Visit 4)	-48.00	3.85
	Week 3 (Visit 5)	-44.00	16.03
	Week 4 (Visit 6)	-48.00	-8.33
Energy/Fatigue	Week 1 (Visit 3)	20.55	12.49
	Week 2 (Visit 4)	19.94	13.47
	Week 3 (Visit 5)	17.79	14.91
	Week 4 (Visit 6)	15.73	7.02
Emotional Well-being	Week 1 (Visit 3)	1.31	-2.05
	Week 2 (Visit 4)	-0.73	4.13
	Week 3 (Visit 5)	-2.23	1.57
	Week 4 (Visit 6)	-2.04	-4.51
Social Functioning	Week 1 (Visit 3)	14.64	22.46
	Week 2 (Visit 4)	26.62	17.51
	Week 3 (Visit 5)	39.91	28.72
	Week 4 (Visit 6)	29.58	35.20
Pain	Week 1 (Visit 3)	-13.64	-11.90
	Week 2 (Visit 4)	-22.73	-11.90
	Week 3 (Visit 5)	-25.00	-28.57
	Week 4 (Visit 6)	-47.73	-57.14
General Health	Week 1 (Visit 3)	4.34	7.54
	Week 2 (Visit 4)	3.95	5.85
	Week 3 (Visit 5)	7.02	9.97
	Week 4 (Visit 6)	8.04	8.73
Health Change	Week 1 (Visit 3)	1.25	-3.95
	Week 2 (Visit 4)	-1.25	0.00
	Week 3 (Visit 5)	1.25	1.32
	Week 4 (Visit 6)	-2.50	-2.63
Treatment A: Arthronat **Treatment B: Placebo** **Source Listing: SF-36 Quality of Life Questionnaire**			

Table 34 provides the analysis of absolute change from baseline to the end of week 1 in SF – 36 score for modified intention-to-treat population.

The LS mean difference obtained for the treatment comparison of Arthronat and placebo at week 1was -0.145. The p-value of 0.9109 indicated that there was no significant difference in absolute change from baseline to the end of week 1 in SF – 36 score between the treatments.

Table 34: Analysis of absolute change from baseline to the end of week 1 in (SF-36 score) (MITT population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	46.1	8.95	40	44.9	8.90	0.6	6.03	-0.145	(-2.718,2.428)	0.9109	0.5668
Week 1	40	46.5	8.42	40	45.8	9.53			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: SF-36 Quality of Life Questionnaire

Post-text Table 19: provides the analysis of absolute change from baseline to the end of week 1 in SF – 36 score for Per-Protocol Population.

Table 35 provides the analysis of absolute change from baseline to the end of week 2 in SF –36 score for modified intention-to-treat population.

The LS mean difference obtained for the treatment comparison of Arthronat and placebo at week 2 was -0.921. The p-value of 0.4869 indicates that there was no significant difference in absolute change from baseline to the end of week 2 in SF – 36 score between the treatments.

Table 35: Analysis of absolute change from baseline to the end of week 2 in (SF-36 score) (MITT population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	46.1	8.95	40	44.9	8.90	-0.1	6.54	-0.921	(-3.546,1.704)	0.4869	0.5036
Week 2	40	45.4	8.24	40	45.5	8.46			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: SF-36 Quality of Life Questionnaire

Post-text Table 20: provides the analysis of absolute change from baseline to the end of week 2 in SF – 36 score for Per-Protocol Population.

Table 36 provides the analysis of absolute change from baseline to the end of week 3 in SF – 36 score for modified intention-to-treat population.

The LS mean difference obtained for the treatment comparison of Arthronat and placebo at week 3 was -1.653. The p-value of 0.2482 indicates that there was no significant difference in absolute change from baseline to the end of week 3 in SF – 36 score between the treatments.

Table 36: Analysis of absolute change from baseline to the end of week 3 in (SF-36 score) (MITT population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	46.1	8.95	40	44.9	8.90	0.5	6.88	-1.653	(-4.482,1.176)	0.2482	0.1906
Week 3	40	45.6	8.92	40	46.4	8.79			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: SF-36 Quality of Life Questionnaire

Post-text Table 21: provides the analysis of absolute change from baseline to the end of week 3 in SF – 36 score for Per-Protocol Population.

Table 37 provides the analysis of absolute change from baseline to the end of week 4 in SF – 36 score for modified intention-to-treat population.

The LS mean difference obtained for the treatment comparison of Arthronat and placebo at week 4was 0.709. The p-value of 0.6246 indicates that there was no significant difference in absolute change from baseline to the end of week 4 in SF – 36 score between the treatments.

Table 37: Analysis of absolute change from baseline to the end of week 4 in (SF-36 score) (MITT population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	46.1	8.95	40	44.9	8.90	-1.8	8.08	0.709	(-2.166,3.585)	0.6246	0.8024
Week 4	40	44.3	8.74	40	43.1	6.02			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: SF-36 Quality of Life Questionnaire

Post-text Table 22: provides the analysis of absolute change from baseline to the end of week 4 in SF – 36 score for Per-Protocol Population.

11.4.1.6 Analysis of Subject Global Assessment of Osteoarthritis

Subject Global Assessment of osteoarthritis is a self – administered scale which was completed by the subject during each study visit (Screening, Baseline, Visit 3, Visit 4, Visit 5 and Visit 6). The subject had to assess on a scale of 1 (indicates 'Very good') to 5 (indicates 'Very poor') as to how severe the OA symptoms are and the severity of limitation of activities due to OA. Please refer to Section 9.5.1 and APPENDIX VIII of the protocol for more details on Subject Global Assessment of osteoarthritis.

Subject Global Assessment of Osteoarthritis mean scores were found to be reduced in the Arthronat group compared to placebo which infers that the Subject Global Assessment of Osteoarthritis scores more improved in Arthronat group from the baseline compared to Placebo.

Table 38 and **Figure 9** provides information on Analysis of absolute change from baseline to the end of week 1, 2, 3 and 4 in Subject Global Assessment of Osteoarthritis.

Table 38: Analysis of absolute change from baseline to the end of week 1, 2, 3 and 4 in Subject Global Assessment of Osteoarthritis

SUBJECT GLOBAL ASSESSMENT OF OSTEOARTHRITIS MEAN SCORES		
Visit	**Arthronat**	**Placebo**
Baseline	3.03	3.05
Week 1	3	3
Week 2	2.95	2.98
Week 3	2.95	3
Week 4	2.98	3
Scale : 1 indicates very good; 5 indicates very poor		

Figure 9: Analysis of absolute change from baseline to the end of week 1, 2, 3 and 4 in Subject Global Assessment of Osteoarthritis

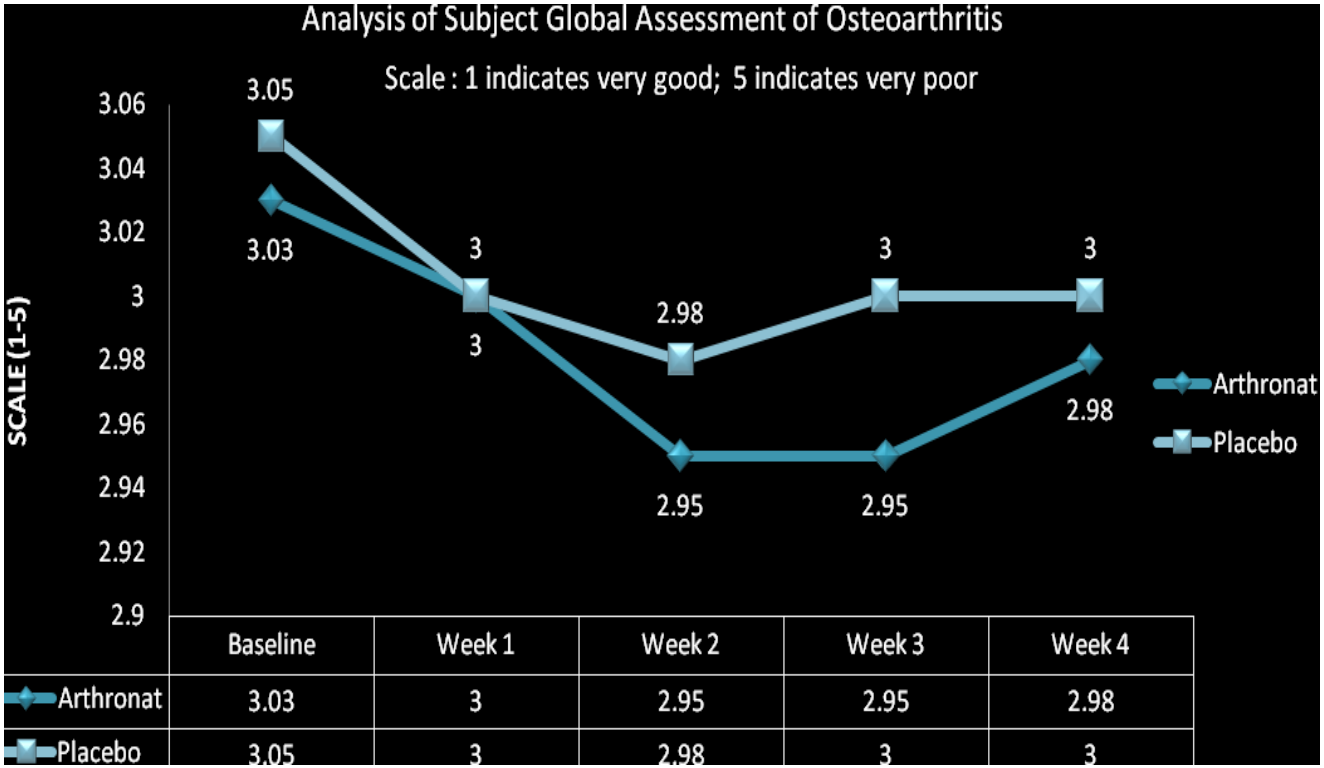


Table 39 provides the analysis of absolute change from baseline to the end of week 1 in Subject Global Assessment of Osteoarthritis for modified intention-to-treat population.

The LS mean difference obtained for the treatment comparison of Arthronat and placebo at week 1was 0.009. The p-value of 0.5536 indicates that there was no significant difference in absolute change from baseline to the end of week 1 in Subject Global Assessment of Osteoarthritis between the treatments.

Table 39: Analysis of absolute change from baseline to the end of week 1 in Subject Global Assessment of Osteoarthritis (MITT population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	3.03	0.158	40	3.05	0.221	-0.04	0.192	0.009	(-0.057,0.075)	0.7840	0.5536
Week 1	40	3.00	0.000	39	3.00	0.229			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: Subject Global Assessment for OA

Post-text Table 23: provides the analysis of absolute change from baseline to the end of week 1 in Subject Global Assessment of Osteoarthritis for Per-Protocol Population.

Table 40 provides the analysis of absolute change from baseline to the end of week 2 in Subject Global Assessment of Osteoarthritis for modified intention-to-treat population.

The LS mean difference obtained for the treatment comparison of Arthronat and placebo at week 2 was -0.025. The p-value of -0.025 indicates that there was no significant difference in absolute change from baseline to the end of week 2 in Subject Global Assessment of Osteoarthritis between the treatments.

Table 40: Analysis of absolute change from baseline to the end of week 2 in Subject Global Assessment of Osteoarthritis (MITT population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	3.03	0.158	40	3.05	0.221	-0.08	0.267	-0.025	(-0.113,0.062)	0.5634	0.9830
Week 2	39	2.95	0.223	40	2.98	0.158			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: Subject Global Assessment for OA

Post-text Table 24: provides the analysis of absolute change from baseline to the end of week 2 in Subject Global Assessment of Osteoarthritis for Per-Protocol Population.

Table 41 provides the analysis of absolute change from baseline to the end of week 3 in Subject Global Assessment of Osteoarthritis for modified intention-to-treat population.

The LS mean difference obtained for the treatment comparison of Arthronat and placebo at week 3 was -0.051. The p-value of 0.6336 indicates that there was no significant difference in absolute change from baseline to the end of week 3 in Subject Global Assessment of Osteoarthritis between the treatments.

Table 41: Analysis of absolute change from baseline to the end of week 3 in Subject Global Assessment of Osteoarthritis (MITT population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	3.03	0.158	40	3.05	0.221	-0.06	0.245	-0.051	(-0.122,0.020)	0.1575	0.6336
Week 3	39	2.95	0.223	40	3.00	0.000			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: Subject Global Assessment for OA

Post-text Table 25: provides the analysis of absolute change from baseline to the end of week 3 in Subject Global Assessment of Osteoarthritis for Per-Protocol Population.

Table 42 provides the analysis of absolute change from baseline to the end of week 4 in Subject Global Assessment of Osteoarthritis for modified intention-to-treat population.

The LS mean difference obtained for the treatment comparison of Arthronat and placebo at week 4 was -0.025.The p-value of 1.0000 indicates that there is no significant difference in absolute change from baseline to the end of week 1 in Subject Global Assessment of Osteoarthritis between the treatments.

Table 42: Analysis of absolute change from baseline to the end of week 4 in Subject Global Assessment of Osteoarthritis (MITT population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	3.03	0.158	40	3.05	0.221	-0.05	0.219	-0.025	(-0.075,0.025)	0.3287	1.0000
Week 4	40	2.98	0.158	40	3.00	0.000			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: Subject Global Assessment for OA

Post-text Table 26: provides the analysis of absolute change from baseline to the end of week 4 in Subject Global Assessment of Osteoarthritis for PP Population.

11.4.1.7 Analysis of OMERACT-OARSI

OMERACT – OARSI responder index used in the study is two sets of responder criteria to present the results of changes from baseline in three symptomatic domains (WOMAC Pain subscale, WOMAC Physical function subscale, and Subject's Global Assessment of osteoarthritis). Please refer to Section 9.5.1 and APPENDIX IX of the protocol in for more details on OMERACT – OARSI responder index.

Percentage of Responders according to OMERACT-OARSI Responder Index at Week 1, 2, 3 and 4 were higher in Arthronat group compared to Placebo.At week 1, there were 39 (97.5%) responders in Arthronat group as compared to 27 (67.5%) responders in placebo group. At week 2, there were 40 (100.0%) responders in Arthronat group as compared to 26 (65.0%) responders in placebo group. At week 3, there were 39 (97.5%) responders in Arthronat group as compared to 28 (70.0%) responders in placebo group. At week 4, there were 39 (97.5%) responders in Arthronat group as compared to 30 (75.0%) responders in placebo group.

Percentage of responders and non-responders according to OMERACT-OARSI Responder Index at Week 1, 2, 3 and 4 is provided in **Table 43**.

Post-text Table 27, **Post-text Table 28**, **Post-text Table 29** and **Post-text Table 30** provides number and percentage of Responders and Non-Responders according to OMERACT-OARSI Responder Index at each visit as compared to baseline visit for at Week 1,2,3and 4 respectively for MITT population.

Post-text Table 31, **Post-text Table 32**, **Post-text Table 33** and **Post-text Table 34** provided the Number (and Percentage) of Responders and Non-Responders according to OMERACT-OARSI Responder Index at week 1, 2, 3 and 4 respectively in the PP Population.

Table 43: Percentage of responders and non-responders according to OMERACT-OARSI Responder Index at Week 1, 2, 3 and 4

PERCENTAGE OF RESPONDERS AND NON-RESPONDERS			
Visit	**Responders/Non-Responders**	**Arthronat**	**Placebo**
Week 1	Responders	97.5	67.5
	Non-Responders	2.5	32.5
Week 2	Responders	100	65
	Non-Responders	0	35
Week 3	Responders	97.5	70
	Non-Responders	2.5	30
Week 4	Responders	97.5	75
	Non-Responders	2.5	25
Source Listing: OMERACT-OARSI Responder Index			

Figure 8: Percentage of Responders according to OMERACT-OARSI Responder Index at Week 1, 2, 3 and 4

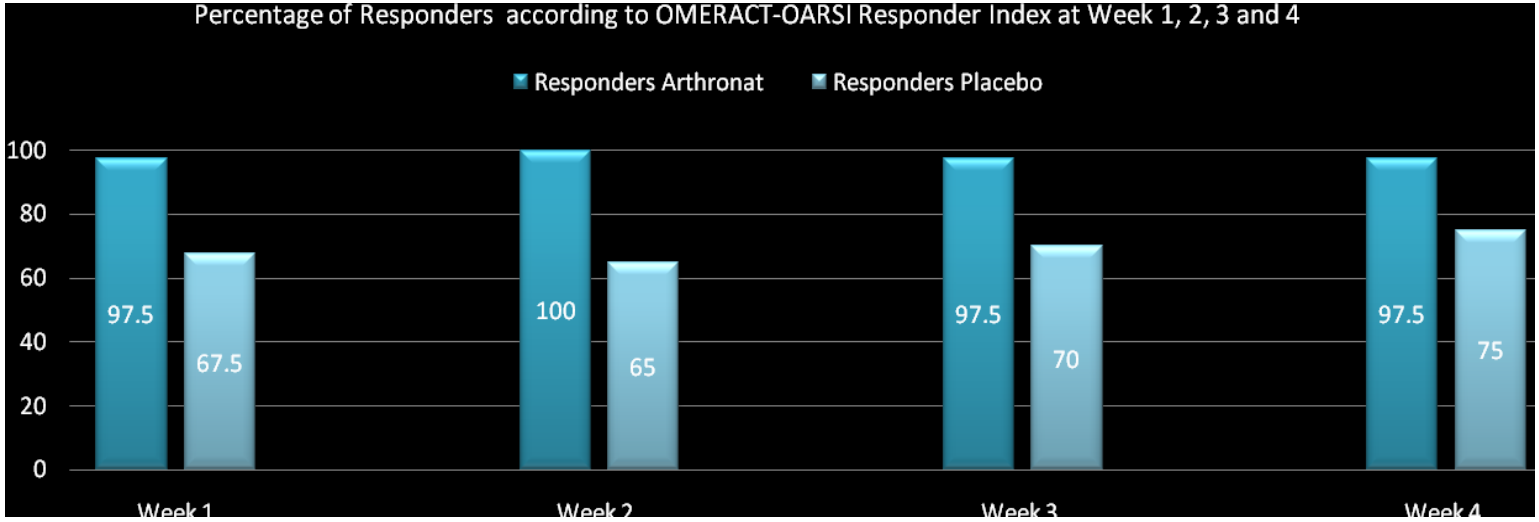
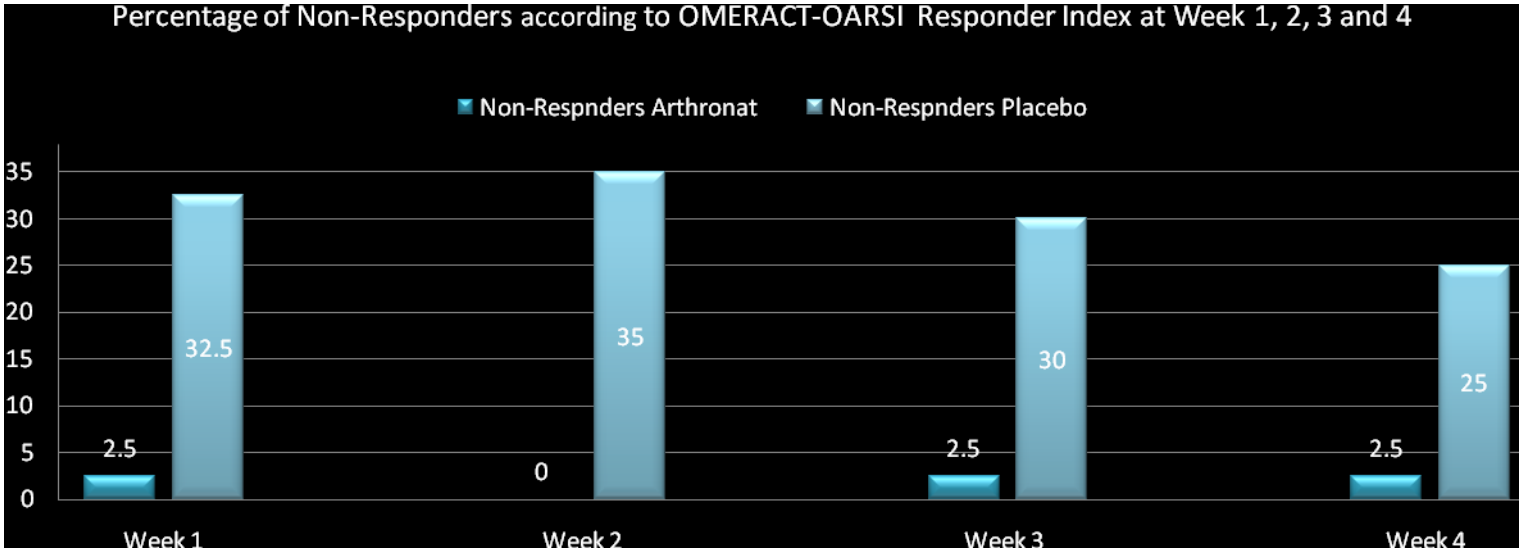


Figure 9: Percentage of Non - Responders according to OMERACT-OARSI Responder Index at Week 1, 2, 3 and 4



11.4.1.8 Analysis of subjects who used rescue medication

All the subjects in the study used only the first line of rescue medication i.e. Paracetamol (Tablet Dolo 500mg). Since all the subjects experienced adequate pain relief with the first line rescue medication, none of the subjects required Ibuprofen (second line) as the rescue medication in the study. The rescue medication was discontinued at least 48 hrs prior to any study assessment visits.

Subjects in the treatment arms, Arthonat and placebo were comparable in terms of NSAIDs usage prior to the enrolment in the study and most of the subjects were on potent NSAIDs. The most commonly used NSAIDs included Galenic (combination of Ibuprofen/Paracetamol) by 15(37.5%) and 8(20%), Aceclofenac by 8(20%) and 9(22.5%), Diclofenac sodium by 7(17.5%) and 9(22.5%) subjects and Aceclo Plus by 6(15%) and 9(22.5%) subjects in Arthonat and placebo groups respectively. An appropriate wash-out was given for the NSAIDs medications as per Appendix III of the protocol. Other than the rescue medication use of NSAIDs was prohibited during the study. For more details on prior medication please refer **Table 12**.

Total number of tablets of rescue medication (paracetamol) consumed at each visit was lesser in Arthronat group (273) compared to Placebo (407) and reduced consistently from baseline to Week 4.

Summary of total number of tablets of rescue medication (Paracetamol) consumed in each visit in both the treatment arms in MITT Population is provided in **Table 44.** Summary on number of tablets of rescue medication consumed in each visit by categories in MITT Population is provided in **Table 45**.

Post-text Table 35, **Post-text Table 36**, **Post-text Table 37** and **Post-text Table 38** provide analysis of number of subjects who used rescue medication at week1, week 2, week 3 and week 4 for MITT population. **Post-text Table 39**, **Post-text Table 40**, **Post-text Table 41** and **Post-text Table 42** provide analysis of number of subjects who used rescue medication at week1, week 2, week 3 and week 4 for PP population. **Post-text Table 43** provides summary of total number of tablets of rescue medication (Paracetamol) consumed in each visit in both the treatment arms in PP Population and **Post-text Table 44** provides Summary on number of tablets of rescue medication consumed in each visit by categories in PP population.

Table 44: Summary of total number of tablets of rescue medication (Paracetamol) consumed in each visit in both the treatment arms (MITT Population)

TOTAL NUMBER OF RESCUE MEDICATION CONSUMED IN EACH VISIT		
Visit	**Treatment A**	**Treatment B**
Baseline	380	465
Week 1 (V3)	331	402
Week 2 (V4)	317	401
Week 3 (V5)	287	385
Week 4 (V6)	273	407
Treatment A: Arthronat **Treatment B: Placebo** **Source Listing: Rescue Medications Dispensing and Retrieval**		

Figure 10: Total number of rescue medication consumed in each visit

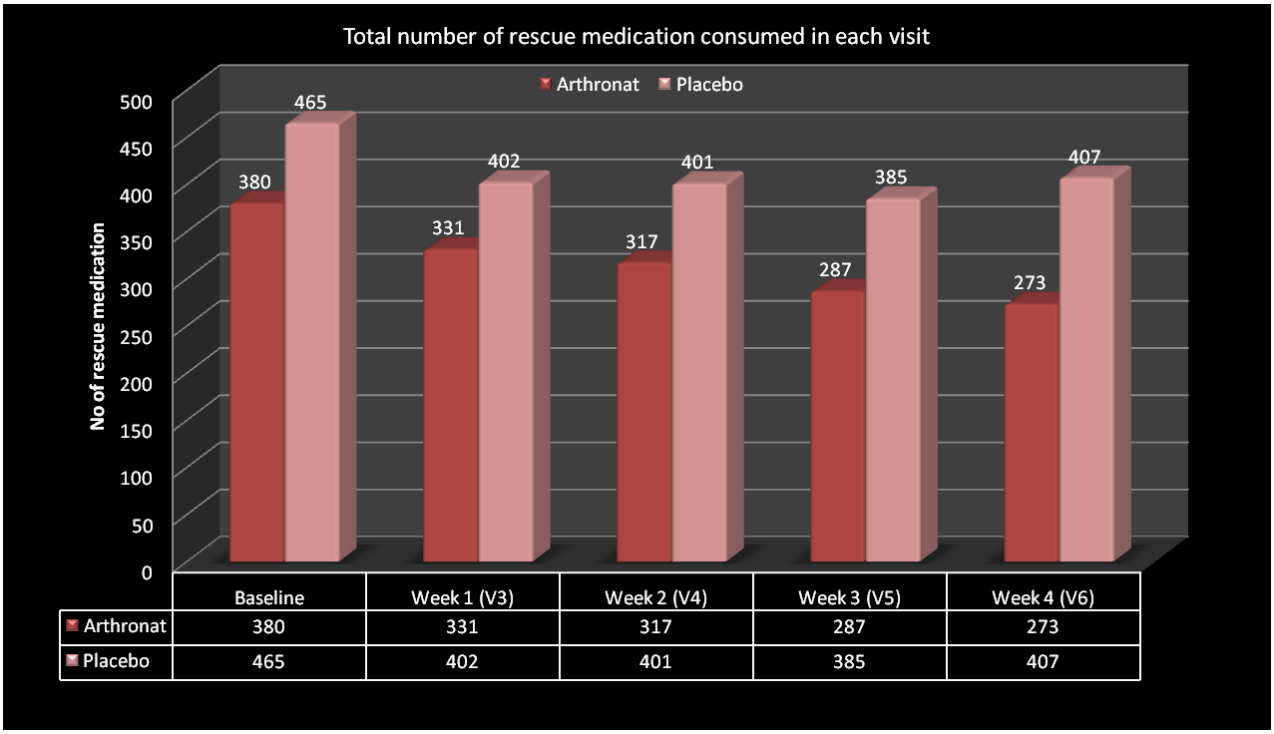


Table 45: Summary on number of tablets of rescue medication consumed in each visit by categories (MITT Population)

NUMBER OF TABLETS OF RESCUE MEDICATION CONSUMED IN EACH VISIT BY CATEGORIES					
		Treatment A (N=40)		Treatment B (N=40)	
Visit	**Number of tablets**	**n**	**%**	**n**	**%**
Baseline	0-5	6	15.0	2	5.0
	6-10	17	42.5	12	30.0
	11-15	17	42.5	26	65.0
Week 1 (V3)	0-5	10	25.0	3	7.5
	6-10	19	47.5	19	47.5
	11-15	11	27.5	18	45.0
Week 2 (V4)	0-5	10	25.0	5	12.5
	6-10	25	62.5	19	47.5
	11-15	5	12.5	16	40.0
Week 3 (V5)	0-5	11	27.5	5	12.5
	6-10	25	62.5	20	50.0
	11-15	4	10.0	15	37.5
Week 4 (V6)	0-5	14	35.0	2	5.0
	6-10	22	55.0	22	55.0
	11-15	4	10.0	16	40.0
Treatment A: Arthronat **Treatment B: Placebo** **Source Listing: Rescue Medications Dispensing and Retrieval**					

Table 46 provides analysis of number of days of rescue medication use at each visit between treatments for MITT population.

The p-value of 0.1647, 0.2776, and 0.0820 indicates that there was no significant difference in number of days of rescue medication use between the treatments at baseline, week 1 and week 2 respectively.

The p-value of 0.0062 and 0.0007 indicates that there was a significant difference in number of days of rescue medication use between the treatments at week 3 and 4 respectively.

Table 46: Analysis of number of days of rescue medication use (MITT population)

	Treatment A					Treatment B					Treatment A-Treatment B
Visit	N	Mean	SD	Minimum	Maximum	N	Mean	SD	Minimum	Maximum	P-Value**
Baseline	40	4.5	1.32	0.0	5.0	40	4.8	0.64	2.0	6.0	0.1647
Week 1	40	4.6	1.30	0.0	6.0	40	4.8	0.64	3.0	6.0	0.2776
Week 2	40	4.5	1.06	0.0	6.0	40	4.9	0.48	3.0	5.0	0.0820
Week 3	40	4.3	1.14	0.0	5.0	40	4.9	0.48	3.0	6.0	0.0062
Week 4	40	4.2	1.11	0.0	5.0	40	4.9	0.59	3.0	7.0	0.0007

Treatment A: Arthronat
Treatment B: Placebo
** : Using t-test
N = Number of subjects with non-missing values
Source Listing: Subject Diary Card

Post-text Table 45 provides analysis of number of days of rescue medication use at each visit between treatments for PP population.

Table 47 provides analysis of amount of first line rescue medication (Paracetamol) at each visit between treatments for MIT population.

The p-value of 0.0115, 0.0202 , 0.0050 , 0.0013 and <.0001 indicates that there was a significant difference in amount (no of tables) of first line rescue medication used between the treatments at baseline, Visit 3, 4, 5 and 6 respectively.

Table 47: Analysis of Amount (no of tables) of first line rescue medication (Paracetamol) used during the study (MITT population)

	Treatment A					Treatment B					Treatment A-Treatment B
Visit	N	Mean	SD	Minimum	Maximum	N	Mean	SD	Minimum	Maximum	P-Value**
Baseline	40	9.5	4.04	0.0	15.0	40	11.6	3.26	2.0	15.0	0.0115
Week 1	40	8.3	3.63	0.0	15.0	40	10.1	3.04	4.0	15.0	0.0202
Week 2	40	7.9	3.24	0.0	15.0	40	10.0	3.26	3.0	15.0	0.0050
Week 3	40	7.2	3.32	0.0	15.0	40	9.6	3.26	3.0	15.0	0.0013
Week 4	40	6.8	3.32	0.0	15.0	40	10.2	2.91	4.0	15.0	<.0001

Treatment A: Arthronat
Treatment B: Placebo
** : Using t-test
N = Number of subjects with non-missing values
Source Listing: Rescue Medications Dispensing and Retrieval

Post-text Table 46: provides analysis of amount of first line rescue medication (Paracetamol) at each visit between treatments for PP population.

11.4.2 Statistical Issues

There were no statistical issues. Statistical analyses used and handling of dropouts and missing data are summarized in section 9.7.1 and 9.7.2 of this clinical study report, respectively, and a detailed documentation of statistical methods is presented in Appendix 16.1.9.

11.4.2.1 Adjustment for Covariates

For the efficacy endpoints, treatment effect was evaluated using an analysis of variance (ANOVA) model with factors for baseline and treatment. Treatment effects were estimated using the least-square means and 95% CIs from the ANOVA model.

11.4.2.2 Handling of dropouts or missing data

All missing data was imputed using the last observation carried forward after baseline for the modified intention-to-treat and no imputation was done for the per protocol analysis. No imputation was done on missing safety data.

11.4.2.3 Interim Analyses

No interim analysis was planned for the study.

11.4.3 Tabulation of Individual Response Data

Not Applicable

11.4.4 Drug Dose, Drug Concentration, and Relationships to Response

Not Applicable

11.4.5 Drug-Drug and Drug-Disease Interactions

Not Applicable

11.4.6 By-Patient Displays

Not Applicable

11.4.7 Efficacy Conclusions

The primary efficacy endpoints were the change in the pain scores as evaluated by Visual Analogue Scale (VAS) at end of Week 1 as compared to baseline (Day 0 / Visit 2) and Improvement (change) in mobility at the end of Week 1 as compared to baseline (day 0 / Visit 2) evaluated by change in the WOMAC sub-scales of Stiffness and Physical function.

There was a statistically significant reduction in pain in the subjects receiving Arthronat as compared to placebo at the end of week 1 as evaluated by VAS(p-value = 0.0013).

The mean value of WOMAC subscales of physical function for Arthonat treatment group at baseline was 26.8 and 27.0 at week 1 whereas the mean value for placebo group at

baseline was 26.7 which increased to 29.0 at week 1. The LS mean difference observed between Arthronat and placebo groups was -2.050 (p=0.0090), which indicates that there was a statistically significant difference in physical function in the Arthronat treatment arm as compared to the placebo. The analysis of results at week 1 showed that the WOMAC subscales of physical function in Arthronat arm were better than placebo arm.

There was no change seen in the mean value of WOMAC subscales of stiffness for Arthronat at baseline and week 1 (score = 3.1) however in the placebo arm the mean value increased from 3.2 at baseline to 3.4 at week 1. There was no statistically significant difference seen in the two treatment arms at week 1 (p= 0.3154).

There was no clear pattern shown in the Total SF-36 scores between Arthronat and Placebo groups during the study from Baseline to end of the study at Week 4. The SF-36 scores were similar in both the groups. There was no significant difference observed in absolute change from baseline to the end of week 1,2,3 and 4 in SF – 36 score between the two treatments. There was no significant difference observed in absolute change from baseline to the end of week 1, 2, 3 and 4 in Subject Global Assessment of Osteoarthritis between the two treatments.

At week 1, there were 39 (97.5%) responders in Arthronat group as compared to 27 (67.5%) responders in placebo group. At week 2, there were 40 (100.0%) responders in Arthronat group as compared to 26 (65.0%) responders in placebo group. At week 3, there were 39 (97.5%) responders in Arthronat group as compared to 28 (70.0%) responders in placebo group. At week 4, there were 39 (97.5%) responders in Arthronat group as compared to 30 (75.0%) responders in placebo group.

All the subjects in the study used only the first line of rescue medication i.e. Paracetamol (Tablet Dolo 500mg). Since all the subjects experienced adequate pain relief with the first line rescue medication, none of the subjects required Ibuprofen (second line) as the rescue medication in the study. Total number of tablets of rescue medication (paracetamol) consumed at each visit was lesser in Arthronat group (273) compared to Placebo (407) and reduced consistently from baseline to Week 4. The number of days of rescue medication use at week 3 and 4 were lower in Arthronat treatment group as compared to placebo and this difference was statistically significant at both the time points [week 3(p=0.0062 and week 4 (p=0.0007)]. The percentage responders at week 1 and 2 stratified by prior history of NSAIDs use could not be calculated since most (98.75%) of the subjects had history of prior NSAIDs use.

12 SAFETY EVALUATION

12.1 EXTENT OF EXPOSURE

A total of 80 patients were randomized to receive Arthronat and Placebo with 40 patients in each arm for duration of 04 weeks.

Forty patients received Arthonat 1500 mg two times a day for duration of 04 weeks Arthronat and another 40 subjects received matching placebo 3 capsules two times a day.

12.2 ADVERSE EVENTS (AE'S)

12.2.1 Brief Summary of Adverse Events

For all adverse experiences reported during the entire study period, the proportion of patients with AEs were classified by MedDRA SOCs and Preferred Terms and summarized by treatment group. All AE summaries are provided for the safety population.

Out of 40 subjects in each arm, 01 (2.5%) subjects while on Treatment A: Arthonat and 01 (2.5%) subjects while on Treatment B: Placebo experienced at least one symptom.

12.2.2 Display of Adverse Events

Table 48 provides the number and percentage of subjects with adverse events classified by MedDRA Primary System Organ Class and Preferred Term during the study.

Overall 2(2.5%) subjects experienced AEs related to system organ class - gastrointestinal disorders. Both the events were diarrhoea.

Table 48: Number and Percentage of subjects with adverse events classified by MedDRA Primary System Organ Class and Preferred Term during the study (Safety Population)

		Treatment A (N=40)		Treatment B (N=40)		All (N=80)	
System Organ Class	**Preferred Term**	n	%	n	%	n	%
At least one symptom		1	2.5	1	2.5	2	2.5
Gastrointestinal Disorders	**Any Adverse Event**	1	2.5	1	2.5	2	2.5
	Diarrhoea	1	2.5	1	2.5	2	2.5

At least one symptom = At least one symptom experienced regardless of the System Organ Class
Treatment A: Arthronat
Treatment B:Placebo
n/% = Number / percentage of subjects reporting at least once a specified symptom during the treatment period
Note: Patient Id 003 (Placebo group) and 005 (Arthronat group) has reported adverse event during the study period
Source Listing: Adverse Event

12.2.3 Analysis of Adverse Events

Table 49 provides the number (and percentage) of subjects with mild, moderate, severe adverse events classified by MedDRA Primary System Organ Class and Preferred Term during the study period

One (2.5%) subject each experienced at least 1 AE that was classified as moderate in Arthronat and placebo.

Table 50 provides number (and percentage) of subjects with adverse events classified by MedDRA Primary System Organ Class and Preferred Term during the study period, assessed as unrelated, unlikely to be, possibly, probably, definitely related to treatment

One (2.5%) subject each reported adverse event which was assessed as possibly related to the treatment in Arthronat and placebo.

Table 49: Number (and percentage) of subjects with mild, moderate, severe adverse events classified by MedDRA Primary System Organ Class and Preferred Term during the study period (Safety Population)

		Mild				Moderate				Severe				All			
		Treatment A (N=40)		Treatment B (N=40)		Treatment A (N=40)		Treatment B (N=40)		Treatment A (N=40)		Treatment B (N=40)		Treatment A (N=40)		Treatment B (N=40)	
System Organ Class	**Preferred Term**	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
At least one symptom		0	0	0	0	1	2.5	1	2.5	0	0	0	0	1	2.5	1	2.5
Gastrointestinal Disorders	**Any Adverse Event**	0	0	0	0	1	2.5	1	2.5	0	0	0	0	1	2.5	1	2.5
	Diarrhoea	0	0	0	0	1	2.5	1	2.5	0	0	0	0	1	2.5	1	2.5

At least one symptom = At least one symptom experienced regardless of the System Organ Class
Treatment A: Arthronat
Treatment B: Placebo
n/% = Number / percentage of subjects reporting at least once a specified symptom during the treatment period
Note: Patient Id 003 (Placebo group) and 005 (Arthronat group) has reported adverse event during the study period
Source Listing: Adverse Event

Table 50: Number (and percentage) of subjects with adverse events classified by MedDRA Primary System Organ Class and Preferred Term during the study period, assessed as unrelated, unlikely to be, possibly, probably, definitely related to treatment (Safety Population)

		Unrelated				Unlikely				Possible				Probable				Definite				All			
		Treatment A (N=40)		Treatment B (N=40)		Treatment A (N=40)		Treatment B (N=40)		Treatment A (N=40)		Treatment B (N=40)		Treatment A (N=40)		Treatment B (N=40)		Treatment A (N=40)		Treatment B (N=40)		Treatment A (N=40)		Treatment B (N=40)	
System Organ Class	Preferred Term	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
At least one symptom		0	0	0	0	0	0	0	0	1	2.5	1	2.5	0	0	0	0	0	0	0	0	1	2.5	1	2.5
Gastrointestinal Disorders	.Any Adverse Event	0	0	0	0	0	0	0	0	1	2.5	1	2.5	0	0	0	0	0	0	0	0	1	2.5	1	2.5
	Diarrhoea	0	0	0	0	0	0	0	0	1	2.5	1	2.5	0	0	0	0	0	0	0	0	1	2.5	1	2.5

At least one symptom = At least one symptom experienced regardless of the System Organ Class
Treatment A: Arthronat
Treatment B: Placebo
n/% = Number / percentage of subjects reporting at least once a specified symptom during the treatment period
Source Listing: Adverse Event

12.2.4 Listing of Adverse Events by Patient

Refer appendix 16.2.7

12.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT AE

No deaths, other SAEs and other significant AE(s) were reported in this study.

12.3.1 Listings of Deaths, other SAEs and other Significant AEs

Not Applicable

12.3.2 Narratives of Deaths, Other SAEs and Other significant AEs

Not Applicable

12.3.3 Analysis and Discussions of Deaths, Other SAEs and Other Significant AEs

Not Applicable

12.4 CLINICAL LABORATORY EVALUATION

12.4.1 Listing of Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value

Refer to Appendix 16.2.8

12.4.2 Evaluation of Each Laboratory Parameter

Hematology

Table 53 provides summary of haematology by visits (categorical variables).No clinically significant finding were found in both the arms at any of the visits. Summary of haematology by visits for continuous variables is provided in **Post-text Table 47**.

Serum chemistry

Table 54 provides the summary of serum chemistry by visits (categorical variables). No clinically significant findings were found in both the arms at any of the visits. Summary of serum chemistry by visits for continuous variables is provided in **Post-text Table 48:**

Urinalysis

Table 55 provides the summary of urinalysis by visits (categorical variables). No clinically significant findings were found in both the arms at any of the visits. Summary of urinalysis by visits for continuous variables is provided in **Post-text Table 49 :**

Table 51: Summary of Hematology by visits: Categorical variable (Safety Population)

		Treatment A (N=40)						Treatment B (N=40)						All (N=80)					
		Normal		Abnormal-NCS		Abnormal-CS		Normal		Abnormal-NCS		Abnormal-CS		Normal		Abnormal-NCS		Abnormal-CS	
Test	Visits	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Basophils (%)	Screening	39	97.5	0	0	0	0	40	100.0	0	0	0	0	79	98.8	0	0	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
Eosinophils (%)	Screening	36	90.0	4	10.0	0	0	37	92.5	3	7.5	0	0	73	91.3	7	8.8	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	39	97.5	1	2.5	0	0	79	98.8	1	1.3	0	0
Haematocrit (%)	Screening	7	17.5	33	82.5	0	0	7	17.5	33	82.5	0	0	14	17.5	66	82.5	0	0
	Week 4 (V6)	6	15.0	34	85.0	0	0	6	15.0	34	85.0	0	0	12	15.0	68	85.0	0	0
Haemoglobin (Gm %)	Screening	18	45.0	22	55.0	0	0	20	50.0	20	50.0	0	0	38	47.5	42	52.5	0	0
	Week 4 (V6)	18	45.0	22	55.0	0	0	22	55.0	18	45.0	0	0	40	50.0	40	50.0	0	0
Lymphocytes (%)	Screening	33	82.5	7	17.5	0	0	32	80.0	8	20.0	0	0	65	81.3	15	18.8	0	0
	Week 4 (V6)	32	80.0	8	20.0	0	0	29	72.5	11	27.5	0	0	61	76.3	19	23.8	0	0
Monocytes (%)	Screening	35	87.5	5	12.5	0	0	36	90.0	4	10.0	0	0	71	88.8	9	11.3	0	0
	Week 4 (V6)	37	92.5	3	7.5	0	0	33	82.5	7	17.5	0	0	70	87.5	10	12.5	0	0
Neutrophils (%)	Screening	38	95.0	2	5.0	0	0	39	97.5	1	2.5	0	0	77	96.3	3	3.8	0	0
	Week 4 (V6)	38	95.0	2	5.0	0	0	35	87.5	5	12.5	0	0	73	91.3	7	8.8	0	0

		Treatment A (N=40)						Treatment B (N=40)						All (N=80)					
		Normal		Abnormal-NCS		Abnormal-CS		Normal		Abnormal-NCS		Abnormal-CS		Normal		Abnormal-NCS		Abnormal-CS	
Platelet Count (/Cumm)	**Screening**	35	87.5	5	12.5	0	0	30	75.0	9	22.5	0	0	65	81.3	14	17.5	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
RBC Count (Millions/Cumm)	**Screening**	7	17.5	32	80.0	0	0	4	10.0	36	90.0	0	0	11	13.8	68	85.0	0	0
	Week 4 (V6)	8	20.0	32	80.0	0	0	9	22.5	31	77.5	0	0	17	21.3	63	78.8	0	0
Total WBC Count (Cells/Cumm)	**Screening**	39	97.5	1	2.5	0	0	37	92.5	2	5.0	0	0	76	95.0	3	3.8	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0

n/% = Number/percentage of subjects with the given characteristics
Treatment A: Arthronat
Treatment B: Placebo
Source Listing: Hematology

Table 52 Summary of Serum Chemistry by visits: Categorical variable (Safety Population)

		Treatment A (N=40)						Treatment B (N=40)						All (N=80)					
		Normal		Abnormal-NCS		Abnormal-CS		Normal		Abnormal-NCS		Abnormal-CS		Normal		Abnormal-NCS		Abnormal-CS	
Test	**Visits**	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Alkaline Phosphatase (U/L)	**Screening**	37	92.5	3	7.5	0	0	34	85.0	6	15.0	0	0	71	88.8	9	11.3	0	0
	Week 4 (V6)	39	97.5	1	2.5	0	0	36	90.0	4	10.0	0	0	75	93.8	5	6.3	0	0
BUN (Mg/Dl)	**Screening**	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
Calcium (Mg/Dl)	**Screening**	27	67.5	13	32.5	0	0	25	62.5	15	37.5	0	0	52	65.0	28	35.0	0	0
	Week 4 (V6)	30	75.0	10	25.0	0	0	27	67.5	13	32.5	0	0	57	71.3	23	28.8	0	0
Chloride (Meq/L)	**Screening**	36	90.0	4	10.0	0	0	33	82.5	7	17.5	0	0	69	86.3	11	13.8	0	0
	Week 4 (V6)	37	92.5	3	7.5	0	0	36	90.0	4	10.0	0	0	73	91.3	7	8.8	0	0
Potassium (Meq/L)	**Screening**	40	100.0	0	0	0	0	39	97.5	1	2.5	0	0	79	98.8	1	1.3	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
S. Albumin (Gm/Dl)	**Screening**	29	72.5	11	27.5	0	0	33	82.5	7	17.5	0	0	62	77.5	18	22.5	0	0
	Week 4 (V6)	32	80.0	8	20.0	0	0	37	92.5	3	7.5	0	0	69	86.3	11	13.8	0	0
Serum Creatinine (Mg/Dl)	**Screening**	39	97.5	1	2.5	0	0	37	92.5	3	7.5	0	0	76	95.0	4	5.0	0	0
	Week 4 (V6)	39	97.5	1	2.5	0	0	40	100.0	0	0	0	0	79	98.8	1	1.3	0	0
SGOT (Iu/L)	**Screening**	38	95.0	2	5.0	0	0	40	100.0	0	0	0	0	78	97.5	2	2.5	0	0

		Treatment A (N=40)						Treatment B (N=40)						All (N=80)					
		Normal		Abnormal-NCS		Abnormal-CS		Normal		Abnormal-NCS		Abnormal-CS		Normal		Abnormal-NCS		Abnormal-CS	
	Week 4 (V6)	39	97.5	1	2.5	0	0	40	100.0	0	0	0	0	79	98.8	1	1.3	0	0
SGPT (Iu/L)	Screening	39	97.5	1	2.5	0	0	40	100.0	0	0	0	0	79	98.8	1	1.3	0	0
	Week 4 (V6)	39	97.5	1	2.5	0	0	40	100.0	0	0	0	0	79	98.8	1	1.3	0	0
Sodium (Meq/L)	Screening	40	100.0	0	0	0	0	39	97.5	1	2.5	0	0	79	98.8	1	1.3	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
Total Bilirubin (Mg/Dl)	Screening	39	97.5	1	2.5	0	0	39	97.5	1	2.5	0	0	78	97.5	2	2.5	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0

n/% = Number/percentage of subjects with the given characteristics
Treatment A: Arthronat
Treatment B: Placebo
Source Listing: Serum Chemistry

Table 53: Summary of Urine analysis by visits: Categorical variable (Safety Population)

		Treatment A (N=40)						Treatment B (N=40)						All (N=80)					
		Normal		Abnormal-NCS		Abnormal-CS		Normal		Abnormal-NCS		Abnormal-CS		Normal		Abnormal-NCS		Abnormal-CS	
Test	Visits	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Bilirubin	Screening	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
Blood	Screening	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
Casts	Screening	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
	Week 4	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0

	(V6)																		
Color	**Screening**	39	97.5	1	2.5	0	0	40	100.0	0	0	0	0	79	98.8	1	1.3	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
Crystals	**Screening**	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
Epithelial (/Hpf)	**Screening**	32	80.0	8	20.0	0	0	33	82.5	7	17.5	0	0	65	81.3	15	18.8	0	0
	Week 4 (V6)	36	90.0	4	10.0	0	0	38	95.0	2	5.0	0	0	74	92.5	6	7.5	0	0
Glucose	**Screening**	36	90.0	4	10.0	0	0	37	92.5	3	7.5	0	0	73	91.3	7	8.8	0	0
	Week 4 (V6)	37	92.5	3	7.5	0	0	36	90.0	4	10.0	0	0	73	91.3	7	8.8	0	0
Ketone Bodies	**Screening**	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
Nitrite	**Screening**	38	95.0	2	5.0	0	0	37	92.5	3	7.5	0	0	75	93.8	5	6.3	0	0
	Week 4 (V6)	39	97.5	1	2.5	0	0	40	100.0	0	0	0	0	79	98.8	1	1.3	0	0
pH	**Screening**	40	100.0	0	0	0	0	39	97.5	1	2.5	0	0	79	98.8	1	1.3	0	0
	Week 4 (V6)	38	95.0	2	5.0	0	0	40	100.0	0	0	0	0	78	97.5	2	2.5	0	0
Protein	**Screening**	40	100.0	0	0	0	0	39	97.5	1	2.5	0	0	79	98.8	1	1.3	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
PUS Cells (/Hpf)	**Screening**	38	95.0	2	5.0	0	0	36	90.0	4	10.0	0	0	74	92.5	6	7.5	0	0
	Week 4 (V6)	39	97.5	1	2.5	0	0	40	100.0	0	0	0	0	79	98.8	1	1.3	0	0
RBC's (/Hpf)	**Screening**	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
Specific Gravity	**Screening**	39	97.5	0	0	0	0	39	97.5	0	0	0	0	78	97.5	0	0	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0

Transparency	**Screening**	39	97.5	1	2.5	0	0	38	95.0	2	5.0	0	0	77	96.3	3	3.8	0	0
	Week 4 (V6)	39	97.5	1	2.5	0	0	39	97.5	1	2.5	0	0	78	97.5	2	2.5	0	0
Urobilinogen	**Screening**	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0

n /% = Number/percentage of subjects with the given characteristics
Treatment A: Arthronat
Treatment B: Placebo
Source Listing: Urine analysis

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

Table 54 provides the summary of vital signs by subject. Vital signs were found to be within the normal range during the course of the study. There were no clinically significant abnormal findings at any of the visits in any of the arms.

Table 55 provides the summary of physical examination by visits. Physical examination was found to be normal during the course of the study for all the subjects. There were no clinically significant abnormal findings at any of the visits.

Table 54 : Summary of vital signs by visit (Safety Population)

Vital Sign	Visit	Summary Statistics	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
Systolic (mm of Hg)	**Screening**	**N**	40	40	80
		Mean	129.1	131.3	130.2
		SD	13.43	15.21	14.30
		Minimum	110.0	100.0	100.0
		Median	130.0	130.0	130.0
		Maximum	160.0	160.0	160.0
	Baseline	**N**	40	40	80
		Mean	126.7	128.7	127.7
		SD	11.09	11.14	11.09

Vital Sign	Visit	Summary Statistics	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
		Minimum	100.0	104.0	100.0
		Median	128.0	130.0	129.0
		Maximum	150.0	158.0	158.0
	Week 1 (V3)	**N**	40	40	80
		Mean	125.1	126.3	125.7
		SD	8.58	9.17	8.84
		Minimum	110.0	100.0	100.0
		Median	123.0	128.0	127.0
		Maximum	144.0	144.0	144.0
	Week 2 (V4)	**N**	40	40	80
		Mean	125.2	126.7	125.9
		SD	10.61	9.36	9.97
		Minimum	110.0	110.0	110.0
		Median	124.0	126.0	125.0
		Maximum	150.0	146.0	150.0
	Week 3 (V5)	**N**	40	40	80
		Mean	123.6	125.7	124.6
		SD	8.20	8.50	8.36
		Minimum	110.0	100.0	100.0
		Median	124.0	127.0	125.0
		Maximum	144.0	142.0	144.0
	Week 4 (V6)	**N**	40	40	80
		Mean	124.5	125.6	125.0
		SD	8.08	9.95	9.02
		Minimum	110.0	100.0	100.0
		Median	122.0	126.0	123.0
		Maximum	144.0	140.0	144.0
Diastolic (mm of Hg)	**Screening**	**N**	40	40	80
		Mean	80.4	82.8	81.6
		SD	6.81	6.31	6.63

Vital Sign	Visit	Summary Statistics	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
		Minimum	60.0	70.0	60.0
		Median	80.0	80.0	80.0
		Maximum	90.0	90.0	90.0
	Baseline	**N**	40	40	80
		Mean	80.9	83.8	82.3
		SD	6.34	5.57	6.10
		Minimum	70.0	70.0	70.0
		Median	80.0	84.0	82.0
		Maximum	92.0	90.0	92.0
	Week 1 (V3)	**N**	40	40	80
		Mean	81.2	83.6	82.4
		SD	5.47	5.33	5.50
		Minimum	70.0	70.0	70.0
		Median	82.0	82.0	82.0
		Maximum	90.0	92.0	92.0
	Week 2 (V4)	**N**	40	40	80
		Mean	81.2	83.1	82.1
		SD	6.44	4.98	5.80
		Minimum	70.0	72.0	70.0
		Median	82.0	84.0	82.0
		Maximum	92.0	90.0	92.0
	Week 3 (V5)	**N**	40	40	80
		Mean	82.8	82.8	82.8
		SD	6.19	5.39	5.77
		Minimum	70.0	70.0	70.0
		Median	83.0	84.0	84.0
		Maximum	92.0	90.0	92.0
	Week 4 (V6)	**N**	40	40	80
		Mean	82.3	83.0	82.6
		SD	5.09	6.26	5.68

Vital Sign	Visit	Summary Statistics	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
		Minimum	70.0	70.0	70.0
		Median	81.0	82.0	82.0
		Maximum	90.0	92.0	92.0
Pulse Rate (beats / min)	**Screening**	**N**	40	40	80
		Mean	79.4	79.4	79.4
		SD	8.16	6.93	7.52
		Minimum	66.0	64.0	64.0
		Median	80.0	80.0	80.0
		Maximum	100.0	96.0	100.0
	Baseline	**N**	40	40	80
		Mean	78.9	79.2	79.0
		SD	3.97	4.02	3.97
		Minimum	70.0	72.0	70.0
		Median	80.0	80.0	80.0
		Maximum	84.0	88.0	88.0
	Week 1 (V3)	**N**	40	40	80
		Mean	79.5	79.9	79.7
		SD	4.72	4.16	4.43
		Minimum	70.0	72.0	70.0
		Median	80.0	80.0	80.0
		Maximum	92.0	90.0	92.0
	Week 2 (V4)	**N**	40	40	80
		Mean	79.7	80.1	79.9
		SD	4.24	4.98	4.60
		Minimum	70.0	70.0	70.0
		Median	80.0	80.0	80.0
		Maximum	90.0	92.0	92.0
	Week 3 (V5)	**N**	40	40	80
		Mean	80.3	80.9	80.6
		SD	4.63	4.83	4.71

Vital Sign	Visit	Summary Statistics	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
		Minimum	72.0	72.0	72.0
		Median	80.0	80.0	80.0
		Maximum	92.0	92.0	92.0
	Week 4 (V6)	**N**	40	40	80
		Mean	78.8	80.1	79.5
		SD	3.84	4.73	4.33
		Minimum	72.0	68.0	68.0
		Median	78.0	80.0	80.0
		Maximum	90.0	88.0	90.0
Respiratory Rate (breaths / min)	**Screening**	**N**	40	40	80
		Mean	19.1	18.9	19.0
		SD	1.35	1.19	1.27
		Minimum	18.0	18.0	18.0
		Median	18.0	18.0	18.0
		Maximum	22.0	22.0	22.0
	Baseline	**N**	40	40	80
		Mean	19.0	18.9	18.9
		SD	1.28	1.10	1.19
		Minimum	18.0	18.0	18.0
		Median	18.0	18.0	18.0
		Maximum	22.0	22.0	22.0
	Week 1 (V3)	**N**	40	40	80
		Mean	19.2	19.4	19.3
		SD	1.19	1.31	1.25
		Minimum	18.0	18.0	18.0
		Median	20.0	20.0	20.0
		Maximum	22.0	22.0	22.0
	Week 2 (V4)	**N**	40	40	80
		Mean	19.0	19.2	19.1
		SD	1.28	1.35	1.31

Vital Sign	Visit	Summary Statistics	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
		Minimum	18.0	18.0	18.0
		Median	18.0	18.0	18.0
		Maximum	22.0	22.0	22.0
	Week 3 (V5)	**N**	40	40	80
		Mean	19.0	18.8	18.9
		SD	1.50	1.18	1.35
		Minimum	18.0	18.0	18.0
		Median	18.0	18.0	18.0
		Maximum	22.0	22.0	22.0
	Week 4 (V6)	**N**	40	40	80
		Mean	18.8	19.2	19.0
		SD	1.17	1.37	1.29
		Minimum	18.0	18.0	18.0
		Median	18.0	19.0	18.0
		Maximum	22.0	22.0	22.0
Oral Temperature (^{o}C)	**Screening**	**N**	40	40	80
		Mean	36.8	37.0	36.9
		SD	0.47	0.60	0.54
		Minimum	36.1	35.9	35.9
		Median	36.9	37.0	37.0
		Maximum	37.7	38.0	38.0
	Baseline	**N**	40	40	80
		Mean	36.7	36.6	36.7
		SD	0.44	0.47	0.46
		Minimum	36.0	36.0	36.0
		Median	36.8	36.5	36.7
		Maximum	37.6	37.6	37.6
	Week 1 (V3)	**N**	40	40	80
		Mean	36.9	36.9	36.9
		SD	0.47	0.40	0.43

Vital Sign	Visit	Summary Statistics	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
		Minimum	36.1	36.1	36.1
		Median	37.0	37.0	37.0
		Maximum	37.8	37.6	37.8
	Week 2 (V4)	**N**	40	40	80
		Mean	36.8	36.7	36.8
		SD	0.42	0.43	0.42
		Minimum	36.0	36.1	36.0
		Median	36.8	36.8	36.8
		Maximum	37.4	37.4	37.4
	Week 3 (V5)	**N**	40	40	80
		Mean	36.7	36.7	36.7
		SD	0.54	0.38	0.46
		Minimum	36.0	36.0	36.0
		Median	36.9	36.8	36.8
		Maximum	37.8	37.2	37.8
	Week 4 (V6)	**N**	40	40	80
		Mean	36.8	36.8	36.8
		SD	0.38	0.45	0.42
		Minimum	36.0	36.1	36.0
		Median	37.0	37.0	37.0
		Maximum	37.2	37.8	37.8

Treatment A: Arthronat
Treatment B: Placebo
Source Listing: Vital signs

Table 55: Summary of physical examination by visits (Safety Population)

		Treatment A (N=40)						Treatment B (N=40)						All (N=80)					
		Normal		Abnormal-NCS		Abnormal-CS		Normal		Abnormal-NCS		Abnormal-CS		Normal		Abnormal-NCS		Abnormal-CS	
Test	Visits	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Abdomen	Screening	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
Extremities	Screening	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
General Appearance	Screening	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
Genito - Urinary	Screening	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
H.E.E.N.T	Screening	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
Heart	Screening	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
Lungs	Screening	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
Lymph Nodes	Screening	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
Musculoskeletal	Screening	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
Neurological	Screening	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
Skin	Screening	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0
	Week 4 (V6)	40	100.0	0	0	0	0	40	100.0	0	0	0	0	80	100.0	0	0	0	0

n/% = Number/percentage of subjects with the given characteristics
Treatment A: Arthronat, Treatment B: Placebo
Source Listing: Physical Examination

12.5.1 Concomitant medication

Table 56 provides the percentage of subjects who used concomitant medication during the study for modified intention-to-treat population.

One subject each used concomitant medication Lactobacillus Sporogenes during Treatment A and Treatment B respectively.

Percentage of subjects who used concomitant medication during the study in PP Population is provided in **Post-text Table 50** and Percentage of subjects who used prior concomitant medication (PP Population) is provided in **Post-text Table 51**.

Table 56 : Percentage of subjects who used concomitant medication during the study (MITT population)

	Treatment A (N=40)		Treatment B (N=40)	
Preferred Term	n	%	n	%
Lactobacillus Sporogenes	1	2.5	1	2.5

n /% = Number /percentage of subjects with the given characteristics
Treatment A: Arthronat
Treatment B: Placebo
Source Listing: Concomitant Medication

12.6 SAFETY CONCLUSIONS

Safety data was presented for the safety population, which included all patients who had been randomized to receive the study medications.

The number of adverse events and the number of patients reporting the adverse events were comparable between the treatment groups. Overall 02(2.5%) subjects experienced AEs related to system organ class - gastrointestinal disorders. Both the events were diarrhoea. One (2.5%) subject each in the Treatment A and Treatment B reported atleast one AE, which were moderate in nature and possibly related to the treatment. One subject each used concomitant medication Lactobacillus Sporogenes during Treatment A and Treatment B respectively.

No deaths, other SAEs and other significant AE(s) were reported in this study.

Vital signs were found to be within the normal range during the course of the study. There were no clinically significant abnormal findings at any of the visits in both the treatment groups. Physical examination was found to be normal during the course of the study for all the subjects. There were no clinically significant abnormal findings at any of the visits.

Arthronat was well tolerated and was comparable with Placebo which was confirmed by the fewer incidences of adverse events and good compliance.

13 DISCUSSIONS AND OVERALL CONCLUSIONS

This was a 4 week prospective, randomized, double blind, parallel group, placebo controlled study. Subjects aged ≥ 18 yrs of age with painful osteoarthritis of hip, knee, shoulders, neck or wrists were randomized to treatment either with Arthronat or a matching placebo. The total duration of the active treatment was for 4 weeks which was preceded by 01 week of placebo run-in between screening and baseline visit.

The study population consisted of male or non-pregnant female patients aged ≥ 18 years of age with a previously diagnosed (at least 3 months prior to the screening visit) case of osteoarthritis of hip, knees based on the ACR (American College of Rheumatology) Clinical Classification criteria for osteoarthritis or a previously diagnosed (at least 3 months prior to screening visit) case on shoulders, neck and wrists based on the clinical and radiographic findings. Subjects experiencing significant arthritic pain confirmed by screening WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index Scale) score between 10 - 40 (only for osteoarthritis of hip and knee) and a baseline VAS (Visual Analogue Scale) score of ≥ 4.

The primary efficacy endpoints were the change in the pain scores as evaluated by VAS at end of week 1 as compared to baseline (Day 0 / Visit 2) and improvement (change) in mobility at the end of week 1 as compared to baseline (day 0 / Visit 2) evaluated by change in the WOMAC sub-scales of Stiffness and Physical function.
There was a statistically significant reduction in pain in the subjects receiving Arthronat as compared to placebo at the end of week 1 as evaluated by VAS(p-value = 0.0013).

The mean value of WOMAC subscales of physical function for Arthonat treatment group at baseline was 26.8 and 27.0 at week 1 whereas the mean value for placebo group at baseline was 26.7 which increased to 29.0 at week 1. The LS mean difference observed between Arthronat and placebo groups was -2.050 (p=0.0090), which indicates that there was a statistically significant difference in physical function in the Arthronat treatment arm as compared to the placebo. The analysis of results at week 1 showed that the WOMAC subscales of physical function in Arthronat arm were better than placebo arm.

There was no change seen in the mean value of WOMAC subscales of stiffness for Arthronat at baseline and week 1 (score = 3.1) however in the placebo arm the mean value increased from 3.2 at baseline to 3.4 at week 1. There was no statistically significant difference seen in the two treatment arms at week 1 (p= 0.3154).

There was no significant difference observed in absolute change from baseline to the end of week 1,2,3 and 4 in SF – 36 score between the two treatments. There was no significant difference observed in absolute change from baseline to the end of week 1, 2, 3 and 4 in Subject Global Assessment of Osteoarthritis between the two treatments.

At week 1, there were 39 (97.5%) responders in Arthronat group as compared to 27 (67.5%) responders in placebo group. At week 2, there were 40 (100.0%) responders in Arthronat group as compared to 26 (65.0%) responders in placebo group. At week 3, there were 39 (97.5%) responders in Arthronat group as compared to 28 (70.0%) responders in placebo group. At week 4, there were 39 (97.5%) responders in Arthronat group as compared to 30 (75.0%) responders in placebo group.

All the subjects in the study used only the first line of rescue medication i.e. Paracetamol (Tablet Dolo 500mg). Since all the subjects experienced adequate pain relief with the first line rescue medication, none of the subjects required Ibuprofen (second line) as the rescue medication in the study. Total number of tablets of rescue medication (paracetamol) consumed at each visit was lesser in Arthronat group (273) compared to Placebo (407) and reduced consistently from baseline to Week 4.This difference was statistically significant at all the visits .The number of days of rescue medication use at week 3 and 4 were lower in Arthronat treatment group as compared to placebo and this difference was statistically significant at both the time points [week 3(p=0.0062 and week 4 (p=0.0007)]. None of the subjects required second line of rescue medication Ibuprofen.

Arthronat was well tolerated and was comparable with Placebo in safety aspects which were confirmed by the fewer incidences of adverse events and good compliance.

Overall 02(2.5%) subjects experienced AEs related to system organ class - gastrointestinal disorders. Both the events were diarrhoea. One (2.5%) subject each in the Treatment A and Treatment B reported atleast one AE, which were moderate in nature and possibly related to the treatment. One subject each used concomitant medication Lactobacillus Sporogenes during Treatment A and Treatment B respectively.

The results of this study demonstrate that the Arthronat had a better efficacy profile compared to placebo, for the reduction in pain scores as evaluated by Visual Analogue Scale (VAS) at end of Week 1 in subjects with painful osteoarthritis of the hip, knee, shoulders, neck or the wrists and is safe and well tolerated.

14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN TEXT

14.1 DEMOGRAPHIC DATA

Nil

14.2 EFFICACY DATA

Post-text Table 1: Summary of pain scores as evaluated by percent change in Visual Analogue Scale (VAS) from baseline (MITT population)

VISIT	CATEGORIES	TREATMENT A (N=40)	TREATMENT B (N=40)
Percent Change at Week 1 (Visit 3)	N	40	40
	Mean	-3.3	1.4
	SD	12.54	11.63
	Median	-7.1	-0.7
	Minimum	-14.3	-8.3
	Maximum	60.0	60.0
Percent Change at Week 2 (Visit 4)	N	40	40
	Mean	-8.7	-0.5
	SD	16.61	14.28
	Median	-13.3	-0.6
	Minimum	-28.6	-20.0
	Maximum	80.0	60.0
Percent Change at Week 3 (Visit 5)	N	40	40
	Mean	-11.4	-1.7
	SD	17.32	15.17
	Median	-17.1	-3.6
	Minimum	-28.6	-23.6
	Maximum	60.0	60.0
Percent Change at Week 4 (Visit 6)	N	40	40
	Mean	-15.8	-5.7
	SD	20.32	16.87
	Median	-20.0	-7.1
	Minimum	-38.5	-30.6
	Maximum	60.0	60.0
Treatment A: Arthronat **Treatment B: Placebo** **Source Listing: Visual Analogue Scale for Pain**			

Post-text Table 2: Summary of pain scores as evaluated by percent change in Visual Analogue Scale (VAS) from baseline (PP Population)

VISIT	CATEGORIES	TREATMENT A (N=40)	TREATMENT B (N=40)
Percent Change at Week 1 (Visit 3)	N	40	40
	Mean	-3.3	1.4
	SD	12.54	11.63
	Median	-7.1	-0.7
	Minimum	-14.3	-8.3
	Maximum	60.0	60.0
Percent Change at Week 2 (Visit 4)	N	40	40
	Mean	-8.7	-0.5
	SD	16.61	14.28
	Median	-13.3	-0.6
	Minimum	-28.6	-20.0
	Maximum	80.0	60.0
Percent Change at Week 3 (Visit 5)	N	40	40
	Mean	-11.4	-1.7
	SD	17.32	15.17
	Median	-17.1	-3.6
	Minimum	-28.6	-23.6
	Maximum	60.0	60.0
Percent Change at Week 4 (Visit 6)	N	40	40
	Mean	-15.8	-5.7
	SD	20.32	16.87
	Median	-20.0	-7.1
	Minimum	-38.5	-30.6
	Maximum	60.0	60.0

Treatment A: Arthronat
Treatment B: Placebo
Source Listing: Visual Analogue Scale for Pain

Post-text Table 3: Summary of pain scores as evaluated by Visual Analogue Scale (VAS) (PP Population)

VISIT	CATEGORIES	TREATMENT A (N=40)	TREATMENT B (N=40)
Screening	**N**	40	40
	Mean	68.6	69.4
	SD	8.11	9.48
	Median	70.0	70.0
	Minimum	50.0	50.0
	Maximum	90.0	95.0
Baseline	**N**	40	40
	Mean	68.0	70.1
	SD	7.90	8.32
	Median	70.0	70.0
	Minimum	50.0	50.0
	Maximum	80.0	86.0
Visit 3	**N**	40	40
	Mean	65.4	70.5
	SD	7.99	7.07
	Median	65.0	70.0
	Minimum	45.0	58.0
	Maximum	80.0	88.0
Visit 4	**N**	40	40
	Mean	61.6	69.1
	SD	9.05	7.80
	Median	60.0	70.0
	Minimum	45.0	55.0
	Maximum	90.0	90.0
Visit 5	**N**	40	40
	Mean	59.8	68.2
	SD	10.00	8.51
	Median	60.0	68.5
	Minimum	40.0	52.0
	Maximum	80.0	90.0
Visit 6	**N**	40	40
	Mean	56.6	65.2
	SD	11.51	8.21
	Median	55.0	65.0
	Minimum	40.0	50.0
	Maximum	80.0	80.0
Treatment A: Arthronat **Treatment B: Placebo** **Source Listing: Visual Analogue Scale for Pain**			

Post-text Table 4:Analysis of absolute change from baseline in pain scores as evaluated by Visual Analogue Scale (VAS) at end of week 1 as compared to Baseline (Day 0 / Visit 2) (PP Population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	68.0	7.90	40	70.1	8.32	-1.1	6.93	-3.878	(-6.539,-1.217)	0.0048	0.0013
Week 1	40	65.4	7.99	40	70.5	7.07			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: Visual Analogue Scale for Pain

Post-text Table 5: Analysis of absolute change from baseline in pain scores as evaluated by Visual Analogue Scale (VAS) at end of week 2 as compared to Baseline (Day 0 / Visit 2) (PP Population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	68.0	7.90	40	70.1	8.32	-3.7	9.37	-6.600	(-10.09,-3.114)	0.0003	0.0001
Week 2	40	61.6	9.05	40	69.1	7.80			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: Visual Analogue Scale for Pain

Post-text Table 6: Analysis of absolute change from baseline in pain scores as evaluated by Visual Analogue Scale (VAS) at end of week 3 as compared to Baseline (Day 0 / Visit 2) (PP Population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	68.0	7.90	40	70.1	8.32	-5.0	10.38	-7.615	(-11.54,-3.691)	0.0002	0.0004
Week 3	40	59.8	10.00	40	68.2	8.51			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: Visual Analogue Scale for Pain

Post-text Table 7: Analysis of absolute change from baseline in pain scores as evaluated by Visual Analogue Scale (VAS) at end of week 4 as compared to Baseline (Day 0 / Visit 2) (Per-Protocol Population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	68.0	7.90	40	70.1	8.32	-8.1	12.15	-8.172	(-12.63,-3.719)	0.0005	0.0019
Week 4	40	56.6	11.51	40	65.2	8.21			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: Visual Analogue Scale for Pain

Post-text Table 8: Summary of improvement in mobility as evaluated by percent change in WOMAC sub-scales of Pain, Stiffness & Physical Function and total-scale from baseline (PP Population)

VISIT	SUBSCALE	CATEGORIES	TREATMENT A (N=40)	TREATMENT B (N=39)
Percent Change at Week 1 (Visit 3)	Pain	N	40	39
		Mean	1.0	7.1
		SD	11.22	26.65
		Median	0.0	0.0
		Minimum	-22.2	-30.0
		Maximum	44.4	120.0
Percent Change at Week 2 (Visit 4)		N	40	39
		Mean	-3.2	2.8
		SD	16.15	33.75
		Median	0.0	0.0
		Minimum	-55.6	-62.5
		Maximum	33.3	140.0
Percent Change at Week 3 (Visit 5)		N	40	39
		Mean	-3.3	4.6
		SD	15.98	31.09
		Median	0.0	0.0
		Minimum	-55.6	-44.4
		Maximum	50.0	120.0
Percent Change at Week 4 (Visit 6)		N	40	39
		Mean	-4.3	6.1
		SD	16.19	28.06
		Median	0.0	0.0
		Minimum	-55.6	-30.0
		Maximum	25.0	120.0
Percent Change at Week 1 (Visit 3)	Stiffness	N	40	39
		Mean	1.9	10.3
		SD	17.65	31.38

VISIT	SUBSCALE	CATEGORIES	TREATMENT A (N=40)	TREATMENT B (N=39)
		Median	0.0	0.0
		Minimum	-40.0	-33.3
		Maximum	50.0	150.0
Percent Change at Week 2 (Visit 4)		N	40	39
		Mean	8.0	8.9
		SD	32.24	35.53
		Median	0.0	0.0
		Minimum	-40.0	-50.0
		Maximum	150.0	150.0
Percent Change at Week 3 (Visit 5)		N	40	39
		Mean	5.9	10.0
		SD	31.01	38.20
		Median	0.0	0.0
		Minimum	-40.0	-40.0
		Maximum	150.0	150.0
Percent Change at Week 4 (Visit 6)		N	40	39
		Mean	3.4	7.2
		SD	32.72	35.05
		Median	0.0	0.0
		Minimum	-40.0	-50.0
		Maximum	150.0	150.0
Percent Change at Week 1 (Visit 3)	Physical Function	N	40	39
		Mean	1.7	11.6
		SD	12.99	23.56
		Median	0.0	6.7
		Minimum	-19.4	-25.8
		Maximum	52.2	100.0
Percent Change at Week 2 (Visit 4)		N	40	39
		Mean	-0.3	12.1
		SD	12.33	26.88

VISIT	SUBSCALE	CATEGORIES	TREATMENT A (N=40)	TREATMENT B (N=39)
		Median	0.0	3.8
		Minimum	-25.8	-35.1
		Maximum	30.4	120.0
Percent Change at Week 3 (Visit 5)		N	40	39
		Mean	0.6	7.3
		SD	14.66	26.73
		Median	-1.8	3.1
		Minimum	-27.3	-29.7
		Maximum	36.8	106.3
Percent Change at Week 4 (Visit 6)		N	40	39
		Mean	-0.2	9.2
		SD	13.47	26.18
		Median	-1.9	0.0
		Minimum	-20.7	-24.3
		Maximum	36.8	106.3
Percent Change at Week 1 (Visit 3)	Total	N	40	39
		Mean	1.4	9.7
		SD	10.41	21.25
		Median	0.0	4.7
		Minimum	-14.3	-19.5
		Maximum	44.4	108.7
Percent Change at Week 2 (Visit 4)		N	40	39
		Mean	-0.8	8.9
		SD	11.14	24.28
		Median	-2.5	2.6
		Minimum	-25.7	-30.6
		Maximum	27.8	100.0
Percent Change at Week 3 (Visit 5)		N	40	39
		Mean	-0.5	6.0
		SD	12.34	24.95

VISIT	SUBSCALE	CATEGORIES	TREATMENT A (N=40)	TREATMENT B (N=39)
		Median	-2.8	2.1
		Minimum	-20.9	-26.5
		Maximum	33.3	113.0
Percent Change at Week 4 (Visit 6)		N	40	39
		Mean	-1.4	7.4
		SD	11.63	23.63
		Median	-4.0	2.6
		Minimum	-17.5	-24.5
		Maximum	25.0	113.0

Treatment A: Arthronat
Treatment B: Placebo
Source Listing: WOMAC Index Questionnaire for Hip and Knee OA

Post-text Table 9: Summary of improvement in mobility as evaluated by WOMAC sub-scales of Stiffness and Physical Function (PP Population)

Visit	Subscale	Categories	Treatment A (N=40)	Treatment B (N=39)
Screening	**Stiffness**	N	40	39
		Mean	3.0	2.8
		SD	0.62	0.74
		Median	3.0	3.0
		Minimum	1.0	1.0
		Maximum	5.0	4.0
Baseline		N	40	39
		Mean	3.1	3.2
		SD	0.74	0.99
		Median	3.0	3.0
		Minimum	2.0	1.0
		Maximum	5.0	5.0

Visit	Subscale	Categories	Treatment A (N=40)	Treatment B (N=39)
Visit 3		N	40	39
		Mean	3.1	3.4
		SD	0.67	0.99
		Median	3.0	3.0
		Minimum	2.0	1.0
		Maximum	5.0	5.0
Visit 4		N	40	39
		Mean	3.2	3.3
		SD	0.70	0.94
		Median	3.0	3.0
		Minimum	2.0	1.0
		Maximum	5.0	5.0
Visit 5		N	40	39
		Mean	3.2	3.3
		SD	0.62	1.00
		Median	3.0	3.0
		Minimum	2.0	1.0
		Maximum	5.0	5.0
Visit 6		N	40	39
		Mean	3.1	3.2
		SD	0.69	0.92
		Median	3.0	3.0
		Minimum	2.0	1.0
		Maximum	5.0	5.0
Screening	**Physical Function**	N	40	39
		Mean	25.9	26.3
		SD	2.54	3.16

Visit	Subscale	Categories	Treatment A (N=40)	Treatment B (N=39)
		Median	26.0	27.0
		Minimum	21.0	16.0
		Maximum	31.0	32.0
Baseline		N	40	39
		Mean	26.8	26.7
		SD	3.88	4.29
		Median	26.5	27.0
		Minimum	18.0	15.0
		Maximum	36.0	37.0
Visit 3		N	40	39
		Mean	27.0	29.0
		SD	3.20	2.79
		Median	26.0	29.0
		Minimum	19.0	23.0
		Maximum	35.0	36.0
Visit 4		N	40	39
		Mean	26.4	29.0
		SD	2.78	2.74
		Median	26.5	29.0
		Minimum	19.0	24.0
		Maximum	32.0	37.0
Visit 5		N	40	39
		Mean	26.6	27.7
		SD	3.11	2.89
		Median	26.0	27.0
		Minimum	21.0	22.0
		Maximum	34.0	33.0

Visit	Subscale	Categories	Treatment A (N=40)	Treatment B (N=39)
Visit 6		N	40	39
		Mean	26.5	28.2
		SD	3.39	2.42
		Median	26.0	28.0
		Minimum	16.0	25.0
		Maximum	34.0	34.0

Treatment A: Arthronat
Treatment B: Placebo
Source Listing: WOMAC Index Questionnaire for Hip and Knee OA

Post-text Table 10: Analysis of absolute change from baseline in improvement in mobility as evaluated by WOMAC subscales of stiffness and physical function at end of week 1 as compared to Baseline (Day 0 / Visit 2) (PP Population)

		Treatment A			Treatment B			Absolute change from baseline					
Visit	Subscale	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	Stiffness	40	3.1	0.74	39	3.2	0.99	0.1	0.65	-0.222	(-0.488,0.044)	0.1005	0.3154
Week 1		40	3.1	0.67	39	3.4	0.99			.		.	.
Baseline	Physical Function	40	26.8	3.88	39	26.7	4.29	1.2	4.05	-2.050	(-3.281,-0.819)	0.0014	0.0090
Week 1		40	27.0	3.20	39	29.0	2.79			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: WOMAC Index Questionnaire for Hip and Knee OA

Post-text Table 11: Analysis of absolute change from baseline in improvement in mobility as evaluated by WOMAC subscales of stiffness and physical function at end of week 2 as compared to Baseline (Day 0 / Visit 2) (PP Population)

		Treatment A			Treatment B			Absolute change from baseline					
Visit	Subscale	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	Stiffness	40	3.1	0.74	39	3.2	0.99	0.1	0.89	-0.009	(-0.343,0.325)	0.9579	0.6845
Week 2		40	3.2	0.70	39	3.3	0.94			.		.	.
Baseline	Physical Function	40	26.8	3.88	39	26.7	4.29	0.9	4.51	-2.614	(-3.821,-1.407)	<.0001	0.0069
Week 2		40	26.4	2.78	39	29.0	2.74			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: WOMAC Index Questionnaire for Hip and Knee OA

Post-text Table 12: Analysis of absolute change from baseline in improvement in mobility as evaluated by WOMAC subscales of stiffness and physical function at end of week 3 as compared to Baseline (Day 0 / Visit 2) (PP Population)

		Treatment A			Treatment B			Absolute change from baseline					
Visit	Subscale	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	Stiffness	40	3.1	0.74	39	3.2	0.99	0.1	0.96	-0.114	(-0.464,0.236)	0.5190	0.7415
Week 3		40	3.2	0.62	39	3.3	1.00			.		.	.
Baseline	Physical Function	40	26.8	3.88	39	26.7	4.29	0.4	4.70	-1.152	(-2.492,0.188)	0.0909	0.2373
Week 3		40	26.6	3.11	39	27.7	2.89			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: WOMAC Index Questionnaire for Hip and Knee OA

Post-text Table 13: Analysis of absolute change from baseline in improvement in mobility as evaluated by WOMAC subscales of stiffness and physical function at end of week 4 as compared to Baseline (Day 0 / Visit 2) (PP Population)

		Treatment A			Treatment B			Absolute change from baseline					
Visit	Subscale	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	Stiffness	40	3.1	0.74	39	3.2	0.99	0.0	0.94	-0.111	(-0.453,0.230)	0.5176	0.5346
Week 4		40	3.1	0.69	39	3.2	0.92			.		.	.
Baseline	Physical Function	40	26.8	3.88	39	26.7	4.29	0.6	4.43	-1.746	(-3.030,-0.462)	0.0084	0.0958
Week 4		40	26.5	3.39	39	28.2	2.42			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: WOMAC Index Questionnaire for Hip and Knee OA

Post-text Table 14: Summary of WOMAC total score (PP Population)

Visit	Categories	Treatment A (N=40)	Treatment B (N=39)
Screening	**N**	40	39
	Mean	36.7	36.8
	SD	2.72	3.54
	Median	37.0	37.0
	Minimum	30.0	23.0
	Maximum	42.0	43.0
Baseline	**N**	40	39
	Mean	37.9	37.7
	SD	4.44	5.45
	Median	37.0	38.0
	Minimum	27.0	23.0
	Maximum	47.0	49.0
Visit 3	**N**	40	39
	Mean	38.2	40.6
	SD	4.22	4.20
	Median	37.0	39.0
	Minimum	30.0	33.0
	Maximum	52.0	50.0
Visit 4	**N**	40	39
	Mean	37.3	40.1
	SD	4.15	4.54
	Median	37.0	39.0
	Minimum	26.0	32.0
	Maximum	49.0	52.0
Visit 5	**N**	40	39
	Mean	37.4	39.0

Visit	Categories	Treatment A (N=40)	Treatment B (N=39)
	SD	4.49	4.62
	Median	36.5	38.0
	Minimum	28.0	29.0
	Maximum	49.0	49.0
Visit 6	**N**	40	39
	Mean	37.2	39.5
	SD	4.92	3.85
	Median	37.0	39.0
	Minimum	24.0	35.0
	Maximum	49.0	49.0
Treatment A: Arthronat Treatment B: Placebo Source Listing: WOMAC Index Questionnaire for Hip and Knee OA			

Post-text Table 15: Analysis of absolute change from baseline in WOMAC total score at end of week 1 as compared to Baseline (Day 0 / Visit 2) (PP Population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	37.9	4.44	39	37.7	5.45	1.5	5.04	-2.438	(-4.148,-0.728)	0.0058	0.0029
Week 1	40	38.2	4.22	39	40.6	4.20			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: WOMAC Index Questionnaire for Hip and Knee OA

Post-text Table 16: Analysis of absolute change from baseline in WOMAC total score at end of week 2 as compared to Baseline (Day 0 / Visit 2) (PP Population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	37.9	4.44	39	37.7	5.45	0.9	5.93	-2.804	(-4.710,-0.898)	0.0045	0.0522
Week 2	40	37.3	4.15	39	40.1	4.54			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: WOMAC Index Questionnaire for Hip and Knee OA

Post-text Table 17: Analysis of absolute change from baseline in WOMAC total score at end of week 3 as compared to Baseline (Day 0 / Visit 2) (PP Population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	37.9	4.44	39	37.7	5.45	0.4	6.11	-1.571	(-3.591,0.449)	0.1254	0.2816
Week 3	40	37.4	4.49	39	39.0	4.62			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: WOMAC Index Questionnaire for Hip and Knee OA

Post-text Table 18: Analysis of absolute change from baseline in WOMAC total score at end of week 4 as compared to Baseline (Day 0 / Visit 2) (PP Population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	37.9	4.44	39	37.7	5.45	0.5	5.73	-2.371	(-4.285,-0.458)	0.0158	0.0767
Week 4	40	37.2	4.92	39	39.5	3.85			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: WOMAC Index Questionnaire for Hip and Knee OA

Post-text Table 19: Analysis of absolute change from baseline to the end of week 1 in (SF-36 score) (PP Population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	46.1	8.95	40	44.9	8.90	0.6	6.03	-0.145	(-2.718,2.428)	0.9109	0.5668
Week 1	40	46.5	8.42	40	45.8	9.53			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: SF-36 Quality of Life Questionnaire

Post-text Table 20: Analysis of absolute change from baseline to the end of week 2 in (SF-36 score) (PP Population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	46.1	8.95	40	44.9	8.90	-0.1	6.54	-0.921	(-3.546,1.704)	0.4869	0.5036
Week 2	40	45.4	8.24	40	45.5	8.46			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: SF-36 Quality of Life Questionnaire

Post-text Table 21: Analysis of absolute change from baseline to the end of week 3 in (SF-36 score) (PP Population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	46.1	8.95	40	44.9	8.90	0.5	6.88	-1.653	(-4.482,1.176)	0.2482	0.1906
Week 3	40	45.6	8.92	40	46.4	8.79			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: SF-36 Quality of Life Questionnaire

Post-text Table 22: Analysis of absolute change from baseline to the end of week 4 in (SF-36 score) (PP Population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	46.1	8.95	40	44.9	8.90	-1.8	8.08	0.709	(-2.166,3.585)	0.6246	0.8024
Week 4	40	44.3	8.74	40	43.1	6.02			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: SF-36 Quality of Life Questionnaire

Post-text Table 23: Analysis of absolute change from baseline to the end of week 1 in Subject Global Assessment of Osteoarthritis (PP Population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	3.03	0.158	40	3.05	0.221	-0.04	0.192	0.009	(-0.057,0.075)	0.7840	0.5536
Week 1	40	3.00	0.000	39	3.00	0.229			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: Subject Global Assessment for OA

Post-text Table 24: Analysis of absolute change from baseline to the end of week 2 in Subject Global Assessment of Osteoarthritis (PP Population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	3.03	0.158	40	3.05	0.221	-0.08	0.267	-0.025	(-0.113,0.062)	0.5634	0.9830
Week 2	39	2.95	0.223	40	2.98	0.158			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: Subject Global Assessment for OA

Post-text Table 25: Analysis of absolute change from baseline to the end of week 3 in Subject Global Assessment of Osteoarthritis (PP Population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	3.03	0.158	40	3.05	0.221	-0.06	0.245	-0.051	(-0.122,0.020)	0.1575	0.6336
Week 3	39	2.95	0.223	40	3.00	0.000			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: Subject Global Assessment for OA

Post-text Table 26: Analysis of absolute change from baseline to the end of week 4 in Subject Global Assessment of Osteoarthritis (PP Population)

	Treatment A			Treatment B			Absolute change from baseline					
Visit	N	Mean	SD	N	Mean	SD	Mean	SD	LS Mean	95% CI*	P-value*	P-value**
Baseline	40	3.03	0.158	40	3.05	0.221	-0.05	0.219	-0.025	(-0.075,0.025)	0.3287	1.0000
Week 4	40	2.98	0.158	40	3.00	0.000			.		.	.

Treatment A: Arthronat
Treatment B: Placebo
* : Using ANOVA, ** : Using Wilcoxon rank sum test
N = Number of subjects with non-missing values
Source Listing: Subject Global Assessment for OA

Post-text Table 27: Number (and Percentage) of Responders and Non-Responders according to OMERACT-OARSI Responder Index at week 1 (MITT population)

	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
Category	n (%)	n (%)	n (%)
Responders	39(97.5)	27(67.5)	66(82.5)
Non-Responders	1(2.5)	13(32.5)	14(17.5)

Treatment A: Arthronat
Treatment B: Placebo
n/% = Number/Percentage of subjects with the given characteristics
Source Listing: OMERACT-OARSI Responder Index

Post-text Table 28: Number (and Percentage) of Responders and Non-Responders according to OMERACT-OARSI Responder Index at week 2 (MITT population)

	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
Category	n (%)	n(%)	n(%)
Responders	40 (100.0)	26 (65.0)	66(82.5)
Non-Responders	0(0.0)	14(35.0)	14(17.5)

Treatment A: Arthronat
Treatment B: Placebo
n/% = Number/Percentage of subjects with the given characteristics
Source Listing: OMERACT-OARSI Responder Index

Post-text Table 29: Number (and Percentage) of Responders and Non-Responders according to OMERACT-OARSI Responder Index at week 3 (MITT population)

	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
Category	n(%)	n(%)	n(%)
Responders	39 (97.5)	28 (70.0)	67(83.8)
Non-Responders	1(2.5)	12(30.0)	13(16.3)

Treatment A: Arthronat
Treatment B: Placebo
n/% = Number/Percentage of subjects with the given characteristics
Source Listing: OMERACT-OARSI Responder Index

Post-text Table 30 : Number (and Percentage) of Responders and Non-Responders according to OMERACT-OARSI Responder Index at week 4 (MITT population)

	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
Category	n(%)	n(%)	n(%)
Responders	39 (97.5)	30 (75.0)	69 (86.3)
Non-Responders	1 (2.5)	10 (25.0)	11(13.8)

Treatment A: Arthronat
Treatment B: Placebo
n/% = Number/Percentage of subjects with the given characteristics
Source Listing: OMERACT-OARSI Responder Index

Post-text Table 31: Number (and Percentage) of Responders and Non-Responders according to OMERACT-OARSI Responder Index at week 1 (PP Population)

	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
Category	n(%)	n(%)	n(%)
Responders	39(97.5)	27(67.5)	66(82.5)
Non-Responders	1(2.5)	13(32.5)	14(17.5)

Treatment A: Arthronat
Treatment B: Placebo
n/% = Number/Percentage of subjects with the given characteristics
Source Listing: OMERACT-OARSI Responder Index

Post-text Table 32: Number (and Percentage) of Responders and Non-Responders according to OMERACT-OARSI Responder Index at week 2 (PP Population)

	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
Category	n(%)	n(%)	n(%)
Responders	40(100.0)	26(65.0)	66(82.5)
Non-Responders		14(35.0)	14(17.5)

Treatment A: Arthronat
Treatment B: Placebo
n/% = Number/Percentage of subjects with the given characteristics
Source Listing: OMERACT-OARSI Responder Index

Post-text Table 33: Number (and Percentage) of Responders and Non-Responders according to OMERACT-OARSI Responder Index at week 3 (PP Population)

	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
Category	n(%)	n(%)	n(%)
Responders	39(97.5)	28(70.0)	67(83.8)
Non-Responders	1(2.5)	12(30.0)	13(16.3)

Treatment A: Arthronat
Treatment B: Placebo
n/% = Number/Percentage of subjects with the given characteristics
Source Listing: OMERACT-OARSI Responder Index

Post-text Table 34: Number (and Percentage) of Responders and Non-Responders according to OMERACT-OARSI Responder Index at week 4 (PP Population)

	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
Category	n(%)	n(%)	n(%)
Responders	39(97.5)	30(75.0)	69(86.3)
Non-Responders	1(2.5)	10(25.0)	11(13.8)

Treatment A: Arthronat
Treatment B: Placebo
n/% = Number/Percentage of subjects with the given characteristics
Source Listing: OMERACT-OARSI Responder Index

Post-text Table 35: Analysis of number of subjects who used rescue medication at week 1 (MITT population)

	Treatment A		Treatment B		
	n	%	n	%	P-Value
Subjects used rescue medication at Baseline	39	97.5	40	100.0	0.9352
Subjects used rescue medication at Week 1	38	95.0	40	100.0	.

Treatment A: Arthronat
Treatment B: Placebo
P-Value = Chi-square test
Source Listing: Rescue Medications Dispensing and Retrieval

Post-text Table 36: Analysis of number of subjects who used rescue medication at week 2 (MITT population)

	Treatment A		Treatment B		
	n	%	n	%	P-Value
Subjects used rescue medication at Baseline	39	97.5	40	100.0	1.0000
Subjects used rescue medication at Week 2	39	97.5	40	100.0	.

Treatment A: Arthronat
Treatment B: Placebo
P-Value = Chi-square test
Source Listing: Rescue Medications Dispensing and Retrieval

Post-text Table 37: Analysis of number of subjects who used rescue medication at week 3 (MITT population)

	Treatment A		Treatment B		
	n	%	n	%	P-Value
Subjects used rescue medication at Baseline	39	97.5	40	100.0	1.0000
Subjects used rescue medication at Week 3	39	97.5	40	100.0	.

Treatment A: Arthronat
Treatment B: Placebo
P-Value = Chi-square test
Source Listing: Rescue Medications Dispensing and Retrieval

Post-text Table 38: Analysis of number of subjects who used rescue medication at week 4 (MITT population)

	Treatment A		Treatment B		
	n	%	n	%	P-Value
Subjects used rescue medication at Baseline	39	97.5	40	100.0	1.0000
Subjects used rescue medication at Week 4	39	97.5	40	100.0	.

Treatment A: Arthronat
Treatment B: Placebo
P-Value = Chi-square test
Source Listing: Rescue Medications Dispensing and Retrieval

Post-text Table 39: Analysis of number of subjects who used rescue medication at week 1 (PP Population)

	Treatment A		Treatment B		
	n	%	n	%	P-Value
Subjects used rescue medication at Baseline	39	97.5	40	100.0	0.9352
Subjects used rescue medication at Week 1	38	95.0	40	100.0	.

Treatment A: Arthronat
Treatment B: Placebo
P-Value = Chi-square test
Source Listing: Rescue Medications Dispensing and Retrieval

Post-text Table 40: Analysis of number of subjects who used rescue medication at week 2 (PP Population)

	Treatment A		Treatment B		
	n	%	n	%	P-Value
Subjects used rescue medication at Baseline	39	97.5	40	100.0	1.0000
Subjects used rescue medication at Week 2	39	97.5	40	100.0	.

Treatment A: Arthronat
Treatment B: Placebo
P-Value = Chi-square test
Source Listing: Rescue Medications Dispensing and Retrieval

Post-text Table 41: Analysis of number of subjects who used rescue medication at week 3 (PP Population)

	Treatment A		Treatment B		
	n	%	n	%	P-Value
Subjects used rescue medication at Baseline	39	97.5	40	100.0	1.0000
Subjects used rescue medication at Week 3	39	97.5	40	100.0	.

Treatment A: Arthronat
Treatment B: Placebo
P-Value = Chi-square test
Source Listing: Rescue Medications Dispensing and Retrieval

Post-text Table 42 : Analysis of number of subjects who used rescue medication at week 4 (PP Population)

	Treatment A		Treatment B		
	n	%	n	%	P-Value
Subjects used rescue medication at Baseline	39	97.5	40	100.0	1.0000
Subjects used rescue medication at Week 4	39	97.5	40	100.0	.

Treatment A: Arthronat
Treatment B: Placebo
P-Value = Chi-square test
Source Listing: Rescue Medications Dispensing and Retrieval

Post-text Table 43: Summary of total number of tablets of rescue medication (Paracetamol) consumed in each visit in both the treatment arms (PP Population)

VISIT	TREATMENT A	TREATMENT B
Baseline	380	465
Week 1 (V3)	331	402
Week 2 (V4)	317	401
Week 3 (V5)	287	385
Week 4 (V6)	273	407
Treatment A: Arthronat **Treatment B: Placebo** **Source Listing: Rescue Medications Dispensing and Retrieval**		

Post-text Table 44: Summary on number of tablets of rescue medication consumed in each visit by categories (PP population)

		TREATMENT A (N=40)		TREATMENT B (N=40)	
Visit	**No of tablets**	**n**	**%**	**n**	**%**
Baseline	0-5	6	15.0	2	5.0
	6-10	17	42.5	12	30.0
	11-15	17	42.5	26	65.0
Week 1 (V3)	0-5	10	25.0	3	7.5
	6-10	19	47.5	19	47.5
	11-15	11	27.5	18	45.0
Week 2 (V4)	0-5	10	25.0	5	12.5
	6-10	25	62.5	19	47.5
	11-15	5	12.5	16	40.0
Week 3 (V5)	0-5	11	27.5	5	12.5
	6-10	25	62.5	20	50.0
	11-15	4	10.0	15	37.5

Week 4 (V6)	0-5	14	35.0	2	5.0
	6-10	22	55.0	22	55.0
	11-15	4	10.0	16	40.0
Treatment A: Arthronat **Treatment B: Placebo** **Source Listing: Rescue Medications Dispensing and Retrieval**					

Post-text Table 45: Analysis of number of days of rescue medication use (PP Population)

	Treatment A					**Treatment B**					**Treatment A-Treatment B**
Visit	N	Mean	SD	Minimum	Maximum	N	Mean	SD	Minimum	Maximum	P-Value**
Screening	40	4.5	1.32	0.0	5.0	40	4.8	0.64	2.0	6.0	0.1647
Baseline	40	4.6	1.30	0.0	6.0	40	4.8	0.64	3.0	6.0	0.2776
Visit 3	40	4.5	1.06	0.0	6.0	40	4.9	0.48	3.0	5.0	0.0820
Visit 4	40	4.3	1.14	0.0	5.0	40	4.9	0.48	3.0	6.0	0.0062
Visit 5	40	4.2	1.11	0.0	5.0	40	4.9	0.59	3.0	7.0	0.0007
Treatment A: Arthronat Treatment B: Placebo ** : Using t-test N = Number of subjects with non-missing values Source Listing: Subject Diary Card											

Post-text Table 46: Analysis of Amount of first line rescue medication (Paracetamol) used during the study (PP Population)

	Treatment A					Treatment B					Treatment A-Treatment B
Visit	N	Mean	SD	Minimum	Maximum	N	Mean	SD	Minimum	Maximum	P-Value**
Baseline	40	9.5	4.04	0.0	15.0	40	11.6	3.26	2.0	15.0	0.0115
Visit 3	40	8.3	3.63	0.0	15.0	40	10.1	3.04	4.0	15.0	0.0202
Visit 4	40	7.9	3.24	0.0	15.0	40	10.0	3.26	3.0	15.0	0.0050
Visit 5	40	7.2	3.32	0.0	15.0	40	9.6	3.26	3.0	15.0	0.0013
Visit 6	40	6.8	3.32	0.0	15.0	40	10.2	2.91	4.0	15.0	<.0001

Treatment A: Arthronat
Treatment B: Placebo
** : Using t-test
N = Number of subjects with non-missing values
Source Listing: Rescue Medications Dispensing and Retrieval

14.3 SAFETY DATA

14.3.1 CLINICAL LABORATORY EVALUATION

Post-text Table 47 : Summary of Hematology by visits: Continuous variable (Safety Population)

Test	Visits	Summary Statistics	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
Basophils (%)	Screening	N	40	40	80
		Mean	0.0	0.0	0.0
		SD	0.00	0.00	0.00
		Minimum	0.0	0.0	0.0
		Median	0.0	0.0	0.0
		Maximum	0.0	0.0	0.0
	Week 4 (V6)	N	40	40	80
		Mean	1.5	0.0	0.8
		SD	9.49	0.00	6.71
		Minimum	0.0	0.0	0.0
		Median	0.0	0.0	0.0
		Maximum	60.0	0.0	60.0
Eosinophils (%)	Screening	N	40	40	80
		Mean	3.8	4.1	3.9
		SD	1.85	1.97	1.90
		Minimum	1.0	1.0	1.0
		Median	3.5	4.0	4.0
		Maximum	9.0	9.0	9.0
	Week 4 (V6)	N	40	40	80
		Mean	3.5	2.4	3.0
		SD	6.03	1.13	4.34

Test	Visits	Summary Statistics	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
		Minimum	1.0	0.0	0.0
		Median	3.0	2.5	3.0
		Maximum	40.0	5.0	40.0
Haematocrit (%)	Screening	N	39	40	79
		Mean	32.2	32.8	32.5
		SD	3.15	3.70	3.43
		Minimum	28.2	26.7	26.7
		Median	31.4	32.1	31.8
		Maximum	40.5	41.2	41.2
	Week 4 (V6)	N	40	40	80
		Mean	32.8	33.6	33.2
		SD	3.00	3.32	3.17
		Minimum	28.5	28.3	28.3
		Median	31.8	32.7	32.0
		Maximum	41.7	40.9	41.7
Haemoglobin (gm %)	Screening	N	39	40	79
		Mean	12.2	12.6	12.4
		SD	1.26	1.89	1.61
		Minimum	10.3	9.1	9.1
		Median	11.9	12.3	12.1
		Maximum	15.2	16.7	16.7
	Week 4 (V6)	N	40	40	80
		Mean	12.3	12.8	12.5
		SD	1.21	1.71	1.49
		Minimum	10.2	9.6	9.6
		Median	11.9	12.6	12.1
		Maximum	15.6	16.3	16.3

Test	Visits	Summary Statistics	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
Lymphocytes (%)	Screening	N	40	40	80
		Mean	35.7	35.3	35.5
		SD	7.05	6.98	6.98
		Minimum	22.0	21.0	21.0
		Median	37.0	34.0	35.0
		Maximum	51.0	51.0	51.0
	Week 4 (V6)	N	40	40	80
		Mean	36.2	36.3	36.3
		SD	6.24	7.44	6.82
		Minimum	25.0	25.0	25.0
		Median	35.0	35.0	35.0
		Maximum	48.0	48.0	48.0
Monocytes (%)	Screening	N	40	40	80
		Mean	2.7	2.5	2.6
		SD	1.68	1.47	1.57
		Minimum	0.0	0.0	0.0
		Median	3.0	3.0	3.0
		Maximum	6.0	6.0	6.0
	Week 4 (V6)	N	40	40	80
		Mean	2.1	1.9	2.0
		SD	1.41	1.19	1.30
		Minimum	0.0	0.0	0.0
		Median	2.0	2.0	2.0
		Maximum	7.0	4.0	7.0
Neutrophils (%)	Screening	N	40	40	80
		Mean	57.8	58.2	58.0
		SD	6.99	6.94	6.92

Test	Visits	Summary Statistics	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
		Minimum	44.0	43.0	43.0
		Median	58.0	59.5	58.0
		Maximum	73.0	72.0	73.0
	Week 4 (V6)	N	38	40	78
		Mean	59.4	59.3	59.3
		SD	6.23	7.89	7.08
		Minimum	47.0	48.0	47.0
		Median	61.0	60.5	61.0
		Maximum	71.0	71.0	71.0
Platelet Count (/cumm)	Screening	N	40	40	80
		Mean	181925.0	178900.0	180412.5
		SD	44717.57	51117.66	47743.70
		Minimum	91000.0	102000.0	91000.0
		Median	178500.0	167500.0	173000.0
		Maximum	285000.0	345000.0	345000.0
	Week 4 (V6)	N	40	40	80
		Mean	180225.0	182475.0	181350.0
		SD	19352.98	26770.62	23237.41
		Minimum	147000.0	151000.0	147000.0
		Median	178500.0	176000.0	178000.0
		Maximum	219000.0	268000.0	268000.0
RBC count (millions/cumm)	Screening	N	39	40	79
		Mean	3.6	3.6	3.6
		SD	0.37	0.42	0.39
		Minimum	3.0	3.1	3.0
		Median	3.5	3.6	3.5
		Maximum	4.5	4.8	4.8

Test	Visits	Summary Statistics	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
	Week 4 (V6)	N	40	40	80
		Mean	3.7	3.8	3.7
		SD	0.34	0.38	0.36
		Minimum	3.2	3.2	3.2
		Median	3.6	3.7	3.6
		Maximum	4.6	4.8	4.8
Total WBC Count (cells/cumm)	Screening	N	40	40	80
		Mean	6305.0	6482.5	6393.8
		SD	1431.15	1918.45	1684.05
		Minimum	3400.0	4400.0	3400.0
		Median	6400.0	6150.0	6250.0
		Maximum	9800.0	13700.0	13700.0
	Week 4 (V6)	N	40	40	80
		Mean	7437.5	6822.5	7130.0
		SD	1331.03	1316.07	1351.08
		Minimum	4900.0	5100.0	4900.0
		Median	7400.0	6700.0	7300.0
		Maximum	9600.0	9300.0	9600.0

Treatment A: Arthronat
Treatment B: Placebo
Source Listing: Hematology

Post-text Table 48: Summary of Serum Chemistry by visits: Continuous variable (Safety Population)

Test	Visits	Summary Statistics	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
Alkaline Phosphatase (U/L)	Screening	N	40	40	80
		Mean	103.6	98.4	101.0
		SD	28.14	29.48	28.75
		Minimum	51.0	56.0	51.0
		Median	97.5	92.0	95.5
		Maximum	183.0	197.0	197.0
	Week 4 (V6)	N	40	40	80
		Mean	103.1	98.6	100.9
		SD	16.53	18.47	17.56
		Minimum	75.0	63.0	63.0
		Median	100.5	94.5	98.5
		Maximum	139.0	146.0	146.0
BUN (mg/dl)	Screening	N	40	40	80
		Mean	14.2	13.7	14.0
		SD	2.49	2.18	2.34
		Minimum	8.3	9.2	8.3
		Median	14.6	13.7	14.0
		Maximum	18.7	19.7	19.7
	Week 4 (V6)	N	40	40	80
		Mean	14.9	14.3	14.6
		SD	1.86	1.64	1.77
		Minimum	10.7	11.3	10.7
		Median	15.0	14.4	14.8
		Maximum	18.3	17.3	18.3
Calcium (mg/dl)	Screening	N	40	40	80

Test	Visits	Summary Statistics	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
		Mean	8.8	8.7	8.7
		SD	0.57	0.65	0.60
		Minimum	7.8	7.9	7.8
		Median	8.8	8.7	8.7
		Maximum	9.9	10.2	10.2
	Week 4 (V6)	N	40	40	80
		Mean	8.9	8.8	8.9
		SD	0.46	0.43	0.45
		Minimum	8.1	8.0	8.0
		Median	9.0	8.8	9.0
		Maximum	9.7	9.8	9.8
Chloride (MEq/l)	Screening	N	40	40	80
		Mean	102.8	103.3	103.1
		SD	4.50	5.07	4.77
		Minimum	93.2	87.4	87.4
		Median	103.5	104.0	103.5
		Maximum	112.5	111.3	112.5
	Week 4 (V6)	N	40	40	80
		Mean	101.3	100.3	100.8
		SD	3.19	3.28	3.25
		Minimum	93.6	90.7	90.7
		Median	101.5	100.5	100.9
		Maximum	109.1	107.2	109.1
Potassium (MEq/l)	Screening	N	40	40	80
		Mean	4.2	4.2	4.2
		SD	0.37	0.44	0.41
		Minimum	3.6	3.4	3.4

Test	Visits	Summary Statistics	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
		Median	4.1	4.1	4.1
		Maximum	5.1	5.5	5.5
	Week 4 (V6)	N	40	40	80
		Mean	4.3	4.3	4.3
		SD	0.30	0.36	0.33
		Minimum	3.8	3.6	3.6
		Median	4.2	4.2	4.2
		Maximum	5.0	5.3	5.3
S. albumin (gm/dl)	Screening	N	40	40	80
		Mean	3.9	3.9	3.9
		SD	0.33	0.30	0.32
		Minimum	3.0	3.2	3.0
		Median	3.9	4.0	4.0
		Maximum	4.9	4.6	4.9
	Week 4 (V6)	N	40	40	80
		Mean	4.0	4.0	4.0
		SD	0.24	0.27	0.26
		Minimum	3.4	3.3	3.3
		Median	3.9	4.0	4.0
		Maximum	4.4	4.6	4.6
SGOT (IU/L)	Screening	N	40	40	80
		Mean	28.6	25.2	26.9
		SD	14.48	8.46	11.90
		Minimum	13.0	12.0	12.0
		Median	25.0	26.0	25.5
		Maximum	97.0	43.0	97.0
	Week 4 (V6)	N	40	40	80

Test	Visits	Summary Statistics	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
		Mean	27.3	26.6	26.9
		SD	7.86	6.65	7.25
		Minimum	19.0	15.0	15.0
		Median	27.0	25.0	26.0
		Maximum	59.0	49.0	59.0
SGPT (IU/L)	Screening	N	40	40	80
		Mean	26.7	25.0	25.9
		SD	13.05	8.63	11.02
		Minimum	14.0	11.0	11.0
		Median	25.0	24.0	25.0
		Maximum	94.0	43.0	94.0
	Week 4 (V6)	N	40	40	80
		Mean	26.7	26.6	26.6
		SD	8.96	5.65	7.44
		Minimum	16.0	13.0	13.0
		Median	25.0	27.0	25.0
		Maximum	71.0	39.0	71.0
Serum Creatinine (mg/dl)	Screening	N	40	40	80
		Mean	0.8	0.8	0.8
		SD	0.15	0.13	0.14
		Minimum	0.6	0.7	0.6
		Median	0.8	0.8	0.8
		Maximum	1.2	1.4	1.4
	Week 4 (V6)	N	40	40	80
		Mean	0.9	0.9	0.9
		SD	0.12	0.10	0.11
		Minimum	0.7	0.7	0.7

Test	Visits	Summary Statistics	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
		Median	0.9	0.9	0.9
		Maximum	1.3	1.3	1.3
Sodium (MEq/l)	Screening	N	40	40	80
		Mean	136.4	130.8	133.6
		SD	5.73	25.17	18.35
		Minimum	105.0	9.1	9.1
		Median	137.4	137.1	137.4
		Maximum	141.5	140.9	141.5
	Week 4 (V6)	N	40	40	80
		Mean	135.2	133.3	134.3
		SD	4.27	3.66	4.06
		Minimum	125.6	125.8	125.6
		Median	135.5	132.1	133.9
		Maximum	142.6	141.3	142.6
Total bilirubin (mg/dl)	Screening	N	40	40	80
		Mean	0.8	0.8	0.8
		SD	0.13	0.13	0.13
		Minimum	0.5	0.5	0.5
		Median	0.8	0.8	0.8
		Maximum	1.0	1.0	1.0
	Week 4 (V6)	N	40	40	80
		Mean	0.7	0.7	0.7
		SD	0.09	0.08	0.09
		Minimum	0.6	0.6	0.6
		Median	0.7	0.7	0.7
		Maximum	1.0	0.9	1.0

Treatment A: Arthronat

Test	Visits	Summary Statistics	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
Treatment B: Placebo Source Listing: Serum Chemistry					

Post-text Table 49 : Summary of Urine analysis by visits: Continuous variable (Safety Population)

Test	Visits	Summary Statistics	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
Specific gravity	Screening	N	39	37	76
		Mean	1.0	1.0	1.0
		SD	0.00	0.00	0.00
		Minimum	1.0	1.0	1.0
		Median	1.0	1.0	1.0
		Maximum	1.0	1.0	1.0
	Week 4 (V6)	N	38	39	77
		Mean	1.0	1.0	1.0
		SD	0.00	0.00	0.00
		Minimum	1.0	1.0	1.0
		Median	1.0	1.0	1.0
		Maximum	1.0	1.0	1.0
pH	Screening	N	40	40	80
		Mean	6.8	6.8	6.8
		SD	0.41	0.41	0.40
		Minimum	6.0	6.0	6.0
		Median	7.0	7.0	7.0
		Maximum	7.0	7.0	7.0
	Week 4 (V6)	N	40	40	80
		Mean	6.8	6.9	6.9

Test	Visits	Summary Statistics	Treatment A (N=40)	Treatment B (N=40)	All (N=80)
		SD	0.41	0.30	0.36
		Minimum	6.0	6.0	6.0
		Median	7.0	7.0	7.0
		Maximum	7.0	7.0	7.0
Treatment A: Arthronat Treatment B: Placebo Source Listing: Urine Analysis					

Post-text Table 50: Percentage of subjects who used concomitant medication during the study (PP Population)

	TREATMENT A (N=40)		TREATMENT B (N=40)	
Preferred Term	n	%	n	%
Lactobacillus Sporogenes	1	2.5	1	2.5
n/% = Number/percentage of subjects with the given characteristics **Treatment A: Arthronat** **Treatment B: Placebo** **Source Listing: Concomitant Medication**				

Post-text Table 51: Percentage of subjects who used prior concomitant medication (PP Population)

	TREATMENT A (N=40)		TREATMENT B (N=40)	
Preferred Term	n	%	n	%
Acarbose	1	2.5	0	0
Aceclo Plus	6	15.0	9	22.5
Aceclofenac	8	20.0	9	22.5
Acetylsalicylic Acid	0	0	1	2.5
Amlodipine	5	12.5	3	7.5
Atenolol	1	2.5	2	5.0
Atorvastatin Calcium	1	2.5	0	0

	TREATMENT A (N=40)		TREATMENT B (N=40)	
Calcitrol /00508501/	1	2.5	0	0
Calcium	5	12.5	4	10.0
Calcium Carbonate	1	2.5	1	2.5
Calcium Citrate	0	0	3	7.5
Calcium With Vitamin D /01233101/	1	2.5	0	0
Clopidogrel Sulfate	0	0	1	2.5
Diapride Forte	3	7.5	0	0
Diclofenac Deanol	1	2.5	1	2.5
Diclofenac Sodium	7	17.5	9	22.5
Enalapril Maleate	1	2.5	1	2.5
Etoricoxib	0	0	1	2.5
Fixocard	0	0	1	2.5
Galenic /Ibuprofen/Paracetamol/	15	37.5	8	20.0
Gemcal	0	0	1	2.5
Gemer-P	1	2.5	0	0
Glibenclamide	1	2.5	0	0
Glimepiride	0	0	1	2.5
Glucosamine Sulfate	0	0	1	2.5
Glynase Mf	2	5.0	0	0
Hyzaar /01284801/	3	7.5	1	2.5
Ibuprofen	0	0	1	2.5
Indometacin	0	0	1	2.5
Lekovit Ca	9	22.5	7	17.5
Lornoxicam	1	2.5	1	2.5
Losartan Potassium	1	2.5	0	0
Mecobalamin	2	5.0	2	5.0
Metaglip	2	5.0	1	2.5
Metformin	2	5.0	3	7.5
Metformin Hydrochloride	0	0	1	2.5
Metoprolol Succinate	1	2.5	0	0

	TREATMENT A (N=40)		TREATMENT B (N=40)	
Metoprolol Tartrate	1	2.5	2	5.0
Nephrovite	1	2.5	0	0
Nifedipine	0	0	1	2.5
Osteocare /01424301/	1	2.5	1	2.5
Paracetamol	8	20.0	5	12.5
Pritor /01506701/	0	0	1	2.5
Propranolol Hydrochloride	1	2.5	0	0
Ramipril	0	0	2	5.0
Rejoint	0	0	1	2.5
Sil-Norboral	2	5.0	0	0
Telmisartan	0	0	2	5.0

n/% = Number/percentage of subjects with the given characteristics
Treatment A: Arthronat
Treatment B: Placebo
Source Listing: Prior Concomitant Medication

14.3.2 Displays of Adverse Events

Refer Section 12.2.2

14.3.3 Listings of Deaths, Other Serious and Significant Adverse Events

There were no Deaths, Other Serious and Significant AEs reported in this study.

14.3.4 Narratives of Deaths, Other Serious and Certain Other Significant AEs

Not Applicable

14.3.5 Abnormal Laboratory Value Listing (Each Patient)

Not applicable

15 REFERENCE LIST

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3. Pham. T, Heijde. V.D, Altman RD, Anderson JJ, Bellamy N; OMERACT OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited; Osteoarthritis and Cartilage: 2004 May; 12(5): 389-399.

16 APPENDICES

16.1 STUDY INFORMATION

16.1.1 Protocol and protocol amendments

16.1.2 Sample case report form

16.1.3 List of IECs or IRBs and sample ICFs

16.1.3.1 List of EC members and EC approval letter

16.1.3.2 Sample ICFs in 4 languages

16.1.4 List and description of investigators and other important participants in the study, including brief CVs or equivalent summaries of training and experience relevant to the performance of the clinical study

16.1.5 Signature of principal or coordinating investigator(s) or sponsor's responsible medical officer.

16.1.6 Listing of patients receiving test/reference product(s) from specific batches, when more than one batch was used – Not applicable.

16.1.7 Randomization scheme and codes (patient identification and treatment assigned)

16.1.8 Quality assurance statement

16.1.9 Documentation of statistical methods

16.1.10 Documentation of inter-laboratory standardization methods and quality assurance procedures if used – Not applicable.

16.1.11 Publications based on study – Not applicable.

16.1.12 Important publications referenced in the report.

16.2 PATIENT DATA LISTINGS

The following individual data listings will be provided:

16.2.1 Discontinued subjects – Not applicable

16.2.2 Protocol deviations – Not applicable

16.2.3 Subjects excluded from efficacy analysis – Not applicable

16.2.4 Demography

16.2.5 Compliance data

16.2.5.1 Run-in period medications dispensing and review of compliance by patient

16.2.5.2 Treatment Period: Review of Compliance

16.2.6 Individual efficacy response data

16.2.6.1 Visual Analogue scale for pain

16.2.6.2 WOMAC Index Questionnaire for Hip and Knee OA

16.2.6.3 SF-36 Quality of Life Questionnaire

16.2.6.4 OMERACT-OARSI Retrieval and Dispensing

16.2.6.5 Rescue medications retrieval and dispensing

16.2.6.6 Patient Global Assessment of OA

16.2.7 Adverse Events

16.2.8 Listing of individual laboratory measurements by patient, when required by regulatory authorities

16.2.8.1 Hematology

16.2.8.2 Urine analysis

16.2.8.3 Urine Pregnancy Test

16.2.9 ACR Classification Criteria of Functional Status in Rheumatoid Arthritis

16.2.10 Concomitant Medication

16.2.11 Alcohol History

16.2.12 Dispensing of Study Medication

16.2.13 Dispensing of Subject Diary

16.2.14 Early Withdrawal/End of Study Form

16.2.15 Inclusion Criteria

16.2.16 Exclusion Criteria

16.2.17 Informed Consent

16.2.18 Investigator's Comments

16.2.19 Investigator's Statement

16.2.20 Medical and Surgical History

16.2.21 Orthopaedic Examination of the Index Joint

16.2.22 Osteoarthritis History

16.2.23 Physical Examination

16.2.24 Prior Concomitant Medication

16.2.25 Randomization

16.2.26 Reproductive Status

16.2.27 Review and Retrieval of Subject Diary

16.2.28 Screening Failure Form

16.2.29 Serum Biochemistry

16.2.30 Smoking History

16.2.31 Vital Signs

16.2.32 X-Ray of the Index Joint

16.3 CASE REPORT FORMS

16.3.1 CRF's of deaths, other SAEs and withdrawals due to AE

– Not applicable

16.3.2 Other CRF's submitted